Principles and Practice of MECHANICAL VENTILATION

THIRD EDITION

MARTIN J. TOBIN

Principles and Practice of Mechanical Ventilation

Notice

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Third Edition

Editor

Martin J. Tobin, MD

Professor of Medicine and Anesthesiology
Edward Hines, Jr., Veterans Administration Hospital and
Loyola University of Chicago Stritch School of Medicine
Editor emeritus, *American Journal of Respiratory and Critical Care Medicine*
Chicago, Illinois

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To Sareen, Damien, Kate, and Kieran

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CONTRIBUTORS

Marcelo B. P. Amato, MD, PhD
Associate Professor
Pulmonary
University of São Paulo
São Paulo, SP, Brazil
Supervisor—Respiratory ICU
Chapter 9: Pressure-Controlled and Inverse-Ratio Ventilation

Elie Azoulay, MD, PhD
Hôpital Saint-Louis
Medical ICU
Université Paris-Diderot
Sorbonne Paris-Cité,
Faculté de médecine
Paris, France
Chapter 66: The Ethics of Withholding and Withdrawing Mechanical Ventilation

Robert B. Banzett, PhD
Associate Professor
Department of Medicine
Harvard Medical School
Boston, Massachusetts

Division of Pulmonary, Critical Care, and Sleep Medicine
Beth Israel Deaconess Medical Center
Boston, Massachusetts
Chapter 55: Addressing Respiratory Discomfort in the Ventilated Patient
Chapter 56: Ventilator-Supported Speech

Ahmet Baydur, MD, FACP, FCCP
Professor of Clinical Medicine
Division of Pulmonary and Critical Care Medicine
Keck School of Medicine
University of Southern California
Los Angeles, California
Chapter 32: Mechanical Ventilation in Neuromuscular Disease

Jennifer C. Beck, PhD
Staff Scientist
Keenan Research Centre
Li Ka Shing Knowledge Institute of St. Michael's Hospital
Toronto, Ontario, Canada

Assistant Professor
Pediatrics
University of Toronto
Toronto, Ontario, Canada
Chapter 13: Neurally Adjusted Ventilatory Assist

Andrew D. Bersten, MBBS, MD
Professor
Critical Care Medicine
Flinders University School of Medicine
Adelaide, South Australia

Director
ICCU
Flinders Medical Centre
Adelaide, South Australia
Chapter 65: Fluid Management in the Ventilated Patient

Lluis Blanch, MD, PhD
Senior
Critical Care Center
Hospital de Sabadell
Sabadell, Spain

Critical Care Center,
Hospital de Sabadell,
Corporació Sanitària Parc Taulí
Institut Universitari Fundació Parc Taulí-Universitat Autònoma de Barcelona
Sabadell, Spain

CIBER Enfermedades Respiratorias—ISCIII, Spain
Chapter 22: Transtracheal Gas Insufflation, Transtracheal Oxygen Therapy, Emergency Transtracheal Ventilation

Michela Bombino, MD
Staff Physician
Department of Perioperative Medicine and Intensive Care
A.O. Ospedale S. Gerardo
Monza, Italy
Chapter 21: Extracorporeal Carbon Dioxide Removal

Richard D. Branson, MSc, RRT
Professor
Surgery
University of Cincinnati
Cincinnati, Ohio

Adjunct Faculty
School of Aerospace Medicine
Wright Patterson Air Force Base
Dayton, Ohio
Chapter 15: Feedback Enhancements on Conventional Ventilator Breaths
Chapter 27: Transport of the Ventilator-Supported Patient

Laurent J. Brochard, MD
Professor
Department of Anesthesiology, Pharmacology,
Intensive Care Medicine
University of Geneva, School of Medicine
Geneva, Switzerland

Head
Intensive Care Unit
Geneva University Hospital
Geneva, Switzerland
Chapter 8: Pressure-Support Ventilation

Robert Brown, MD
Pulmonary and Critical Care Unit
Department of Medicine
Massachusetts General Hospital
Boston, Massachusetts

Harvard Medical School
Boston, Massachusetts
Chapter 55: Addressing Respiratory Discomfort in the Ventilated Patient
Chapter 56: Ventilator-Supported Speech

Claudia Brusasco, MD
Researcher
Department of Surgical Sciences and Integrated Diagnostics
University of Genova
Genova, Italy
Chapter 24: Mechanical Ventilation during General Anesthesia

Shannon S. Carson, MD
Associate Professor
Pulmonary and Critical Care Medicine
University of North Carolina School of Medicine
Chapel Hill, North Carolina
Chapter 67: Economics of Ventilator Care

Jean E. Chastre, MD
Professor of Medicine
Réanimation Médicale
University Pierre-et-Marie Curie, Paris 6
Paris, France

Head of Department
Réanimation Médicale
Hôpital Pitié-Salpêtrière
Paris, France
Chapter 46: Pneumonia in the Ventilator-Dependent Patient

Robert L. Chatburn, MHHS, RRT-NPS, FAARC
Professor
Medicine
Lerner College of Medicine of Case Western Reserve University
Clevelan, Ohio

Clinical Research Manager
Respiratory Institute
Cleveland Clinic
Cleveland, Ohio
Chapter 2: Classification of Mechanical Ventilators and Modes of Ventilation
Chapter 3: Basic Principles of Ventilator Design

Gene L. Colice, MD
Professor
Medicine
The George Washington University School of Medicine
Washington, District of Columbia

Director, Pulmonary, Critical Care and Respiratory Services
Medicine
Washington Hospital Center
Washington, District of Columbia
Chapter 1: Historical Perspective on the Development of Mechanical Ventilation

Antonio Corrado, MD
Unità di Terapia Intensiva Respiratoria-Fisiopatologia Toracica
Azienda Ospedaliera-Universitaria Careggi
Firenze, Italy
Chapter 16: Negative-Pressure Ventilation

Heidi J. Dalton, MD, FCCM
Division and Section Chief, Critical Care Medicine
Director, ECMO
Phoenix Children's Hospital
Phoenix, Arizona
Chapter 20: Extracorporeal Life Support for Cardiopulmonary Failure

Nicolas de Prost, MD
Hôpitaux de Paris
Hôpital Henri Mondor
Service de Réanimation Médicale
Créteil, France
Chapter 42: Ventilator-Induced Lung Injury

Steven Deem, MD
Professor
Anesthesiology and Medicine
University of Washington
Seattle, Washington

Director, Neurocritical Care
Harborview Medical Center
Seattle, Washington
Chapter 38: Airway Management

Rajiv Dhand, MD, FCCP, FACP, FAARC
Professor
Medicine
University of Tennessee Graduate School of Medicine
Knoxville, Tennessee

Chairman
Medicine
University of Tennessee Graduate School of Medicine
Knoxville, Tennessee
Chapter 63: Bronchodilator Therapy

Anthony F. DiMarco, MD
Professor
Department of Physiology & Biophysics
Case Western Reserve University
Cleveland, Ohio

Professor
MetroHealth Research Institute
MetroHealth Medical Center
Cleveland, Ohio
Chapter 62: Diaphragmatic Pacing

Didier Dreyfuss, MD
Professor
Department of Critical Care
Université Sorbonne Paris Cité and Hôpital Louis Mourier, Colombes
Colombes, France
Chapter 42: Ventilator-Induced Lung Injury
Chapter 51: Humidification

Mark W. Elliott, MD, FRCP (UK)
Department of Respiratory Medicine
St James's University Hospital
Leeds, West Yorkshire, United Kingdom
Chapter 34: Noninvasive Ventilation on a General Ward

Ali A. El-Solh, MD, MPH
Professor of Medicine, Anesthesiology, and Social and Preventive Medicine
Department of Medicine
University at Buffalo
Buffalo, New York

Director of Critical Care
VA Western New York Healthcare System
Buffalo, New York
Chapter 41: Complications Associated with Mechanical Ventilation

Jean-Yves Fagon, MD, PhD
Professor
Critical Care
Hôpiotal Européen Georges Pompidou, AP-HP and Paris Descarte University
Paris, France
Chapter 46: Pneumonia in the Ventilator-Dependent Patient

Niall D. Ferguson, MD, MSc
Associate Professor
Interdepartmental Division of Critical Care Medicine
University of Toronto
Toronto, Ontario, Canada

Director, Critical Care
Department of Medicine, Division of Respirology
University Health Network & Mount Sinai Hospital
Toronto, Ontario, Canada
Chapter 19: High-Frequency Ventilation

Antoni Ferrer, MD
Servei de Pneumologia
Hospital de Sabadell
Corporació Parc Taulí
Institut Universitari Fundació Parc Taulí
Universitat Autònoma de Barcelona
Sabadell, Spain
Chapter 37: Effect of Mechanical Ventilation on Gas Exchange

Alison B. Froese, MD, FRCP(C)
Professor
Departments of Anesthsiology and Perioperative Medicine, Pediatrics, Physiology
Queen's University
Kingston, Ontario, Canada

Attending Physician
Department of Anesthesiology and Perioperative Medicine
Kingston General Hospital
Kingston, Ontario, Canada
Chapter 19: High-Frequency Ventilation

Marcelo Gama de Abreu, MD, PhD, DESA
Professor of Anesthesiology and Intensive Care
Department of Anesthesiology and Intensive Care
University Hospital Carl Gustav Carus,
Dresden University of Technology
Dresden, Germany
Chapter 24: Mechanical Ventilation during General Anesthesia

Pamela C. Garcia-Filion, PhD, MPH
Research Scientist
Critical Care
Phoenix Children's Hospital
Phoenix, Arizona
Chapter 20: Extracorporeal Life Support for Cardiopulmonary Failure

Luciano Gattinoni, MD
Full Professor
Dipartimento di Anestesiologia, Terapia Intensiva e Scienze Dermatologiche
Fondazione IRCCS CaUniversità degli Studi di Milano
Milan, Italy

Dipartimento di Anestesia, Rianimazione e Terapia del Dolore
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico
Milan, Italy
Chapter 21: Extracorporeal Carbon Dioxide Removal
Chapter 49: Prone Positioning in Acute Respiratory Failure

Dimitris Georgopoulos, MD, PhD
Professor
Intensive Care Medicine
University of Crete, Scool of Medine
Heraklion, Crete
Chapter 35: Effects of Mechanical Ventilation on Control of Breathing

Ivan Goldstein, MD, PhD
Réanimation Chirugicale Polyvalente Pierre Viars
Hôpital Pitié-Salpêtrière
Assistance Publique Hôpitaux de Paris
Université Pierre et Marie Curie
Paris, France
Chapter 64: Inhaled Antibiotic Therapy

Hernando Gomez, MD
Assistant Professor
Department of Critical Care Medicine
University of Pittsburgh Medical Center
Pittsburgh, Philadelphia
Chapter 36: Effect of Mechanical Ventilation on Heart–Lung Interactions

Massimo Gorini, MD
Federico II University Hospital
School of Medicine
Naples, Italy
Chapter 16: Negative-Pressure Ventilation

Jesse B. Hall, MD
Section Chief
Professor of Medicine
Pulmonary and Critical Care
University of Chicago
Chicago, Illinois
Chapter 50: Pain Control, Sedation, and Neuromuscular Blockade

Jürg Hammer, MD
Associate Professor
Division of Intensive Care and Pulmonology
University Children's Hospital Basel (UKBB)
Basel, Switzerland

Medical Director
Division of Intensive Care and Pulmonology
University Children's Hospital Basel (UKBB)
Basel, Switzerland
Chapter 23: Mechanical Ventilation in the Neonatal and Pediatric Setting

Patrick J. Hanly, MD, FRCPC, MRCPI, D, ABSM
Professor
Medicine
University of Calgary, Faculty of Medicine
Calgary, Alberta

Medical Director
Sleep Centre
Foothills Medical Centre
Calgary, Alberta
Chapter 57: Sleep in the Ventilator-Supported Patient

John E. Heffner, MD
Professor
Department of Medicine
Oregon Health & Science University
Portland, Oregon

Garnjobst Chair
Department of Medicine
Providence Portland Medical Center
Portland, Oregon
Chapter 40: Care of the Mechanically Ventilated Patient with a Tracheotomy

Holger Herff, MD
Department of Anesthesiology and Critical Care Medicine
Innsbruck Medical University
Innsbruck, Austria
Chapter 26: Mechanical Ventilation during Resuscitation

Margaret Sutherland Herridge, MSc, MD, FRCPC, MPH
Associate Professor
Department of Medicine
University of Toronto
Toronto, Ontario, Canada

Attending Staff Critical Care and Respiratory Medicine
Department of Medicine
University Health Network
Toronto, Ontario, Canada
Chapter 68: Long-Term Outcomes after Mechanical Ventilation

Nicholas S. Hill, MD
Professor
Medicine
Tufts University School of Medicine
Boston, Massachussetts

Chief
Division of Pulmonary, Critical Care and Sleep Medicine
Tufts Medical Center
Boston, Massachussetts
Chapter 17: Noninvasive Respiratory Aids: Rocking Bed, Pneumobelt, and Glossopharyngeal Breathing
Chapter 18: Noninvasive Positive-Pressure Ventilation

Jeannette D. Hoit, PhD, CCC-SLP
Professor
Department of Speech, Language, and Hearing Sciences
University of Arizona
Tucson, Arizona
Chapter 56: Ventilator-Supported Speech

Steven R. Holets, RRT
Assistant Professor of Anesthesiology
Department of Respiratory Care
Mayo Clinic
Rochester, Minnesota
Chapter 5: Setting the Ventilator

David L. Hotchkin, MD, MSc
Chief Pulmonary & Critical Care Medicine
Internal Medicine Residency Program
Providence Portland Medical Center
Portland, Oregon

Attending Physician
Division of Pulmonary, Critical Care and Sleep Medicine
The Oregon Clinic
Portland, Oregon
Chapter 40: Care of the Mechanically Ventilated Patient with a Tracheotomy

Rolf D. Hubmayr, MD
Professor
Department of Medicine
Mayo Clinic
Rochester, Minnesota
Chapter 5: Setting the Ventilator

Aaron M. Joffe, DO
Assistant Professor
Department of Anesthesiology and Pain Medicine
University of Washington, Harborview Medical Center
Seattle, Washington

Division Head of Otolaryngology, Oral and Maxillofacial Anesthsia Services
University of Washington, Harborview Medical Center
Seattle, Washington
Chapter 38: Airway Management

Jay A. Johannigman, MD
Professor
Department of Surgery
University of Cincinnati COM
Cincinnati, Ohio

Division Chief
Division of Trauma, Surgical Critical Care and Acute Care Surgery
University Hospital
Cincinnati, Ohio
Chapter 27: Transport of the Ventilator-Supported Patient

Amal Jubran, MD
Professor of Medicine
Division of Pulmonary and Critical Care Medicine
Edward Hines Jr., Veterans Affairs Hospital and Loyola University of Chicago Stritch School of Medicine
Hines, Illinois
Chapter 48: Monitoring during Mechanical Ventilation
Chapter 53: Fighting the Ventilator
Chapter 58: Weaning from Mechanical Ventilation

Brian P. Kavanagh, MB, FRCPC, FFARCSI (hon)
Professor & Chair
Department of Anesthesia
University of Toronto
Toronto, Canada

Staff Physician
Department of Critical Care Medicine
Hospital for Sick Children
Toronto, Canada
Chapter 14: Permissive Hypercapnia

John P. Kress, MD
Associate Professor
Department of Medicine, Section of Pulmonary and Critical Care
University of Chicago
Chicago, Illinois
Chapter 50: Pain Control, Sedation, and Neuromuscular Blockade

John G. Laffey, MD, MA, FCARCSI
Professor
Department of Anesthesia
University of Toronto Faculty of Medicine
Toronto, Ontario, Canada

Anesthetist-in-Chief
Department of Anestheisa
St Michael's Hospital
Toronto, Ontario, Canada
Chapter 14: Permissive Hypercapnia

Franco Laghi, MD
Professor
Division of Pulmonary and Critical Care Medicine
Edward Hines Jr. Veterans Affairs Hospital and Loyola University of Chicago Stritch School of Medicine
Hines, Illinois
Chapter 4: Indications for Mechanical Ventilation
Chapter 31: Mechanical Ventilation in Chronic Obstructive Pulmonary Disease
Chapter 53: Fighting the Ventilator
Chapter 59: Extubation

James W. Leatherman, MD
Professor
Medicine
University of Minnesota
Minneapolis, Minnesota

Director, Medical ICU
Pulmonary and Critical Care Medicine
Hennepin County Medical
Minneapolis, Minnesota
Chapter 30: Mechanical Ventilation for Severe Asthma

Francois Lellouche, MD, PhD
Associante Professor
Medicine
Laval University
Québec, Québec

Critical Care Physician
Cardiac Surgery ICU
Institut Universitaire de Cardiologie et de Pneumologie de Québec
Québec, Québec
Chapter 8: Pressure-Support Ventilation

Klaus Lewandowski, MD
Professor of Anesthesia and Intensive Care Medicine
Klinik für Anästhesiologie, Intensivmedizin und Schmerztherapie
Elisabeth-Krankenhaus Essen
Essen, Germany
Chapter 61: Nitric Oxide as an Adjunct

James F. Lewis, MD, FRCP
Professor of Medicine and Physiology
Medicine
Western University
London, Ontario, Canada
Chapter 60: Surfactant

Gianluigi Li Bassi, MD
Attending Physician
Respiratory Intensive Care Unit
Hospital Clinic
Barcelona, Spain

Senior Researcher
Department of Pneumology
Institut d'investigacions Biomèdiques August Pi i Sunyer
Barcelona, Spain
Chapter 52: Airway Secretions and Suctioning

Robert F. Lodato, MD, PhD
Associate Professor
Division of Pulmonary, Critical Care, and Sleep Medicine
The University of Texas Health Science Center
Houston, Texas
Chapter 45: Oxygen Toxicity

Qin Lu, MD
Multidisciplinary Intensive Care Unit Pierre Viars
Department of Anesthesiology and Critical Care Medicine
La Pitié-Salpêtrière Hospital
Assistance Publique-Hôpitaux de Paris
Université Pierre et Marie Curie
Paris, France
Chapter 47: Sinus Infections in the Ventilated Patient
Chapter 64: Inhaled Antibiotic Therapy

Umberto Lucangelo, MD
Assistan Professor
Department of Perioperative Medicine,
Intensive Care and Emergency
University of Trieste School of Medicine
Trieste, Italy
Chapter 22: Transtracheal Gas Insufflation, Transtracheal Oxygen Therapy, Emergency Transtracheal Ventilation

Andrew M. Luks, MD
Assistant Professor
Department of Medicine, Division of Pulmonary and
Critical Care Medicine
University of Washington
Seattle, Washington
Chapter 44: Barotrauma and Bronchopleural Fistula

Charles-Edouard Luyt, MD, PhD
Associate Professor
Medical Intensive Care Unit
Université Paris 6-Pierre et Marie Curie
Paris, France

Attending Physician
Medical Intensive Care Unit
Groupe Hospitalier Pitié-Salpêtrière, APHP
Paris, France
Chapter 46: Pneumonia in the Ventilator-Dependent Patient

Neil MacIntyre, MD
Professor
Medicine
Duke University
Durham, North Carolina
Chapter 15: Feedback Enhancements on Conventional Ventilator Breaths

Salvatore Maurizio Maggiore, MD, PhD
Assistant Professor
Department of Anesthesiology and Intensive Care
Policlinico Agostino Gemelli, Università Cattolica del Sacro Cuore
Rome, Italy
Chapter 10: Positive End-Expiratory Pressure

Jordi Mancebo, MD
Director
Medicina Intensiva
Hospital de Sant Pau
Barcelona, Spain

Associate Professor
Medicine
Universitat Autònoma de Barcelona
Barcelona, Spain
Chapter 6: Assist-Control Ventilation

John J. Marini, MD
Professor of Medicine
Pulmonary & Critical Care
University of Minnesota
Minneapolis/St. Paul, Minnesota

Director of Physiologic & Translational Research
Dept. of Medicine
Regions Hospital
St. Paul, Minnesota
Chapter 9: Pressure-Controlled and Inverse-Ratio Ventilation
Chapter 29: Mechanical Ventilation in the Acute Respiratory Distress Syndrome

Daniele Mascheroni, MD
Dipartimento di Anestesia, Rianimazione e Terapia del Dolore
FONDAZIONE IRCCS CA' GRANDA,
Ospedale Maggiore Policlinico
Milano, Italy
Chapter 49: Prone Positioning in Acute Respiratory Failure

Phillip E. Mason, MD
Staff Physician
Department of Emergency Medicine
San Antonio Military Medical Center
San Antonio, Texas
Chapter 27: Transport of the Ventilator-Supported Patient

Eduardo Mireles-Cabodevila, MD
Assistant Professor
Division of Pulmonary and Critical Care
University of Arkasnas for Medical Sciences
Little Rock, Arizona

Director, Medical Intensive Care Unit
University of Arkasnas for Medical Sciences
Little Rock, Arizona
Chapter 3: Basic Principles of Ventilator Design

Avi Nahum, MD, PhD
Associate Professor
Pulmonary and Critical Care Medicine
University of Minnesota
Minneapolis, Minnesota

Staff Physician
Department of Pulmonary and Critical Care
Regions Hospital
St. Paul, Minnesota
Chapter 22: Transtracheal Gas Insufflation, Transtracheal Oxygen Therapy, Emergency Transtracheal Ventilation

Stefano Nava, MD
Chief
Respiratory and Critical Care
Sant' Orsola Malpighi Hospital, University of Bologna
Bologna, Italy
Chapter 33: Chronic Ventilator Facilities

Paolo Navalesi, MD
Associate Professor
Department of Translational Medine
Università del Piemonte Orientale "A. Avogadro"
Novara, Italy

Head
Anesthesia and Intensive Care
Ospedale Sant'Andrea
Vercelli, Italy
Chapter 10: Positive End-Expiratory Pressure

Paolo Pelosi, MD
Full Professor in Anesthesiology
Department of Surgical Sciences and Integrated Diagnostics
University of Genoa
Genoa, Italy
Chapter 24: Mechanical Ventilation during General Anesthesia
Chapter 49: Prone Positioning in Acute Respiratory Failure

Antonio Pesenti, MD
Professor
Department of Experimental Medicine
University of Milan Bicocca
Milan, Italy

Chief
Department of Emergency
San Gerardo Hospital
Monza, Italy
Chapter 21: Extracorporeal Carbon Dioxide Removal

David J. Pierson, MD
Professor Emeritus
Pulmonary and Critical Care Medicine
University of Washington School of Medicine
Seattle, Washington
Chapter 44: Barotrauma and Bronchopleural Fistula

Michael R. Pinsky, MD, Dr hc, FCCP, MCCM
Professor
Department of Critical Care Medicine
University of Pittsburgh
Pittsburgh, Philadelphia

Vice Chair for Academic Affairs
Department of Critical Care Medicine
University of Pittsburgh
Pittsburgh, Philadelphia
Chapter 36: Effect of Mechanical Ventilation on Heart–Lung Interactions

Karin A. Provost, DO, PhD
Research Assistant Professor
Division of Pulmonary, Critical Care and Sleep Medicine
State University of New York at Buffalo, School of Medicine and Biomedical Sciences
Buffalo, New York
Chapter 41: Complications Associated with Mechanical Ventilation

Valeria Puntorieri, MD
University of Western Ontario
London, Ontario, Canada
Chapter 60: Surfactant

Christian Putensen, MD
Professor
Anesthesiology and Intensive Care Medicine
University Hospital Bonn
Bonn, Germany

Head of Intensive Care Medicine
Anesthesiology and Intensive Care Medicine
University Hospital Bonn
Bonn, Germany
Chapter 11: Airway Pressure Release Ventilation

Jean-Damien Ricard, MD, PhD
Professor
Service de Réanimation Médico-chirurgicale
Assistance Publique—Hôpitaux de Paris, Hopital Louis Mourier
Colombes, France

Researcher
UMR-S INSERM U722
Université Paris Diderot
Paris, France
Chapter 42: Ventilator-Induced Lung Injury
Chapter 51: Humidification

Peter C. Rimensberger, MD
Professor of Pediatrics and Intensive Care Medicine
Service of Neonatogy and Pediatric Intensive Care,
Department of Pediatrics
University Hospital of Geneva
Geneva, Switzerland

Director
Chapter 23: Mechanical Ventilation in the Neonatal and Pediatric Setting

Roberto Rodriguez-Roisin, MD, PhD
Full Professor of Medicine
Department of Medicine
Universitat de Barcelona
Barcelona, Spain

Senior Consultant Physician
Institute of Thorax-Servei de Pneumologia
Hospital Clínic
Barcelona, Spain
Chapter 37: Effect of Mechanical Ventilation on Gas Exchange

Jean-Jacques Rouby, MD, PhD
Professor of Anesthesiology and Critical Care
Department of Anesthesiology
Université Pierre et Marie Curie Paris 06
Paris, France
Chapter 47: Sinus Infections in the Ventilated Patient
Chapter 64: Inhaled Antibiotic Therapy

Catherine S. Sassoon, MD
Professor of Medicine
Division of Pulmonary and Critical Care Medicine
Department of Medicine
University of California School of Medicine
Irvine, California

Staff Physician
Department of Medicine
VA Long Beach Healthcare System
Long Beach, California
Chapter 7: Intermittent Mandatory Ventilation

Georges Saumon, MD
Institut National de la Santé et de la Recherche Médicale
Faculté Xavier Bichat
Paris, France
Chapter 42: Ventilator-Induced Lung Injury

Thomas Similowski, MD, PhD
Professor
Department of Respiratory and Critical Care Medicine
GH Pitié-Salpêtrière
Paris, France
Chapter 55: Addressing Respiratory Discomfort in the Ventilated Patient

Christer Sinderby, MD
Staff Scientist
Critical Care
Li Ka Shing Knowledge Institute of the Keenan Research Center at St-Michael's Hospital
Toronto, Ontario, Canada

University of Toronto, Department of Medicine
Toronto, Ontario, Canada
Chapter 13: Neurally Adjusted Ventilatory Assist

Yoanna Skrobik, MD FRCP(C)
Professor
Department of Medicine
Université de Montréal
Montréal, Québec, Canada

Lise and Jean Saine Critical Care Chair
Critical Care Division
Hopital Maisonneuve Rosemont
Montréal, Québec, Canada
Chapter 54: Psychological Problems in the Ventilated Patient

John L. Stauffer, MD
Senior Director
Clinical Development
FibroGen, Inc.
San Francisco, California

Physician/Consultant
Medical Service
Department of Veterans Affairs
Palo Alto Health Care System
Palo Alto, California
Chapter 39: Complications of Translaryngeal Intubation

Paolo Taccone, MD
Attending Physician
Dipartimento di Anestesia, Rianimazione (Intensiva e Subintensiva) e Terapia del Dolore
Fondazione IRCCS Cà Granda—Ospedale Maggiore Policlinico
Milan, Italy
Chapter 49: Prone Positioning in Acute Respiratory Failure

Martin J. Tobin, MD
Professor of Medicine and Anesthesiology
Edward Hines, Jr., Veterans Administration Hospital and Loyola University of Chicago Stritch School of Medicine
Editor emeritus, *American Journal of Respiratory and Critical Care Medicine*
Chicago, Illinois
Chapter 4: Indications for Mechanical Ventilation
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David V. Tuxen, MBBS, FRACP, DipDHM, MD, CICM
Adjunct Professor
Department of Intensive Care
The Alfred Hospital
Melbourne, Australia

Senior Intensivist
Chapter 25: Independent Lung Ventilation

Franco Valenza, MD
Assistant Professor
Dipartimento di Anestesia, Rianimazione e Scienze Dermatologiche
Università degli Studi di Milano
Milano, Italy

Dipartimento di Anestesia e Rianimazione
Fondazione IRCCS Ca' Granda—Ospedale Maggiore Policlinico
Milano, Italy
Chapter 49: Prone Positioning in Acute Respiratory Failure

Theodoros Vassilakopoulos, MD
Associate Professor
1st Department of Critical Care and Pulmonary Services
University of Athens Medical School
Athens, Greece

Physician in Chief
Pulmonary Division/Critical Care Department
Evangelismos Hospital
Athens, Greece
Chapter 43: Ventilator-Induced Diaphragmatic Dysfunction

Michele Vitacca, MD
Rehabilitative Respiratory Division—Weaning Unit
Fondazione Salvatore Maugeri, IRCCS
Lumezzane, Brescia, Italy
Chapter 33: Chronic Ventilator Facilities

Volker Wenzel, MD, MSc, FERC
Associate Professor and Vice Chairman
Department of Anesthesiology and Critical Care Medicine
Innsbruck Medical University
Innsbruck, Austria
Chapter 26: Mechanical Ventilation during Resuscitation

Michael E. Wilson, MD
Instructor
Department of Internal Medicine
Mayo Clinic
Rochester, Minnesota
Chapter 66: The Ethics of Withholding and Withdrawing Mechanical Ventilation

Wolfram Windisch, MD
Department of Pneumology
University Hospital Freiburg
Freiburg, Germany
Chapter 28: Home Mechanical Ventilation

Magdy Younes, MD, FRCP(C), PhD
Distinguished Professor Emeritus
Internal Medicine
University of Manitoba
Winnipeg, Manitoba, Canada

Research Professor
Department of Medicine
University of Calgary
Calgary, Alberta, Canada
Chapter 12: Proportional-Assist Ventilation

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PREFACE

More than twenty years have passed since *Principles and Practice of Mechanical Ventilation* was first conceived. With this third edition, the textbook has come of age. When the first proposal of the book was under consideration, reviewers thought that the corpus of knowledge pertaining to mechanical ventilation would not be sufficient to merit the publication of a large tome; they opined that the contents of such a book would require much padding. This time around, the challenge has been to fit everything into a constrained number of pages. Virtually every aspect of mechanical ventilation has evolved substantially over the past twenty years, and many new areas have emerged. Novel ventilator modes have been introduced, previously discarded modes have acquired a new lease of life, and long-surviving methodologies have undergone considerable refinement. Much of the progress has stemmed from research into the mechanisms whereby ventilators harm patients. In turn, we have learned how minor adjustments to ventilator settings can markedly enhance patient comfort and survival. A comparison of the third and first editions of *Principles and Practice of Mechanical Ventilation* provides proof of the tremendous progress in this field during the past twenty years.

Trainees hear much about the practice of medicine, as in phrases such as clinical practice guidelines. As physicians grow older, they realize that many popular practices turn out to be ephemeral—it is biomedical principles that remain evergreen. Mechanical ventilation remains rooted in physiological principles; it is these principles that guide practice. The wise physician is ever mindful of the need to balance principles with practice—to achieve the right equilibrium between theory and pragmatic action. Without a sound knowledge of the biomedical principles that govern ventilator management, a physician is reduced to setting a ventilator in a hit-or-miss manner or to follow a cookbook recipe. With a deep understanding of physiologic principles, a physician is better equipped to make expert iterative adjustments to the ventilator as a patient's condition changes over time. As with previous editions, readers will find detailed accounts of both biomedical principles and practical advice throughout this textbook.

Electronic technology has transformed medical publishing, providing rapid access to a rich store of information. Contrasted with the hours previously spent in the periodical rooms of a library, authors now retrieve pertinent articles at the click of a mouse. But reading material online is not an unalloyed good. Deeply engaged reading requires focused attention and commitment, whereas reading online is accompanied by a dramatic increase in the opportunities for distraction. Media do not simply act as passive channels of communication, they also shape the process of thought. Cognitive scientists have begun to uncover the differences between reading online and off. Deep reading without distraction leads to the formation of rich mental connections across regions of the brain that govern such cognitive functions as memory and interpretation. Neuroscientists expect the internet to have far-reaching effects on cognition and memory. In contrast to a book, which is a machine for focusing attention and demanding the deep thinking that generates memory, the internet is a machine that scatters attention and diffuses concentration. Given the importance of rapid decisions in critical care medicine, which demand instant memory recall, a trainee is best advised to acquire the foundations for his or her storehouse of knowledge from a textbook rather than from online resources.

Another advantage of a textbook is that it provides a comprehensive account of a discipline in a single source, where clinicians can turn to find answers to their questions about mechanical ventilation. Commonly used online resources, such as *UpToDate*, are directed toward generalists and do not provide the depth of knowledge expected of a subspecialist. The information presented in medical journals is fragmentary by design; no attempt is made to fit published information into the mosaic of existing knowledge and topics deemed unfashionable by editors are ignored. Trainees who rely on bundles of reprints tend to be ignorant of the boundaries of a subspecialty and unaware of major lacunae in their knowledge base. No series of journal articles can compete with a textbook in this regard.

For a textbook to provide authoritative coverage of a field, the selection of authors is crucial. For each chapter, I selected scientists and clinicians who are at the forefront of research in a given subfield. Many of these authors undertook the seminal research that established a new area of mechanical ventilation, which was subsequently enriched and expanded by the work of other investigators. Being at the forefront of an area, these authors are attuned to evolving developments in a subfield, which makes their accounts extremely current and guards against early obsolescence of the material

included in their chapter. Each chapter has been extensively revised; twenty-five new authors provide fresh accounts of previously covered areas; many new topics have been added; and several chapters found in previous editions were deleted. I personally edited every line of each manuscript to ensure reliability of the presented information and to achieve a uniform style throughout the book.

Given that *Principles and Practice of Mechanical Ventilation* has become one of the classics on the McGraw-Hill list, the publisher decided to introduce color printing throughout the new edition. The result is a book that is not only informative but also aesthetically attractive. The large number of high-quality illustrations provides a pedagogical resource for readers who are preparing slides for lectures.

This book would not have been possible without the help of several people, and to them I am extremely grateful. First and foremost are the more than 100 authors, whose knowledge, commitment and wisdom form the core of the book. As with the two previous editions, I am most grateful to Amal Jubran and Franco Laghi for advice at several stages of this project. I thank Lynnel Hodge for invaluable assistance on a day-to-day basis. Richard Adin copyedited the manuscripts with a lawyer's eye for precision, and Brain Belval and Karen Edmondson at McGraw-Hill and Aakriti Kathuria at Thomson Digital skillfully guided the book through its production. Finally, I thank my family for their forbearance.

Martin J. Tobin

I

HISTORICAL BACKGROUND

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1

HISTORICAL PERSPECTIVE ON THE DEVELOPMENT OF MECHANICAL VENTILATION

Gene L. Colice

The history of mechanical ventilation is intimately intertwined with the history of anatomy, chemistry, and physiology; exploration under water and in the air; and of course, modern medicine. Anatomists described the structural connections of the lungs to the heart and vasculature and developed the earliest insights into the functional relationships of these organs. They emphasized the role of the lungs in bringing air into the body and probably expelling waste products, but showed little understanding of how air was used by the body. Chemists defined the constituents of air and explained the metabolic processes by which the cells used oxygen and produced carbon dioxide. Physiologists complemented these studies by exploring the relationships between levels of oxygen and carbon dioxide in the blood and ventilation. Explorers tested the true limits of physiology. Travel in the air and under water exposed humans to extremes in ventilatory demands and prompted the development of mechanical adjuncts to ventilation. Following the various historical threads provided by the anatomists, chemists, physiologists, and explorers provides a useful perspective on the tapestry of a technique modern physicians accept casually: mechanical ventilation.

ANATOMISTS OF THE HEART AND LUNGS

Early Greeks

Early Greek physicians endorsed Empedocles' view that all matter was composed of four essential elements: earth, air, fire, and water. Each of these elements had primary qualities of heat, cold, moisture, and dryness.[1] Empedocles applied this global philosophic view to the human body by stating that "innate heat," or the soul, was distributed from the heart via the blood to various parts of the body.

The Hippocratic corpus stated that the purpose of respiration was to cool the heart. Air was thought to be pumped by the atria from the lungs to the right ventricle via the pulmonary artery and to the left ventricle through

the pulmonary vein.[2] Aristotle believed that blood was an indispensable part of animals but that blood was found only in veins. Arteries, in contrast, contained only air. This conclusion probably was based on his methods of sacrificing animals. The animals were starved, to better define their vessels, and then strangled. During strangulation, blood pools in the right side of the heart and venous circulation, leaving the left side of the heart and arteries empty.[2] Aristotle described a three-chamber heart connected with passages leading in the direction of the lung, but these connections were minute and indiscernible.[3] Presumably, the lungs cooled the blood and somehow supplied it with air.[4]

Erasistratus (born around 300 BC) believed that air taken in by the lungs was transferred via the pulmonary artery to the left ventricle. Within the left ventricle, air was transformed into *pneuma zotikon*, or the "vital spirit," and was distributed through air-filled arteries to various parts of the body. The *pneuma zotikon* carried to the brain was secondarily changed to the *pneuma psychikon* ("animal spirit"). This animal spirit was transmitted to the muscles by the hollow nerves. Erasistratus understood that the right ventricle facilitated venous return by suction during diastole and that venous valves allowed only one-way flow of blood.[1]

The Greek physician Claudius Galen, practicing in Rome around AD 161, demonstrated that arteries contain blood by inserting a tube into the femoral artery of a dog.[5,6] Blood flow through the tube could be controlled by adjusting tension on a ligature placed around the proximal portion of the artery. He described a four-chamber heart with auricles distinct from the right and left ventricles. Galen also believed that the "power of pulsation has its origin in the heart itself" and that the "power [to contract and dilate] belongs by nature to the heart and is infused into the arteries from it."[5,6] He described valves in the heart and, as did Erasistratus, recognized their essential importance in preventing the backward discharge of blood from the heart. He alluded several times to blood flowing, for example, from the body through the vena cava into the right ventricle and even made the remarkable statement that "in the entire body the arteries come together with the veins and exchange air and blood through extremely fine invisible orifices."[6] Furthermore, Galen believed that "fuliginous wastes" were somehow discharged from the blood through the lung.[6] Galen's appreciation that the lungs supplied some property of air to the body and discharged a waste product from the blood was the first true insight into the lung's role in ventilation. However, he failed in two critical ways to appreciate the true interaction of the heart and lungs. First, he believed, as did Aristotle and other earlier Greeks, that the left ventricle is the source of the innate heat that vitalizes the animal. Respiration in animals exists for the sake of the heart, which requires the substance of air to cool it. Expansion of the lung caused the lightest substance, that is, the outside air, to rush in and fill the bronchi. Galen provided no insight, though, into how air, or *pneuma*, might be drawn out from the bronchi and lungs into the heart. Second, he did not clearly describe the true circular nature of blood flow from the right ventricle through the lungs and into the left ventricle and then back to the right ventricle. His writings left the serious misconception that blood was somehow transported directly from the right to the left ventricle through the interventricular septum.[1,5,6]

Renaissance Physicians

Byzantine and Arab scholars maintained Galen's legacy during the Dark Ages and provided a foundation for the rebirth of science during the Renaissance.[1,6,7] Around 1550, Vesalius corrected many inaccuracies in Galen's work and even questioned Galen's concept of blood flow from the right ventricle to the left ventricle. He was skeptical about the flow of blood through the interventricular pores Galen described.[1,6,8] Servetus, a fellow student of Vesalius in Paris, suggested that the vital spirit is elaborated both by the force of heat from the left ventricle and by a change in color of the blood to reddish yellow. This change in color "is generated in the lungs from a mixture of inspired air with elaborated subtle blood which the right ventricle of the heart communicates to the left. This communication, however, is made not through the middle wall of the heart, as is commonly believed, but by a very ingenious arrangement: the subtle blood courses through the lungs from the pulmonary artery to pulmonary vein, where it changes color. During this passage the blood is mixed with inspired air and through expiration it is cleansed of its sooty vapors. This mixture, suitably prepared for the production of the vital spirit, is drawn onward to the left ventricle of the heart by diastole."[6,9] Although Servetus' views proved ultimately to be correct, they were considered heretical at the time, and he was subsequently burned at the stake, along with most copies of his book, in 1553.

Columbus, a dissectionist to Vesalius at Padua, in 1559 suggested that blood travels to the lungs via the pulmonary artery and then, along with air, is taken to the left ventricle through the pulmonary vein. He further advanced the concept of circulation by noting that the left ventricle distributes blood to the body through the aorta, blood returns to the right ventricle in the vena cava, and venous valves in the heart allow only one-way flow.[1,6,10]

These views clearly influenced William Harvey, who studied anatomy with Fabricius in Padua from 1600 to 1602. Harvey set out to investigate the "true movement, pulse, action, use and usefulness of the heart and arteries." He questioned why the left ventricle and right ventricle traditionally were felt to play such fundamentally different roles. If the right ventricle existed simply to nourish the lungs, why was its structure so similar to that of the left ventricle? Furthermore, when one directly observed the beating heart in animals, it was clear that the function of both right and left ventricles also was similar. In both cases, when the ventricle contracted, it expelled blood, and when it relaxed, it received blood. Cardiac systole coincided with

arterial pulsations. The motion of the auricles preceded that of the ventricles. Indeed, the motions are consecutive with a rhythm about them, the auricles contracting and forcing blood into the ventricles and the ventricles, in turn, contracting and forcing blood into the arteries. "Since blood is constantly sent from the right ventricle into the lungs through the pulmonary artery and likewise constantly is drawn the left ventricle from the lungs…it cannot do otherwise than flow through continuously. This flow must occur by way of tiny pores and vascular openings through the lungs. Thus, the right ventricle may be said to be made for the sake of transmitting blood through the lungs, not for nourishing them."[6,11]

Harvey described blood flow through the body as being circular. This was easily understood if one considered the quantity of blood pumped by the heart. If the heart pumped 1 to 2 drams of blood per beat and beat 1000 times per half-hour, it put out almost 2000 drams in this short time. This was more blood than was contained in the whole body. Clearly, the body could not produce amounts of blood fast enough to supply these needs. Where else could all the blood go but around and around "like a stage army in an opera." If this theory were correct, Harvey went on to say, then blood must be only a carrier of critical nutrients for the body. Presumably, the problem of the elimination of waste vapors from the lungs also was explained by the idea of blood as the carrier.[1,6,11]

With Harvey's remarkable insights, the relationship between the lungs and the heart and the role of blood were finally understood. Only two steps remained for the anatomists to resolve. First, the nature of the tiny pores and vascular openings through the lungs had to be explained. About 1650, Malpighi, working with early microscopes, found that air passes via the trachea and bronchi into and out of microscopic saccules with no clear connection to the bloodstream. He further described capillaries: "… and such is the wandering about of these vessels as they proceed on this side from the vein and on the other side from the artery, that the vessels no longer maintain a straight direction, but there appears a network made up of the articulations of the two vessels…blood flowed away along [these] tortuous vessels … always contained within tubules."[1,6] Second, Borelli, a mathematician in Pisa and a friend of Malpighi, suggested the concept of diffusion. Air dissolved in liquids could pass through membranes without pores. Air and blood finally had been linked in a plausible manner.[1]

CHEMISTS AND PHYSIOLOGISTS OF THE AIR AND BLOOD

Understanding Gases

The anatomists had identified an entirely new set of problems for chemists and physiologists to consider. The right ventricle pumped blood through the pulmonary artery to the lungs. In the lungs the blood took up some substance, evidenced by the change in color observed as blood passes through the pulmonary circulation. Presumably the blood released "fuliginous wastes" into the lung. The site of this exchange was thought to be at the alveolar–capillary interface, and it probably occurred by the process of diffusion. What were the substances exchanged between blood and air in the lung? What changed the color of blood and was essential for the production of the "innate heat"? What was the process by which "innate heat" was produced, and where did this combustion occur, in the left ventricle as supposed from the earliest Greek physician-philosophers or elsewhere? Where were the "fuliginous wastes" produced, and were they in any way related to the production of "innate heat"? If blood were a carrier, pumped by the left ventricle to the body, what was it carrying to the tissues and then again back to the heart?

Von Helmont, about 1620, added acid to limestone and potash and collected the "air" liberated by the chemical reaction. This "air" extinguished a flame and seemed to be similar to the gas produced by fermentation. This "air" also appeared to be the same gas as that found in the Grotto del Cane. This grotto was notorious for containing air that would kill dogs but spare their taller masters.[1] The gas, of course, was carbon dioxide. In the late seventeenth century, Boyle recognized that there is some substance in air that is necessary to keep a flame burning and an animal alive. Place a flame in a bell jar, and the flame eventually will go out. Place an animal in such a chamber, and the animal eventually will die. If another animal is placed in that same chamber soon thereafter, it will die suddenly. Mayow showed, around 1670, that enclosing a mouse in a bell jar resulted eventually in the mouse's death. If the bell jar were covered by a moistened bladder, the bladder bulged inward when the mouse died. Obviously, the animals needed something in air for survival. Mayow called this the "nitro-aereal spirit," and when it was depleted, the animals died.[1,12] This gas proved to be oxygen. Boyle's suspicions that air had other qualities primarily owing to its ingredients seemed well founded.[13,14]

In a remarkable and probably entirely intuitive insight, Mayow suggested that the ingredient essential for life, the "nitro-aereal spirit," was taken up by the blood and formed the basis of muscular contraction. Evidence supporting this concept came indirectly. In the early 1600s, the concept of air pressure was first understood. von Guericke invented a pneumatic machine that reduced air pressure.[1,15] Robert Boyle later devised the pneumatic pump that could extract air from a closed vessel to produce something approaching a vacuum (Fig. 1-1). Boyle and Hooke used this pneumatic engine to study animals under low-pressure conditions. Apparently Hooke favored dramatic experiments, and he often demonstrated in front of crowds that small animals died after air was evacuated from the chamber. Hooke actually built a human-sized chamber in 1671 and volunteered to enter it. Fortunately, the pump effectively removed only about a quarter of the air, and Hooke survived.[16] Boyle

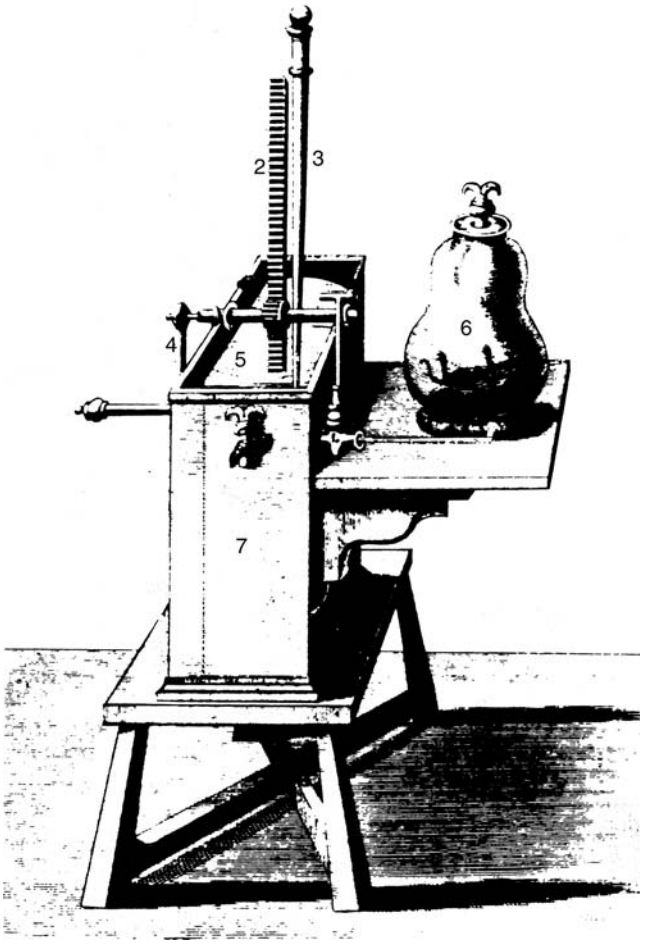


FIGURE 1-1 A pneumatical engine, or vacuum pump, devised by Hooke in collaboration with Boyle around 1660. The jar (6) contains an animal in this illustration. Pressure is lowered in the jar by raising the tightly fitting slide (5) with the crank (4). (Used, with permission, from Graubard.[6])

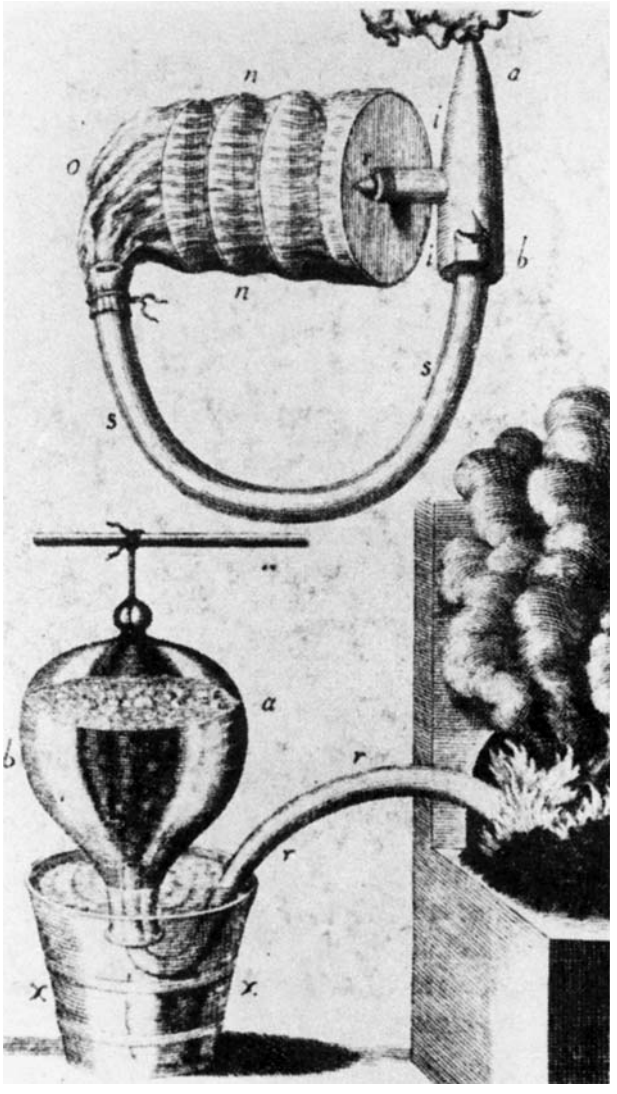


FIGURE 1-2 In 1727, Hales developed the pneumatic trough, shown on the bottom of this illustration. This device enabled him to collect gases produced by heating. On the top is a closed-circuit respiratory apparatus for inhaling the collected gases. (Used, with permission, from Perkins.[1])

believed that the difficulty encountered in breathing under these conditions was caused solely by the loss of elasticity in the air. He went on to observe, however, that animal blood bubbled when placed in a vacuum. This observation clearly showed that blood contained a gas of some type.[13,14] In 1727, Hales introduced the pneumatic trough (Fig. 1-2). With this device he was able to distinguish between free gas and gas no longer in its elastic state but combined with a liquid.[1] The basis for blood gas machines had been invented.

The first constituent of air to be truly recognized was carbon dioxide. Joseph Black, around 1754, found that limestone was transformed into caustic lime and lost weight on being heated. The weight loss occurred because a gas was liberated during the heating process. The same results occurred when the carbonates of alkali metals were treated with an acid such as hydrochloric acid. He called the liberated gas "fixed air" and found that it would react with lime water to form a white insoluble precipitate of chalk. This reaction became an invaluable marker for the presence of "fixed air." Black subsequently found that "fixed air" was produced by burning charcoal and fermenting beer. In a remarkable experiment he showed that "fixed air" was given off by respiration. In a Scottish church where a large congregation gathered for religious devotions, he allowed lime water to drip over rags in the air ducts. After the service, which lasted about 10 hours, he found a precipitate of crystalline lime ($CaCO_3$) in the rags, proof that "fixed air" was produced during the services. Black recognized that "fixed air" was the same gas described by von Helmont that would extinguish flame and life.[1,4,14]

In the early 1770s, Priestley and Scheele, working independently of each other, both produced and isolated "pure

air." Priestley used a 12-inch lens to heat mercuric oxide. The gas released in this process passed through the long neck of a flask and was isolated over mercury. This gas allowed a flame to burn brighter and a mouse to live longer than in ordinary air.[1,4,15] Scheele also heated chemicals such as mercuric oxide and collected the gases in ox or hog bladders. Like Priestley, Scheele found that the gas isolated made a flame burn brighter. This gas was the "nitro-aereal spirit" described by Mayow. Priestley and Scheele described their observations to Antoine Lavoisier. He repeated Priestley's experiments and found that if mercuric oxide was heated in the presence of charcoal, Black's "fixed air" would be produced. Further work led Lavoisier to the conclusion that ordinary air must have at least two separate components. One part was respirable, combined with metals during heating, and supported combustion. The other part was nonrespirable. In 1779, Lavoisier called the respirable component of air "oxygen." He also concluded from his experiments that "fixed air" was a combination of coal and the respirable portion of air. Lavoisier realized that oxygen was the explanation for combustion.[1,4,17]

Metabolism

In the 1780s, Lavoisier performed a brilliant series of studies with the French mathematician Laplace on the use of oxygen by animals. Lavoisier knew that oxygen was essential for combustion and necessary for life. Furthermore, he was well aware of the Greek concept of internal heat presumably produced by the left ventricle. The obvious question was whether animals used oxygen for some type of internal combustion. Would this internal combustion be similar to that readily perceived by the burning of coal? To answer this question, the two great scientists built an ice calorimeter (Fig. 1-3). This device could do two things. Because the melting ice consumed heat, the rate at which ice melted in the calorimeter could be used as a quantitative measure of heat production within the calorimeter. In addition, the consumption of oxygen could be measured. It then was a relatively simple task to put an animal inside the calorimeter and carefully measure heat production and oxygen consumption. As Lavoisier suspected, the amount of heat generated by the animal was similar to that produced by burning coal for the quantity of oxygen consumed.[1,4]

The Greeks suspected that the left ventricle produced innate heat, and Lavoisier himself may have thought that internal combustion occurred in the lungs.[4] Spallanzani, though, took a variety of tissues from freshly killed animals and found that they took up oxygen and released carbon dioxide.[1] Magnus, relying on improved methods of analyzing the gas content of blood, found higher oxygen levels in arterial blood than in venous blood but higher carbon dioxide levels in venous blood than in arterial blood. He believed that inhaled oxygen was absorbed into the blood, transported throughout the body, given off at the capillary level to the tissues, and there formed the basis for the formation of carbon dioxide.[18] In 1849, Regnault and Reiset perfected a closed-circuit metabolic chamber with devices for circulating air, absorbing carbon dioxide, and periodically adding oxygen (Fig. 1-4). Pettenkofer built a closed-circuit metabolic chamber large enough for a man and a bicycle ergometer (Fig. 1-5).[19] This device had a steam engine to pump air, gas meters to measure air volumes, and barium hydroxide to collect carbon dioxide. Although these devices were intended to examine the relationship between inhaled oxygen and exhaled carbon dioxide, they also could be viewed as among some of the earliest methods of controlled ventilation.

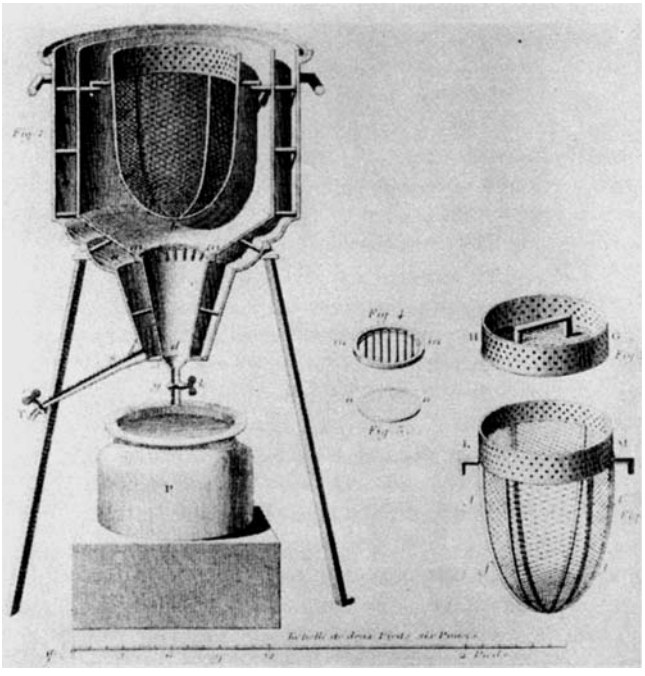


FIGURE 1-3 The ice calorimeter, designed by Lavoisier and Laplace, allowed these French scientists to measure the oxygen consumed by an animal and the heat produced by that same animal. With careful measurements, the internal combustion of animals was found to be similar, in terms of oxygen consumption and heat production, to open fires. (Used, with permission, from Perkins.[1])

Blood Gases and Ventilation

In separate experiments, the British scientist Lower and the Irish scientist Boyle provided the first evidence that uptake of gases in the lungs was related to gas content in the blood. In 1669, Lower placed a cork in the trachea of an animal and found that arterial blood took on a venous appearance. Removing the cork and ventilating the lungs with a bellows made the arterial blood bright red again. Lower felt that the blood must take in air during its course through the lungs and therefore owed its bright color entirely to an admixture of air. Moreover, after the air had

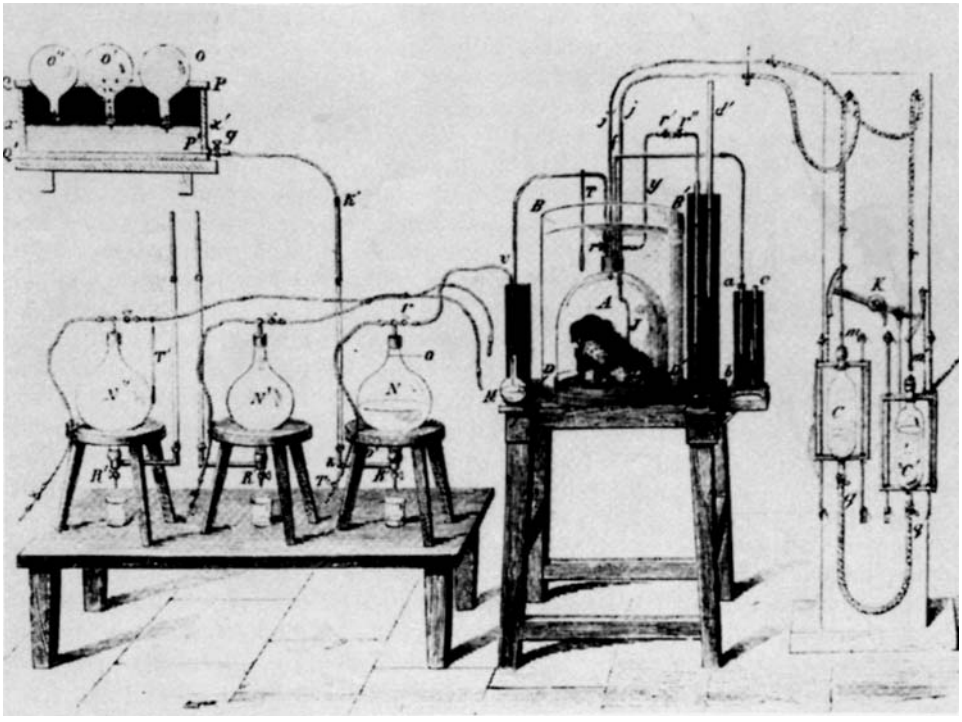
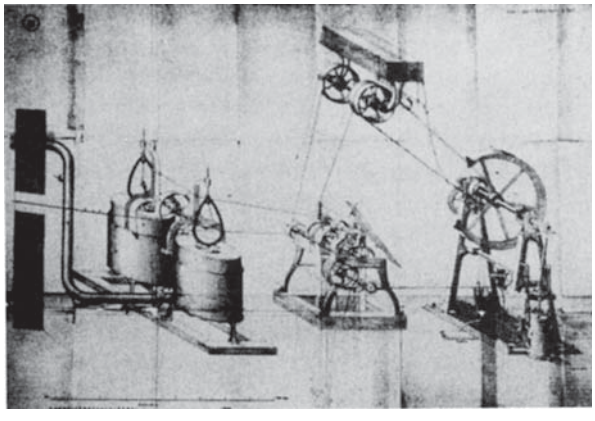


FIGURE 1-4 Regnault and Reiset developed a closed-circuit metabolic chamber in 1849 for studying oxygen consumption and carbon dioxide production in animals. (Used, with permission, from Perkins.[1])



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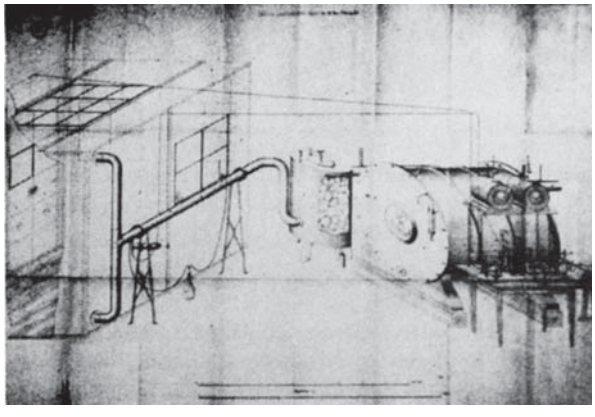

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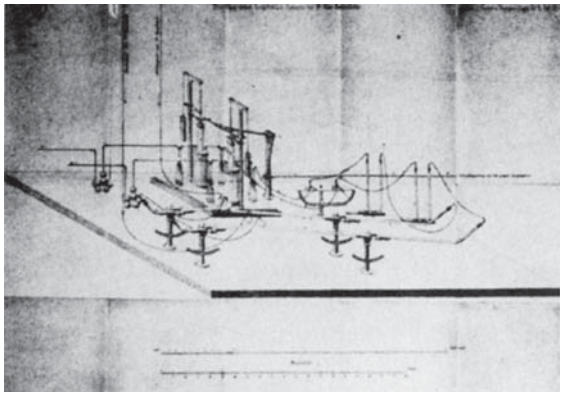


C

FIGURE 1-5 **A.** This huge device, constructed by Pettenkoffer, was large enough for a person. **B.** The actual chamber. The gas meters used to measure gas volumes are shown next to the chamber. The steam engine and gasometers for circulating air are labeled A. **C.** A close-up view of the gas-absorbing device adjacent to the gas meter in B. With this device Pettenkoffer and Voit studied the effect of diet on the respiratory quotient. (Used, with permission, from Perkins.[1])

in large measure left the blood again in the viscera, the venous blood became dark red.[20] A year later Boyle showed with his vacuum pump that blood contained gas. Following Lavoisier's studies, scientists knew that oxygen was the component of air essential for life and that carbon dioxide was the "fuliginous waste."

About 1797, Davey measured the amount of oxygen and carbon dioxide extracted from blood by an air pump.[4] Magnus, in 1837, built a mercurial blood pump for quantitative analysis of blood oxygen and carbon dioxide content.[18] Blood was enclosed in a glass tube in continuity with a vacuum pump. Carbon dioxide extracted by means of the vacuum was quantified by the change in weight of carbon dioxide–absorbent caustic potash. Oxygen content was determined by detonating the gas in hydrogen.[15] A limiting factor in Magnus's work was the assumption that the quantity of oxygen and carbon dioxide in blood simply depended on absorption. Hence, the variables determining gas content in blood were presumed to be the absorption coefficients and partial pressures of the gases. In the 1860s, Meyer and Fernet showed that the gas content of blood was determined by more than just simple physical properties. Meyer found that the oxygen content of blood remained relatively stable despite large fluctuations in its partial pressure.[21] Fernet showed that blood absorbed more oxygen than did saline solution at a given partial pressure.[15]

Paul Bert proposed that oxygen consumption could not strictly depend on the physical properties of oxygen dissolving under pressure in the blood. As an example, he posed the problem of a bird in flight changing altitude abruptly. Oxygen consumption could be maintained with the sudden changes in pressure only if chemical reactions contributed to the oxygen-carrying capacity of blood.[15] In 1878, Bert described the curvilinear oxygen dissociation curves relating oxygen content of blood to its pressure. Hoppe-Seyler was instrumental in attributing the oxygen-carrying capacity of the blood to hemoglobin.[22] Besides his extensive experiments with animals in either high- or low-pressure chambers, Bert also examined the effect of ventilation on blood gas levels. Using a bellows to artificially ventilate animals through a tracheostomy, he found that increasing ventilation would increase oxygen content in blood and decrease the carbon dioxide content. Decreasing ventilation had the opposite effect.[15] Dohman, in Pflüger's laboratory, showed that both carbon dioxide excess and lack of oxygen would stimulate ventilation.[23] In 1885, Miescher-Rusch demonstrated that carbon dioxide excess was the more potent stimulus for ventilation.[1] Haldane and Priestley, building on this work, made great strides in analyzing the chemical control of ventilation. They developed a device for sampling end-tidal, or alveolar exhaled, gas (Fig. 1-6). Even small changes in alveolar carbon dioxide fraction greatly increased minute ventilation, but hypoxia did not increase minute ventilation until the alveolar oxygen fraction fell to 12% to 13%.[24]

Early measurements of arterial oxygen and carbon dioxide tensions led to widely divergent results. In Ludwig's laboratory the arterial partial pressure of oxygen was thought to be approximately 20 mm Hg. The partial pressure of carbon dioxide reportedly was much higher. These results could not entirely support the concept of passive gas movement between lung blood and tissues based on pressure gradients. Ludwig and others suspected that an active secretory process was involved in gas transport.[4] Coincidentally, the French biologist Biot observed that some deep-water fish had extremely large swim bladders. The gas composition in those swim bladders seemed to be different than that of atmospheric air. Biot concluded that gas was actively secreted into these bladders.[4,15,24,25] Pflüger and his coworkers developed the aerotonometer, a far more accurate device for measuring gas tensions than that used by Ludwig. When they obstructed a bronchus, they found no difference in the gas composition of air distal to the bronchial obstruction and that of pulmonary venous blood draining the area. They concluded that the lung did not rely on active processes for transporting oxygen and carbon dioxide; passive diffusion was a sufficient explanation.[26]

FIGURE 1-6 This relatively simple device enabled Haldane and Priestley to collect end-tidal expired air, which they felt approximated alveolar air. The subject exhaled through the mouthpiece at the right. At the end of expiration, the stopcock on the accessory collecting bag was opened, and a small aliquot of air was trapped in this device. (Used, with permission, from Best CH, Taylor NB, *Physiological Basis of Medical Practice.* Baltimore, MD: Williams & Wilkins; 1939:509.)

Although Pflüger's findings were fairly convincing at the time, Bohr resurrected this controversy.[27] He found greater variability in blood and air carbon dioxide and oxygen tensions than previously reported by Pflüger and suspected that under some circumstances secretion of gases might occur. In response, Krogh, a student of Bohr's, developed an improved blood gas–measuring technique relying on the microaerotonometer (Fig. 1-7). With his wife, Krogh convincingly showed that alveolar air oxygen tension was higher than blood oxygen tension and vice versa for carbon dioxide tensions, even when the composition of inspired air was varied.[28] Douglas and Haldane confirmed Krogh's findings but wondered whether they were applicable only to people at rest. Perhaps during the stress of either exercise or high-altitude exposure, passive diffusion might not be sufficient. Indeed, the ability to secrete oxygen might explain the tolerance to high altitude developed by repeated or chronic exposures. Possibly carbon dioxide excretion might occur with increased carbon dioxide

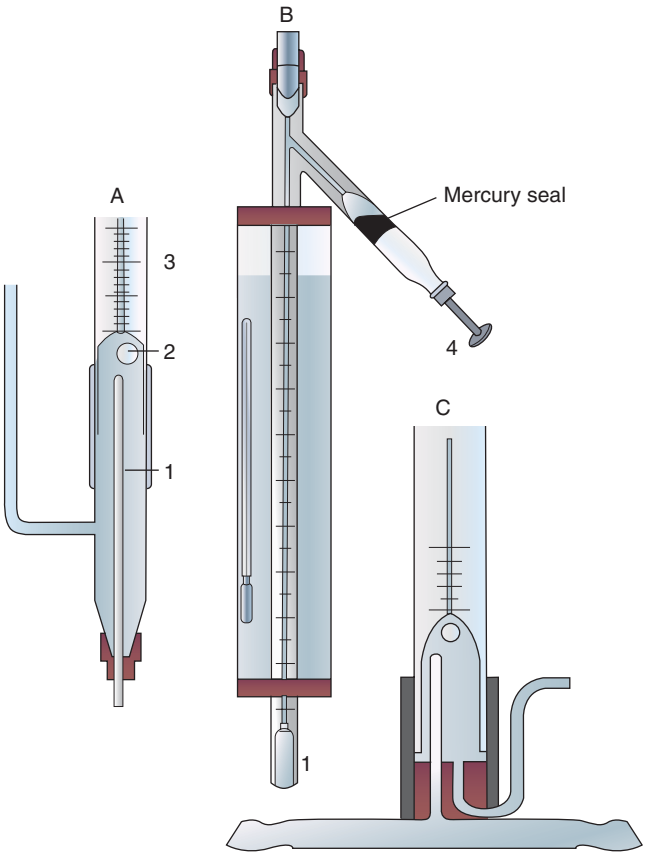


FIGURE 1-7 Krogh's microaerotonometer. **A.** An enlarged view of the lower part of *B*. Through the bottom of the narrow tube (1) in A, blood is introduced. The blood leaves the upper end of the narrow tube (1) in a fine jet and plays on the air bubble (2). Once equilibrium is reached between the air bubble and blood, the air bubble is drawn by the screw plunger (4) into the graduated capillary tube shown in **B.** The volume of the air bubble is measured before and after treatment with KOH to absorb CO_2 and potassium pyrogallate to absorb O_2. The changes in volume of the bubble reflect blood CO_2 and O_2 content. **C.** A model of A designed for direct connection to a blood vessel. (Used, with permission, from Best CH, Taylor NB, *Physiological Basis of Medical Practice.* Baltimore, MD: Williams & Wilkins; 1939:521.)

levels.[26] In a classic series of experiments, Marie Krogh showed that diffusion increased with exercise secondary to the concomitant increase in cardiac output.[29] Barcroft put to rest the diffusion-versus-secretion controversy with his "glass chamber" experiment. For 6 days he remained in a closed chamber subjected to hypoxia similar to that found on Pike's Peak. Oxygen saturation of radial artery blood was always less than that of blood exposed to simultaneously obtained alveolar gas, even during exercise. These were expected findings for gas transport based simply on passive diffusion.[30]

With this body of work, the chemists and physiologists had provided the fundamental knowledge necessary for the development of mechanical ventilation. Oxygen was the component of atmospheric gas understood to be essential for life. Carbon dioxide was the "fuliginous waste" gas released from the lungs. The exchange of oxygen and carbon dioxide between air and blood was determined by the tensions of these gases and simple passive diffusion. Blood was a carrier of these two gases, as Harvey first suggested. Oxygen was carried in two ways, both dissolved in plasma and chemically combined with hemoglobin. Blood carried oxygen to the tissues, where oxygen was used in cellular metabolism, that is, the production of the body's "innate heat." Carbon dioxide was the waste product of this reaction. Oxygen and carbon dioxide tensions in the blood were related to ventilation in two critical ways. Increasing ventilation would secondarily increase oxygen tensions and decrease carbon dioxide levels. Decreasing ventilation would have the opposite effect. Because blood levels of oxygen and carbon dioxide could be measured, physiologists now could assess the adequacy of ventilation. Decreased oxygen tensions and increased carbon dioxide tensions played a critical role in the chemical control of ventilation.

It was not understood, though, how carbon dioxide was carried by the blood until experiments performed by Bohr[31] and Haldane.[32] The concept of blood acid–base activity was just beginning to be examined in the early 1900s. By the 1930s, a practical electrode became available for determining anaerobic blood pH,[33] but pH was not thought to be useful clinically until the 1950s. In 1952, during the polio epidemic in Copenhagen, Ibsen suggested that hypoventilation, hypercapnia, and respiratory acidosis caused the high mortality rate in polio patients with respiratory paralysis. Clinicians disagreed because high blood levels of "bicarbonate" indicated an alkalosis. By measuring pH, Ibsen was proved correct, and clinicians became acutely aware of the importance of determining both carbon dioxide levels and pH.[4] Numerous workers looked carefully at such factors as base excess, duration of hypercapnia, and renal buffering activity before Siggaard-Anderson published a pH/log P_{CO_2} acid–base chart in 1971.[34] This chart proved to be an invaluable basis for evaluating acute and chronic respiratory and metabolic acid–base disturbances. The development of practical blood gas machines suitable for use in clinical medicine did not occur until electrodes became available for measuring oxygen and carbon dioxide tensions in liquid solutions. Stow built the first electrode capable of measuring blood P_{CO_2}. As the basis for this device, he used a glass pH electrode with a coaxial central calomel electrode opening at its tip. A unique adaptation, however, was the use of a rubber finger cot to wrap the electrode. This wrap trapped a film of distilled water over the electrode. The finger cot then acted as a semipermeable membrane to separate the measuring electrode from the sample.[35] Clark used a similar idea in the development of an oxygen measuring device. Platinum electrodes were used as the measuring device, and polyethylene served as the semipermeable membrane.[36] By 1973, Radiometer was able to commercially produce the first automated blood gas analyzer, the ABL, capable of measuring P_{O_2}, P_{CO_2}, and pH in blood.[4]

EXPLORERS AND WORKING MEN OF SUBMARINES AND BALLOONS

Travel in the deep sea and flight have intrigued humankind for centuries. Achieving these goals has followed a typical pattern. First, individual explorers tested the limits of human endurance. As mechanical devices were developed to extend those limits, the deep sea and the air became accessible to commercial and military exploration. These forces further intensified the need for safe and efficient underwater and high-altitude travel. Unfortunately, the development of vehicles to carry humans aloft and under water proceeded faster than the appreciation of the physiologic risks. Calamitous events ensued, with serious injury and death often a consequence. Only a clear understanding of the ventilatory problems associated with flight and deep-sea travel has enabled human beings to reach outer space and the depths of the ocean floor.

Exploration Under Water

Diving bells undoubtedly were derived from ancient humans' inverting a clay pot over their heads and breathing the trapped air while under water. These devices were used in various forms by Alexander the Great at the siege of Tyre in 332 BC, the Romans in numerous naval battles, and pirates in the Black Sea.[37,38] In the 1500s, Sturmius constructed a heavy bell that, even though full of air, sank of its own weight. When the bell was positioned at the bottom of fairly shallow bodies of water, workers were able to enter and work within the protected area. Unfortunately, these bells had to be raised periodically to the surface to refresh the air. Although the nature of the foul air was not understood, an important principle of underwater work, the absolute need for adequate ventilation, was appreciated.[15]

Halley devised the first modern version of the diving bell in 1690 (Fig. 1-8). To drive out the air accumulated in the bell and "made foul" by the workers' respiration, small barrels of air were let down periodically from the surface and opened within the bell. Old air was released through the top of the bell by a valve. In 1691, Papin developed a technique for constantly injecting fresh air from the surface directly into the bell by means of a strong leather bellows. In 1788, Smeaton replaced the bellows with a pump for supplying fresh air to the submerged bell.[15,37,38]

Techniques used to make diving bells practical also were applied to divers. Xerxes used them to recover sunken treasure.[39] Sponge divers in the Mediterranean in the 1860s could stay submerged for 2 to 4 minutes and reach depths of 45 to 55 m.[40] *Amas,* female Japanese divers using only goggles and a weight to facilitate rapid descent, made dives to similar depths.[41] Despite the remarkable adaptations of breath-holding measures developed by these naked divers,[42] the commercial and military use of naked divers was limited. In 77 AD, Pliny described divers breathing through tubes while submerged and engaged in warfare. More sophisticated diving suits with breathing tubes were described by Leonardo da Vinci in 1500 and Renatus in 1511. Although these breathing tubes prolonged underwater activities, they did not enable divers to reach even moderate depths.[15] Borelli described a complete diving dress with tubes in the helmet for recirculating and purifying air in 1680 (Fig. 1-9).[37]

Klingert described the first modern diving suit in 1797.[37] It consisted of a large helmet connected by twin breathing pipes to an air reservoir that was large enough to have an associated platform. The diver stood on the platform and inhaled from the air reservoir through an intake pipe on the top of the reservoir and exhaled through a tube connected to the bottom of the reservoir. Siebe made the first commercially viable diving dress. The diver wore a metal helmet riveted to a flexible waterproof jacket. This jacket extended to the diver's waist but was not sealed. Air under pressure was pumped from the surface into the diver's helmet and escaped through the lower end of the jacket. In 1837, Siebe modified this diving dress by extending the jacket to cover the whole body. The suit was watertight at the wrists and ankles. Air under pressure entered the suit through a one-way valve at the back of the helmet and was released from the suit by an adjustable valve at the side of the helmet (Fig. 1-10).[37] In 1866, Denayouze incorporated a metal air reservoir on the back of the diver's suit. Air was pumped directly into the reservoir, and escape of air from the suit was adjusted by the diver.[15]

Siebe, Gorman, and Company produced the first practical self-contained diving dress in 1878. This suit had a copper chamber containing potash for absorbing carbon dioxide and a cylinder of oxygen under pressure.[37] Fleuss cleverly revised this diving suit in 1879 to include an oronasal mask with an inlet and an exhaust valve. The inlet valve allowed inspiration from a metal chamber containing oxygen under pressure. Expiration through the exhaust valve was directed into metal chambers under a breastplate that contained carbon dioxide absorbents. Construction of this appliance was so precise that Fleuss used it not only to stay under water for hours but also to enter chambers containing noxious gases. The Fleuss appliance was adapted rapidly and successfully to mine rescue work, where explosions and toxic gases previously had prevented such efforts.[43]

As Siebe, Gorman, and Company successfully marketed diving suits, commercial divers began to dive deeper and longer. Unfortunately, complications developed for two separate reasons. Decompression illness was recognized first. In 1830, Lord Cochrane took out a patent in England for "an apparatus for compressing atmospheric air within the interior capacity of subterraneous excavations [to]… counteract the tendency of superincumbent water to flow by gravitation into such excavations…and which apparatus at the same time is adapted to allowing workmen to carry out their ordinary operations of excavating, sinking, and mining."[38] In 1841, Triger described the first practically applied caisson for penetrating the quicksands of the Loire River (Fig. 1-11).[44] This caisson, or hollow iron tube, was sunk to a depth of 20 m. The air within the caisson was

FIGURE 1-8 Halley's version of the diving bell. Small barrels of fresh air were lowered periodically to the bell, and the worker inside the bell released the air. "Foul air" often was released by way of a valve at the top of the bell. Workers could exit the bell for short periods. (Used, with permission, from Hill.[38])

compressed by a pump at the surface. The high air pressure within the caisson was sufficient to keep water out of the tube and allow workers to excavate the bottom. Once the excavation reached the prescribed depth, the caisson was filled with cement, providing a firm foundation. During the excavation process, workers entered and exited the caisson through an airlock. During this work, Triger described the first cases of "caisson disease," or decompression illness, in workers after they had left the pressurized caisson. As this new technology was applied increasingly in shaft and tunnel work (e.g., the Douchy mines in France in 1846; bridges across the Midway and Tamar rivers in England in

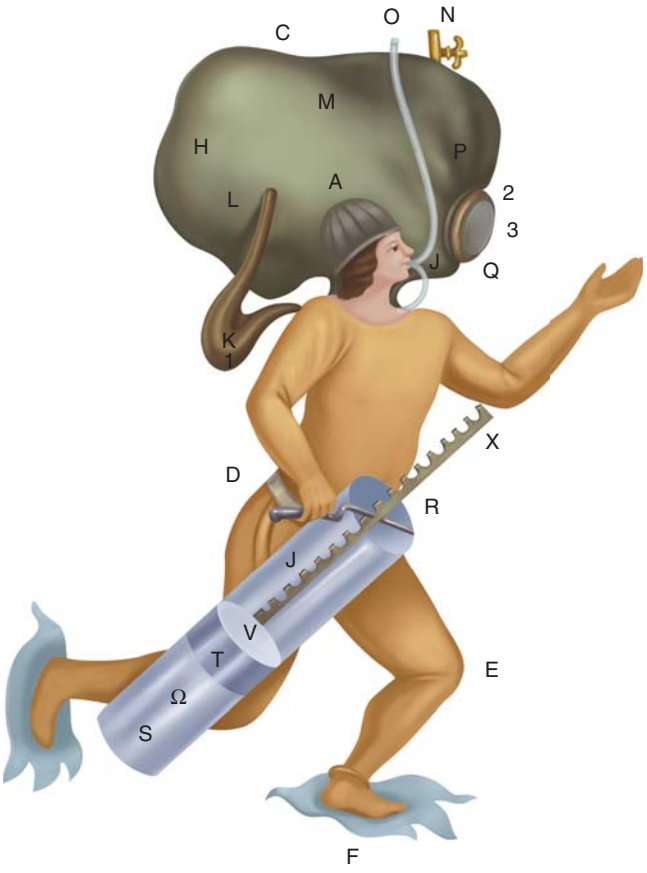
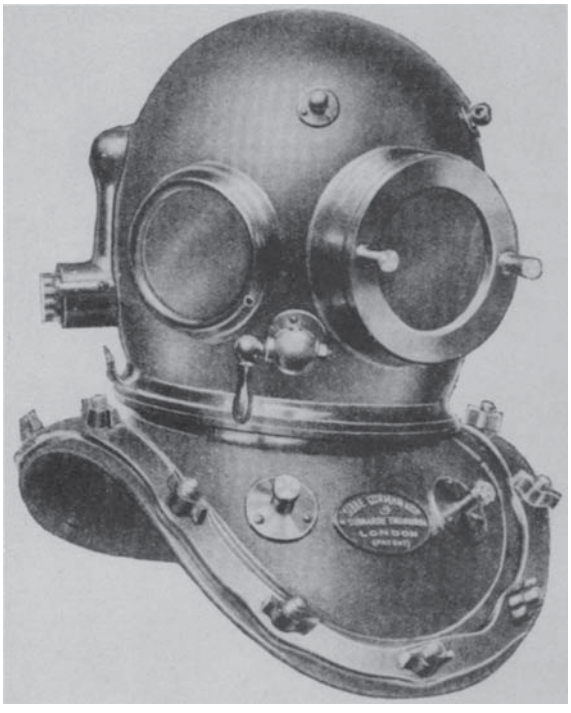


FIGURE 1-9 A fanciful diving suit designed by Borelli in 1680. (Used, with permission, from Hill.[38])



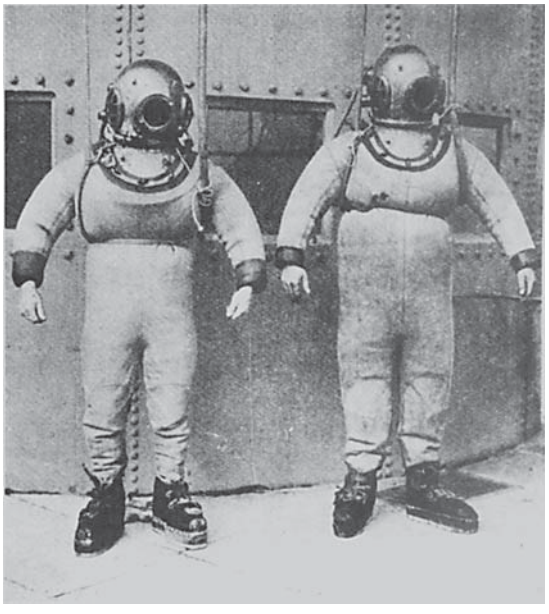


FIGURE 1-10 **A.** The metal helmet devised by Siebe is still used today. **B.** The complete diving suit produced by Siebe, Gorman, and Company in the nineteenth century included the metal helmet, a diving dress sealed at the wrists and ankles, and weighted shoes. (Used, with permission, from Hill.[38])

1851 and 1855, respectively; and the Brooklyn Bridge, constructed between 1870 and 1873), caisson disease was recognized more frequently. Bert was especially instrumental in pointing out the dangers of high pressure.[15] Denayouze supervised many commercial divers and probably was among the first to recognize that decompression caused illness in these divers.[15] In the early 1900s, Haldane developed safe and acceptable techniques for staged decompression based on physiologic principles.[38]

Haldane also played a critical role in examining how well Siebe's closed diving suit supplied the ventilation needs of divers. This work may have been prompted by Bert's studies with animals placed in high-pressure chambers. Bert found that death invariably occurred when inspired carbon dioxide levels reached a certain threshold. Carbon dioxide absorbents placed in the high-pressure chamber prevented deaths.[15] Haldane's studies in this area were encouraged by a British Admiralty committee studying the risks of deep diving in 1906. Haldane understood that minute ventilation varied directly with alveolar carbon dioxide levels. It appeared reasonable that the same minute ventilation needed to maintain an appropriate $P_{A_{CO_2}}$ at sea level would be needed to maintain a similar $P_{A_{CO_2}}$ under water. What was not appreciated initially was that as the diver descended and pressure increased, pump ventilation at the surface necessarily also would have to increase to maintain minute ventilation. Haldane realized that at 2 atmospheres of pressure, or 33 ft under water, pump ventilation would have to double to ensure appropriate ventilation. This does

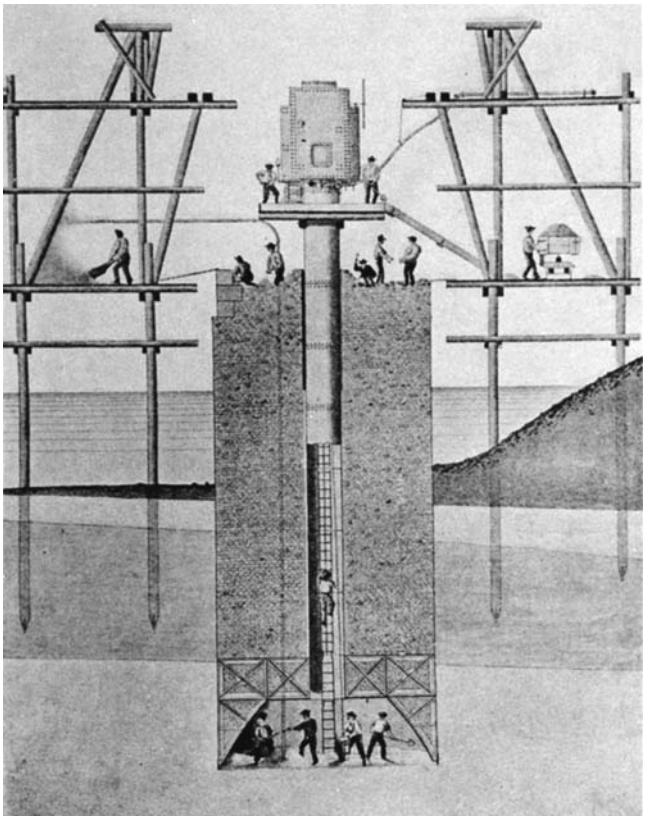


FIGURE 1-11 The caisson is a complex device enabling workers to function in dry conditions under shallow bodies of water or in other potentially flooded circumstances. A tube composed of concentric rings opens at the bottom to a widened chamber, where workers can be seen. At the top of the tube is a blowing chamber for maintaining air pressure and dry conditions within the tube. Workers enter at the top through an air lock and gain access to the working area via a ladder through the middle of the tube. (Used, with permission, from Hill.[38])

not take into account muscular effort, which would further increase ventilatory demands. Unfortunately, early divers did not appreciate the need to adjust ventilation to the diving suit. Furthermore, air pumps often leaked or were maintained inadequately. Haldane demonstrated the relationship between divers' symptoms and hypercapnia by collecting exhaled gas from divers at various depths. The fraction of carbon dioxide in the divers' helmets ranged from 0.0018 to 0.10 atm.[26,38] The investigations of Bert and Haldane finally clarified the nature of "foul air" in diving bells and suits and the role of adequate ventilation in protecting underwater workers from hypercapnia. Besides his work with divers, Haldane also demonstrated that the "black damp" found in mines actually was a dangerously toxic blend of 10% CO_2 and 1.45% O_2.[45] He developed a self-contained rescue apparatus for use in mine accidents that apparently was more successful than the Fleuss appliance.[46]

Diving boats were fancifully described by Marsenius, in 1638, and others. Only the boat designed by Debrell in 1648 appeared plausible because "besides the mechanical contrivances of his boat, he had a chemical liquor, the fumes of which, when the vessel containing it was unstopped, would speedily restore to the air, fouled by the respiration, such a portion of vital spirits as would make it again fit for that office." Although the liquor was never identified, it undoubtedly was an alkali for absorbing carbon dioxide.[38] Payerne built a submarine for underwater excavation in 1844. Since 1850, the modern submarine has been developed primarily for military actions at sea.

Submarines are an intriguing physiologic experiment in simultaneously ventilating many subjects. Ventilation in submarines is complex because it involves not only oxygen and carbon dioxide levels but also heat, humidity, and body odors. Early work in submarines documented substantial increases in temperature, humidity, and carbon dioxide levels.[47] Mechanical devices for absorption of carbon dioxide and air renewal were developed quickly,[48] and by 1928, Du Bois thought that submarines could remain submerged safely for up to 96 hours.[49] With the available carbon dioxide absorbents, such as caustic soda, caustic potash, and soda lime, carbon dioxide levels could be kept within relatively safe levels of less than 3%. Supplemental oxygen carried by the submarine could maintain a preferred fractional inspired oxygen concentration above 17%.[39,50–52]

Exploration in the Air

In 1782, the Montgolfier brothers astounded the world by constructing a linen balloon about 18 m in diameter, filling it with hot air, and letting it rise about 2000 m into the air. On November 21, 1783, two Frenchmen, de Rozier and the Marquis d'Arlandes, were the first humans to fly in a Montgolfier balloon.[53] Within a few years, Jeffreys and Blanchard had crossed the English Channel in a balloon, and Charles had reached the astonishing height of 13,000 ft in a hydrogen-filled balloon. As with diving, however, the machines that carried them aloft brought human passengers past the limits of their physiologic endurance. Glaisher and Coxwell reached possibly 29,000 ft in 1862, but suffered temporary paralysis and loss of consciousness.[4,26,54]

Acoste's description in 1573 of vomiting, disequilibrium, fatigue, and distressing grief as he traversed the Escaleras (Stairs) de Pariacaca, between Cuzco and Lima, Peru ("one of the highest places in the universe"), was widely known in Europe.[55] In 1804, von Humboldt attributed these high altitude symptoms to a lack of oxygen. Surprisingly, however, he found that the fraction of inspired oxygen in high-altitude air was similar to that found in sea-level air. He actually suggested that respiratory air might be used to prevent mountain sickness.[56] Longet expanded on this idea in 1857 by suggesting that the blood of high-altitude dwellers should have a lower oxygen content than that of sea-level natives. In a remarkable series of observations during the 1860s, Coindet described respiratory patterns of French people living at high altitude in Mexico City. Compared with sea-level values, respirations were deeper and more

frequent, and the quantity of air expired in 1 minute was somewhat increased. He felt that "this is logical since the air of altitudes contains in a given volume less oxygen at a lower barometric pressure…[and therefore] a greater quantity of this air must be absorbed to compensate for the difference."[15] Although these conclusions might seem reasonable now, physiologists of the time also considered decreased air elasticity, wind currents, exhalations from harmful plants, expansion of intestinal gas, and lack of support in blood vessels as other possible explanations for the breathing problems experienced at high altitude. Bert, the father of aviation medicine, was instrumental in clarifying the interrelationship among barometric pressure, oxygen tension, and symptoms. In experiments on animals exposed to low-pressure conditions in chambers (Fig. 1-12), carbonic acid levels increased within the chamber, but carbon dioxide absorbents did not prevent death. Supplemental oxygen, however, protected animals from dying under simulated high-altitude conditions (Fig. 1-13). More importantly, he recognized that death occurred as a result of the interaction of both the fraction of inspired oxygen and barometric pressure. When a multiple of these two variables—that is, the partial pressure of oxygen—reached a critical threshold, death ensued.[15,39]

Croce-Spinelli, Sivel, and Tissandier were adventurous French balloonists eager to reach the record height of 8000 m. At Bert's urging, they experimented with the use of oxygen tanks in preliminary balloon flights and even in Bert's decompression chamber. In 1875, they began their historic attempt to set an altitude record supplied with oxygen cylinders (Fig. 1-14). Unfortunately, at 24,600 ft they released too much ballast, and their balloon ascended so rapidly that they were stricken unconscious before they could use the oxygen. When the balloon eventually returned to earth, only Tissandier remained alive.[4,54] This tragedy shook France. The idea that two men had died in the air was especially disquieting.[53] Unfortunately, the reasons for the deaths of Croce-Spinelli and Sivel were not clearly attributed to hypoxia. Von Schrotter, an Austrian physiologist, believed Bert's position regarding oxygen deficit as the lethal threat and encouraged Berson to attempt further high-altitude balloon flights. He originally devised a system for supplying oxygen from a steel cylinder with tubing leading to the balloonists. Later, von Schrotter conceived the idea of a face mask to supply oxygen more easily and also began to use liquid oxygen. With these devices, Berson reached 36,000 ft in 1901.[4,54]

The Wright brothers' historic flight at Kitty Hawk in 1903 substantially changed the nature of flight. The military value of airplanes soon was appreciated and applied during World War I. The Germans were especially interested in increasing the altitude limits for their pilots. They applied the concepts advocated by von Schrotter and provided liquid oxygen supplies for high-altitude bombing

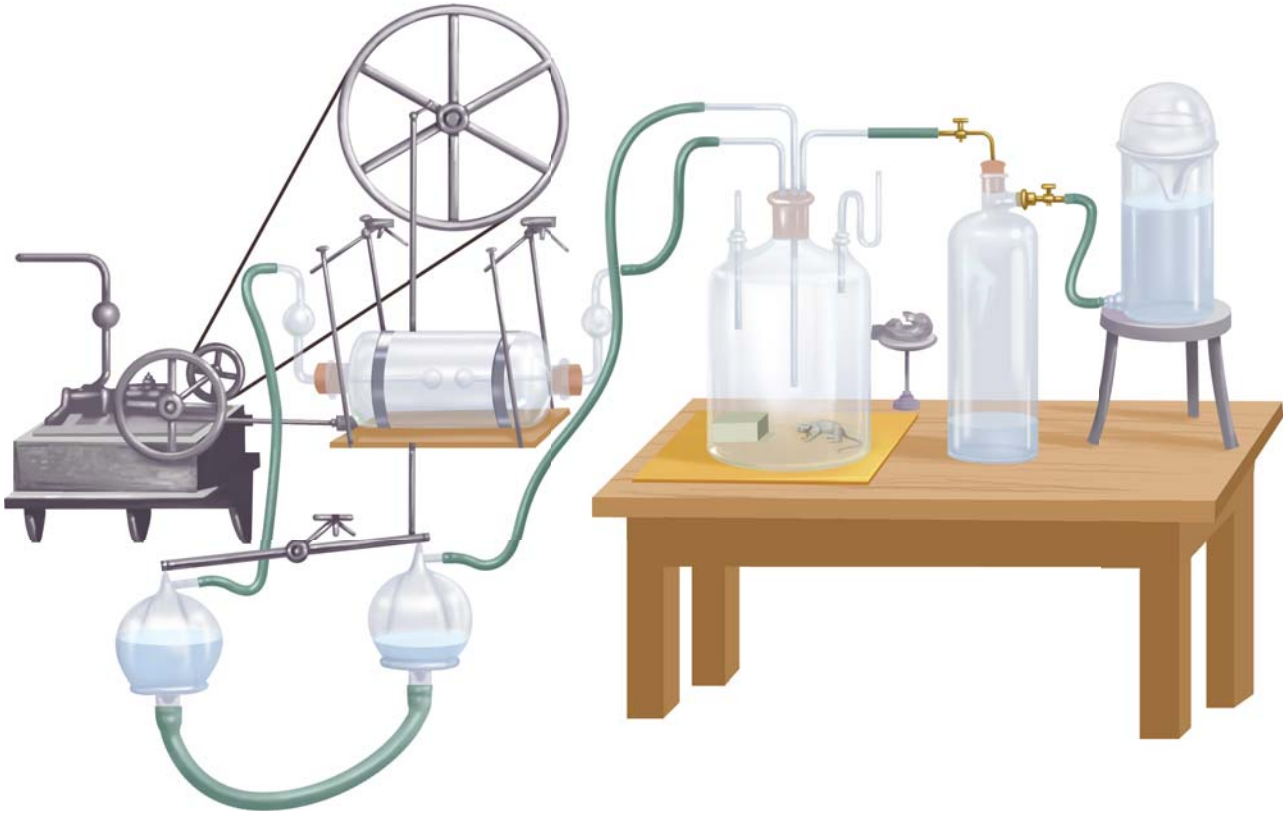


FIGURE 1-12 A typical device used by Bert to study animals under low-pressure conditions. (Used, with permission, from Bert.[15])

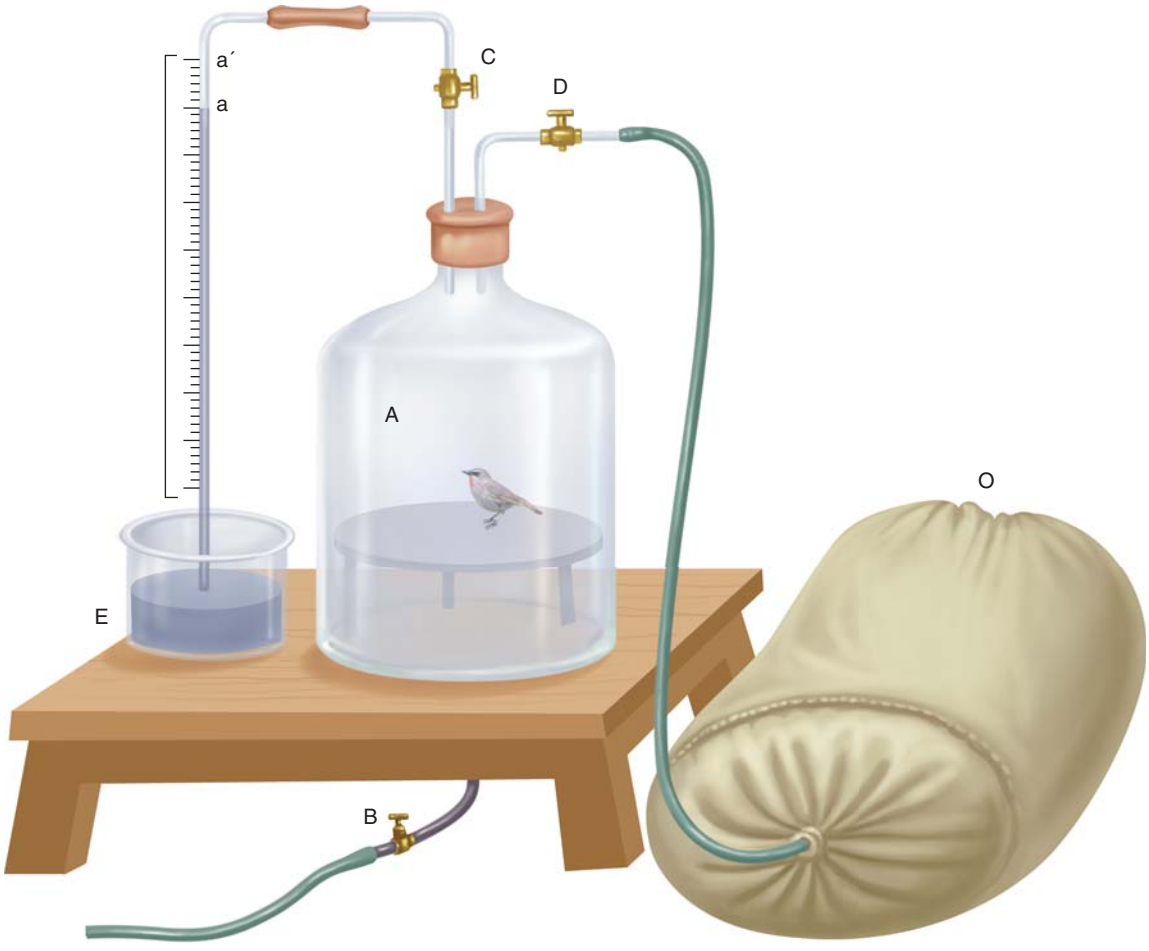


FIGURE 1-13 A bird placed in a low-pressure bell jar can supplement the enclosed atmospheric air with oxygen inspired from the bag labeled O. Supplemental oxygen prolonged survival in these experiments. (Used, with permission, from Bert.[15])

flights. Interest in airplane flights for commercial and military uses was especially high following Lindbergh's solo flight across the Atlantic in 1927. Much work was done on valves and oxygen gas regulators in the hope of further improving altitude tolerance. A series of high-altitude airplane flights using simple face masks and supplemental oxygen culminated in Donati's reaching an altitude of 47,358 ft in 1934. This was clearly the limit for human endurance using this technology.[4,54]

Somewhat before Donati's record, a breakthrough in flight was achieved by Piccard, who enclosed an aeronaut in a spherical metal chamber sealed with an ambient barometric pressure equivalent to that of sea level. The aeronaut easily exceeded Donati's record and reached 55,000 ft. This work recapitulated the important physiologic concept, gained from Bert's earlier experimental work in high-altitude chambers, that oxygen availability is a function of both fractional inspired oxygen and barometric pressure. Piccard's work stimulated two separate investigators to adapt pressurized diving suits for high-altitude flying. In 1933, Post devised a rubberized, hermetically sealed silk suit. In the same year, Ridge worked with Siebe, Gorman, and Company to modify a self-contained diving dress for flight. This suit provided oxygen under pressure and an air circulator with a soda lime canister for carbon dioxide removal. These suits proved quite successful, and soon pilots were exceeding heights of 50,000 ft. Parallel work with sealed gondolas attached to huge balloons led to ascents higher than 70,000 ft. In 1938, Lockheed produced the XC-35, which was the first successful airplane with a pressurized cabin (Fig. 1-15).[4,54] These advances were applied quickly to military aviation in World War II. The German Air Ministry was particularly interested in developing oxygen regulators and valves and positive-pressure face masks for facilitating high-altitude flying.[57]

Work throughout World War II defined limits for technological support of high-altitude flight. Pilots could reach up to 12,000 ft safely without oxygen supplements. Above this limit, oxygen-enriched air was essential. With flights going above 25,000 ft, oxygen supplementation alone usually was insufficient, and some type of pressurized system—cabin, suit, or mask—was needed. Pressurization as an adjunct, however, reached its limit of usefulness at approximately 80,000 ft. At this altitude, air compressors

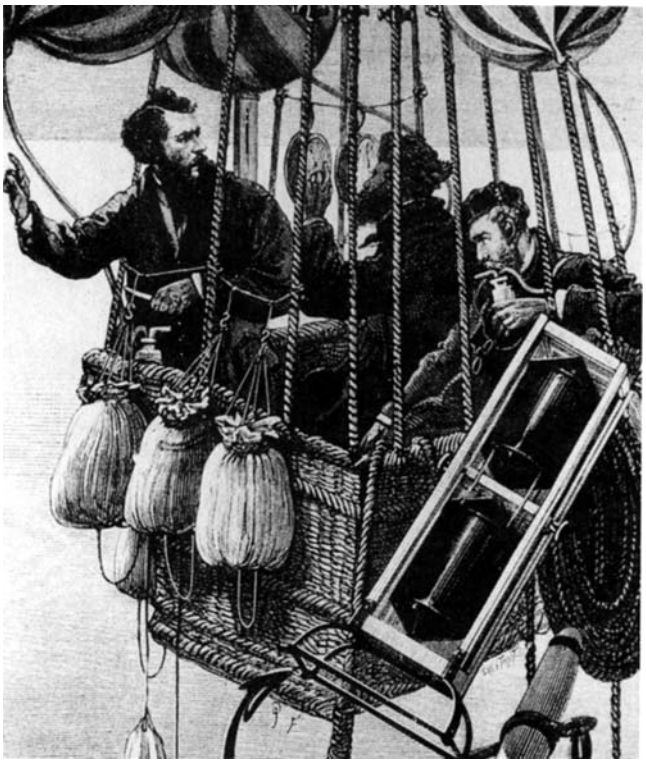


FIGURE 1-14 The adventurous French balloonists Croce-Spinelli, Sivel, and Tissandier begin their attempt at a record ascent. The balloonist at the right can be seen inhaling from an oxygen tank. Unfortunately, the supplemental oxygen did not prevent tragic results from a too rapid ascent. (Used, with permission, from Armstrong HG. *Principles and Practice of Aviation Medicine.* Baltimore, MD: Williams & Wilkins; 1939:4.)

became too leaky and inefficient to maintain adequate pressurization. A completely sealed cabin was essential to protect passengers adequately from the rarefied atmosphere outside. An altitude of 80,000 ft thus became a functional definition of space because at this height complete control of the atmosphere in the plane (i.e., the supply of oxygen, a means of removing carbon dioxide, and adequate control of temperature and humidity) was required.[58,59] Advances in submarine ventilatory physiology were adapted to the space program. In 1947, the American Air Force began the XI program, which culminated in the production in 1952 of the X15 aircraft. This plane reached a top speed of 4159 miles per hour at an altitude of 314,750 ft. More importantly, the technology developed for this plane was a prelude to manned satellite programs. The United States Mercury and the Russian Vostok programs both relied on rockets to boost small, one-person capsules into space orbit. The Mercury capsule had a pure oxygen atmosphere at a reduced cabin pressure. In addition, the pilot wore a pressurized suit with an independent, closed oxygen supply. In April 1961, Gagarin was the first person to be launched into space. Shepard followed soon after, in May 1961, and reached an altitude of 116 miles. More sophisticated space flight—in the Gemini, Apollo, and space station programs—was based on similar ventilation systems and principles.[60]

FIGURE 1-15 Lockheed produced the XC-35 in 1938. This was the first plane to have a pressurized cabin. (Used, with permission, Armstrong HG. *Principles and Practice of Aviation Medicine.* Baltimore, MD: Williams & Wilkins; 1939:337.)

MECHANICAL VENTILATION OF RESUSCITATION AND ANESTHESIA

Vivisection

Galen described ventilating an animal as follows: "If you take a dead animal and blow air through its larynx [through a reed], you will fill its bronchi and watch its lungs attain the greatest distention."[61] Unfortunately, Galen failed to appreciate how ventilating the lungs could help him in his vivisection work. Galen operated on many living animals, but his studies on the function of the heart were limited by the risk of pneumothorax. Opening the thoracic cavity almost certainly resulted in death of the animal.[1,6] More than a thousand years later, Vesalius realized that ventilation could protect animals from pneumothorax.[62,63] The lungs would collapse and the beating heart would almost stop when Vesalius opened the chest cavity, but the heart could be restarted by inflating the lungs through a reed tied into the trachea. Paracelsus, a contemporary of Vesalius, is reported to have used a similar technique around 1530 in attempting to resuscitate a human. Did Paracelsus adapt Vesalius's research efforts, or vice versa?[63] It is also unclear whether Vesalius himself tried artificial ventilation during the dissection of a Spanish nobleman. Legend has it that when the nobleman's heart began to beat once more, Vesalius's medical associates were so outraged that they reported him to the religious authorities. Vesalius only avoided being burned at the stake by embarking on a pilgrimage to the Holy Land, but he died during the voyage.[64]

Presumably, Harvey became familiar with Vesalius's use of ventilation during vivisection because he mentioned artificial ventilation in his work later in England.[63] Other English scientists soon after began to mention artificial

ventilation in their own studies.[65] In 1664, Hooke dramatically described dissecting a dog, placing a pipe into the windpipe of the animal, and using a pair of bellows to ventilate the dog (and keep the heart beating) for longer than an hour.[63] Lower, an associate of Hooke, showed that artificial respiration kept the color of blood red during dissection.[63]

Resuscitating the Apparantly Drowned

Artificial respiration with a bellows and tracheal tube remained popular for vivisection work but was applied to humans only after a curious turn of events. Attempts to resuscitate apparently dead people were first recorded in the mid-eighteenth century. The origins of this movement are not entirely clear. Indeed, there were strong reasons for people to fear the dead. The risk of contagious disease was well known—memories of the plague were still fresh—and religious beliefs dissuaded many from believing in the wisdom of resuscitation. Despite these disincentives, sporadic attempts were made at organized resuscitation. In 1740, the Académie des Sciences in Paris issued an *avis* strongly advising mouth-to-mouth respiration for resuscitating the apparently drowned.[63] In 1744, Tossach used this technique successfully in saving a life.[66] Fothergill soon after provided an excellent description of the mouth-to-mouth resuscitation technique, including the use of bellows if the "blast of a man's mouth" was not sufficient.[63,64,67,68] In 1760, Buchan went on to advise creating "an opening in the windpipe" when air cannot be forced into the chest through the mouth or nose.[69] Societal pressures led to widespread dissemination of knowledge about resuscitation techniques. In response to citizens' concerns about the large number of lives lost in canals, a group of influential laymen in Amsterdam formed the Society for the Rescue of Drowned Persons (*Maatschappy tot Redding von Dreykhingen*) in 1767.[63,64,67] The express purpose of this society was to publicize the need for and the techniques of resuscitation. Similar societies soon were formed in other maritime cities, such as Venice and Milan in 1768, Paris in 1771, London in 1774, and Philadelphia in 1780.

The Dutch method emphasized five steps: keeping the patient warm, artificial respiration through the mouth, fumigation with tobacco smoke through the rectum (Fig. 1-16), stimulants placed orally or rectally, and bleeding. Cogan, an English physician with a Dutch wife, translated a pamphlet describing the Dutch method into English. Hawes, an apothecary, read the pamphlet and led a concerted effort to introduce this technique into England. In encouraging this work, Hawes' activities led directly to the formation of the Royal Humane Society in 1774.[67] Through this society, many physicians were encouraged to develop techniques for resuscitating the apparently drowned. In 1776, Hunter advocated the use of a double bellows for artificial ventilation. The first stroke blew fresh air into the lung, and the second stroke sucked out stale air. He had perfected this technique during physiologic studies with dogs. Hunter advised the use of Priestley's pure air (oxygen) for resuscitation, but it is unclear whether this advice was ever followed.[64,67,70] In 1776, Cullen suggested relying on tracheal intubation and bellows ventilation for reviving the apparently dead.[71] In 1791, Curry developed an intralaryngeal cannula for this purpose, as did Fine in 1800. These cannulas could be placed through the nose, mouth, or trachea.

FIGURE 1-16 An attempt at resuscitating an apparently drowned person using the modified Dutch method. One resuscitator is assisting respiration by massaging the chest. The fumigator is instilling tobacco smoke through the rectum. (Used, with permission, from Morch.[64])

Many other physicians were encouraged to develop ingenious devices as resuscitation aids by the Royal Humane Society (Fig. 1-17). This society held competitions and offered prizes and medals for the best work in this area.[63,64,67,72] As an alternative to tracheal intubation, Chaussier constructed a simple bag and face mask for artificial ventilation in 1780 (Fig. 1-18). He thought that this device would protect the rescuer from the deleterious effects of exhaled air. Chaussier devised accessory tubing for the face mask to allow the use of supplemental oxygen.[73] Kite, Curry, and Chaussier also developed devices to assist the operator in cannulating the trachea through the mouth.[73,74]

As these techniques for resuscitation were gaining widespread acceptance, concerns were being raised about the effectiveness of bellows ventilation. Leroy, in a dramatic series of studies in 1827 and 1828, subjected an animal to overzealous bellows inflation and caused fatal pneumothorax.[75,76] Although later it was realized that the pressures reached in this demonstration were unlikely to be achieved in clinical practice,[63] the French Academy quickly condemned the technique. Despite adaptations of bellows to limit ventilatory volumes,[77] the Royal Humane Society also abandoned the use of tracheal intubation and bellows ventilation for resuscitation.[63] Consequently, positive-pressure ventilation was banned from medical practice early in its infancy, not to be routinely relied on for patient care until well into the twentieth century.

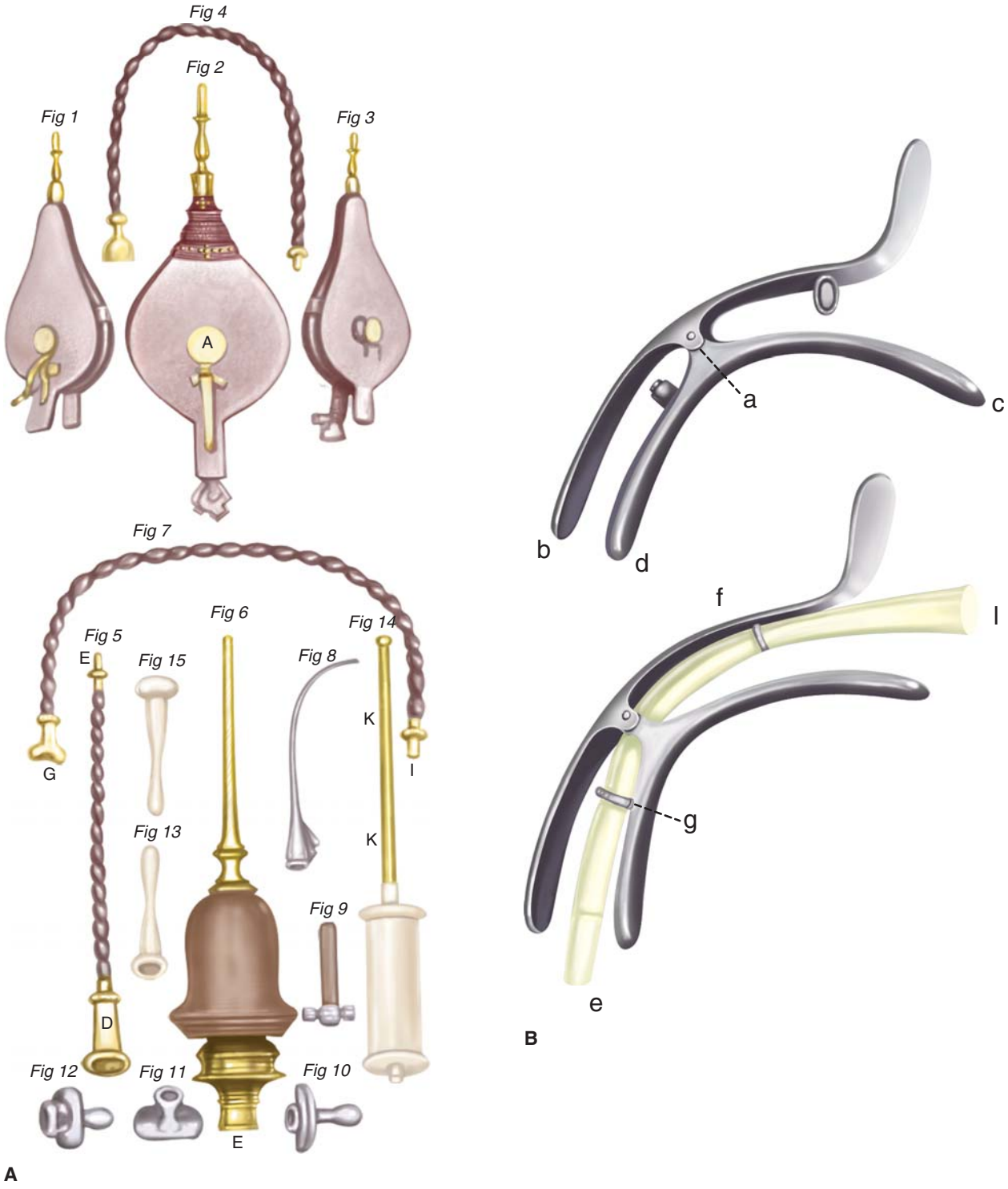
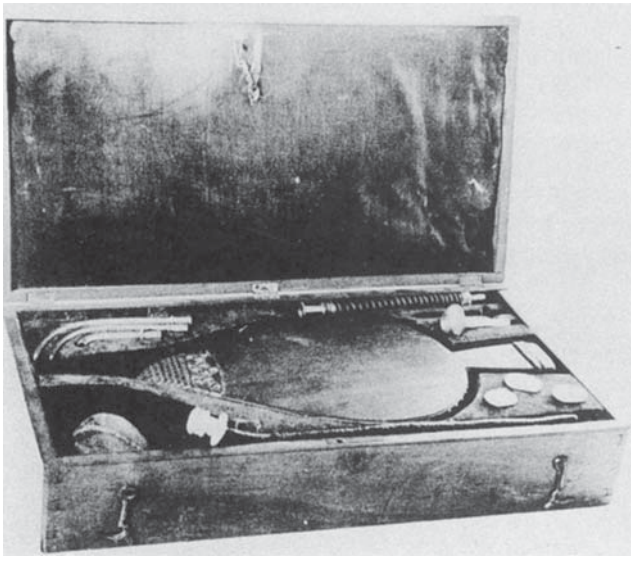


FIGURE 1-17 **A.** Examples of some of the devices included in the Royal Humane Society's compendium of resuscitation techniques in 1806. Figures 1, 2, and 3 are bellows of different sizes. Figure 6 is a brass box for holding a stimulating substance. Various connecting tubes and nozzles are also enclosed. (Used, with permission, from Mushin WW, Rendell-Baker L, *The Principles of Thoracic Anesthesia.* Oxford, England: Blackwell Scientific Publications; 1953:32.) **B.** A two-bladed intubating spatula was developed to hold the mouth open and allow passage of the tracheal tube through the larynx. (Used, with permission, from Mushin WW, Rendell-Baker L, *The Principles of Thoracic Anesthesia*. Oxford, England: Blackwell Scientific Publications; 1953:36.)



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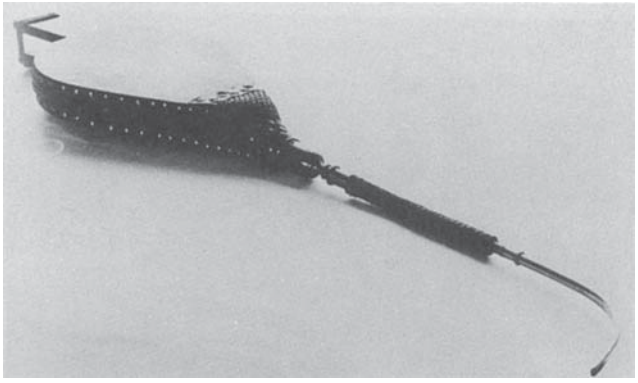


D

FIGURE 1-17 (*Continued*) **C.** The Royal Humane Society approved this type of box of intubation equipment with a bellows ventilator for distribution in 1806. (Used, with permission, from McClellan I. Nineteenth century resuscitation apparatus. *Anaesthesia.* 1981;36(3):308.) **D.** The bellows is shown connected to the otolaryngeal cannula and ready for use. (Used, with permission, from McClellan I. Nineteenth century resuscitation apparatus. *Anaesthesia.* 1981;36(3):308.)

Negative-Pressure Ventilators

As an alternative to positive-pressure ventilation, physicians began to develop machines for negative-pressure ventilation. The first tank respirator was produced by Dalziel, of Scotland, in 1832. It was an airtight box in which the patient sat enclosed up to the neck. Negative pressure was created by bellows placed within the box but operated from the outside by a piston rod and one-way valve.[78,79]

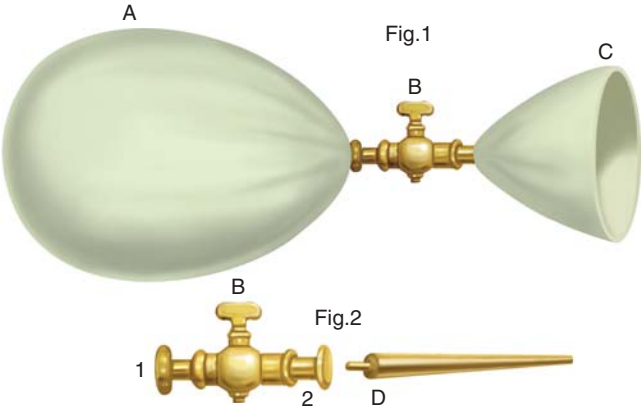


FIGURE 1-18 Chaussier developed this face mask and bag for artificial ventilation in 1780. (Used, with permission, from Mushin WW, Rendell-Baker L. *The Principles of Thoracic Anesthesia.* Oxford, England: Blackwell Scientific Publications; 1953:39.)

Jones, of Kentucky, patented the first tank respirator in America in 1864. The design appears similar to that of Dalziel's apparatus (Fig. 1-19).[78,80] Although Jones used this device to treat asthma and bronchitis, he also claimed cures for paralysis, neuralgia, rheumatism, seminal weakness, and dyspepsia.[80] Von Hauke designed a series of cuirass and tank respirators in the 1870s that were intended specifically to treat patients with respiratory diseases, but he showed little insight into the physiologic basis for how this type of respirator might be of benefit in lung disease. Woillez presented his version of a tank respirator to the French Academy of Medicine in 1876 (Fig. 1-20). It was basically a hollow cylinder of metal with a rigid lower end and an upper end enclosing a neck made of a rubber diaphragm seal. Air was evacuated from the cylinder by a bellows. Woillez understood the physiologic basis of ventilation and incorporated a bar placed on the patient's sternum to measure tidal excursions and adequacy of ventilation. Unfortunately, this device seemed to have been used only for resuscitating the apparently drowned and with little success.[78,81]

Many other ingenious devices were invented for negative-pressure ventilation over the next 50 years. Breuillard, of Paris, patented a tank respirator operated by a steam boiler.[78,80] Bell devised a vacuum jacket for newborns with neonatal respiratory distress. A resuscitation box developed by Braun reportedly was quite useful for children with respiratory distress (Fig. 1-21).[78,80,82] Eisenmenger designed a prototype respirator that extended from the upper part of the sternum to the pubis (Fig. 1-22A). A more

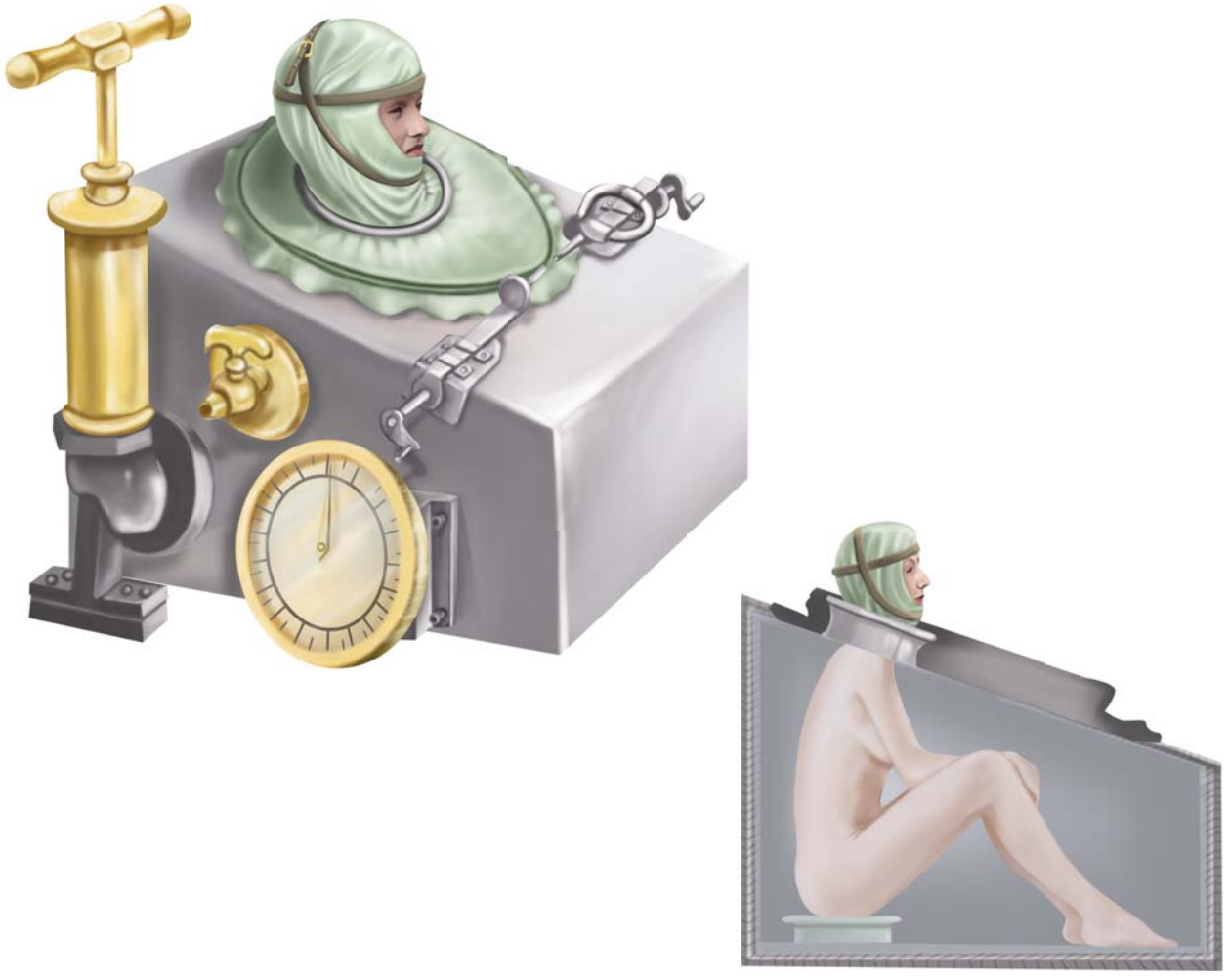


FIGURE 1-19 The body-enclosing tank respirator constructed by Jones in 1864. The large syringe was used to create negative pressure. (Used, with permission, from Emerson JH. *Evolution of Iron Lungs.* Cambridge, MA: JH Emerson; 1978:fig. 1.)

sophisticated device covered the chest and only a portion of the abdomen (Fig. 1-22B). These devices allowed positive-pressure compression of the chest to assist exhalation and negative-pressure suction to facilitate inhalation.[78,80,83] A later device, called the *Eisenmenger biomotor,* was patented in 1927, and had only an abdominal cuirass shell.[84] An important advantage of these devices was the access they allowed to the patient for nursing care. This consideration prompted Lord, of Worcester, to build a respirator room (Fig. 1-23). Huge pistons in the ceiling created the pressure changes but required heavy equipment.[78,80] Severy, in 1916, and Schwake, in 1926, built negative-pressure ventilators that required the patient to stand (Fig. 1-24). Although they incorporated ingenious mechanical elements, their practicality for severely ill patients was limited.[80]

The first negative-pressure ventilator to be used successfully in clinical practice on a widespread basis was the Drinker-Shaw "iron lung" developed in 1928 (Fig. 1-25).[80,84–86] With this device, the body was enclosed entirely within a cylindrical sheet-metal tank sealed at the lower end. The patient's head protruded out the upper end through a close-fitting rubber collar. Pressure within the chamber could be either increased or decreased by air blowers. This design is remarkably similar to the spirophore first built by Woillez in 1876. Unfortunately, it suffered from several of the same disadvantages, being cumbersome and inconvenient for patient care. Despite these limitations, this iron lung saved many lives during polio epidemics. When the Consolidated Gas Company of New York paid for large numbers of these machines to be built, their use spread quickly worldwide.[80] A severe poliomyelitis epidemic in 1931 prompted Emerson to build a simplified and improved tank respirator (Fig. 1-26). Because of its low cost, ease of operation, and technologic improvements, the Emerson tank respirator became the mainstay in treating patients with respiratory paralysis from polio[80] until reintroduction of positive-pressure ventilation in the 1950s.

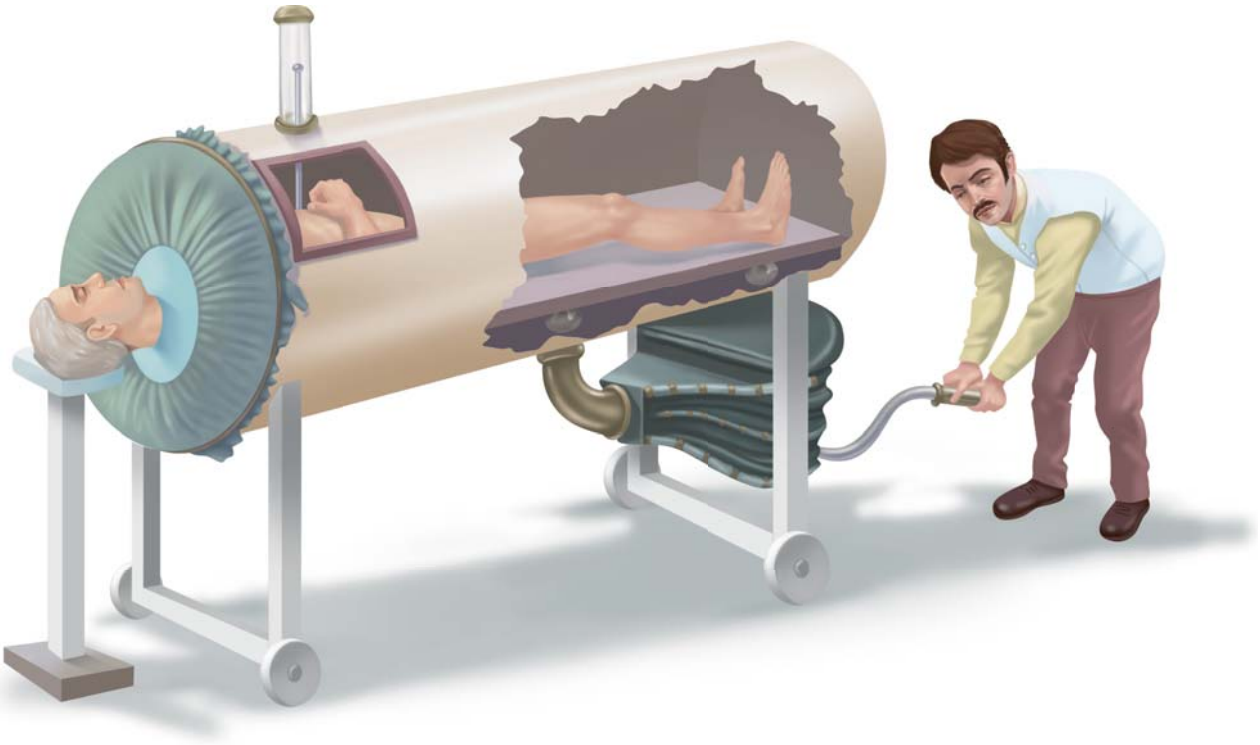


FIGURE 1-20 The spirophore produced by Woillez in 1876 had a rod placed on the patient's sternum to indicate the adequacy of tidal excursions. (Used, with permission, from Emerson JH: *Evolution of Iron Lungs.* Cambridge, MA: JH Emerson; 1978:fig. 2.)

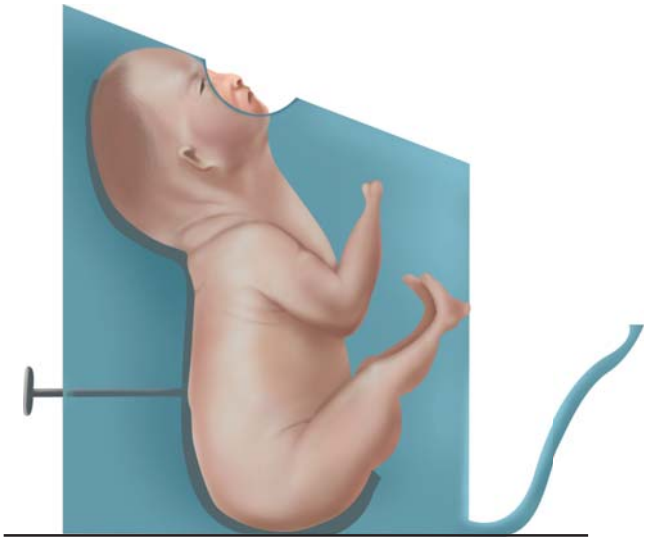


FIGURE 1-21 In Egon Braun's resuscitation box, children were seated in a plaster mold with their noses and mouths protruding through a rubber diaphragm. The operator blew through the tube on the right first, compressing the chest. Then suction was applied to the tube expanding the chest. (Used, with permission, from Emerson JH. *Evolution of Iron Lungs.* Cambridge, MA: JH Emerson; 1978:fig. 4.)

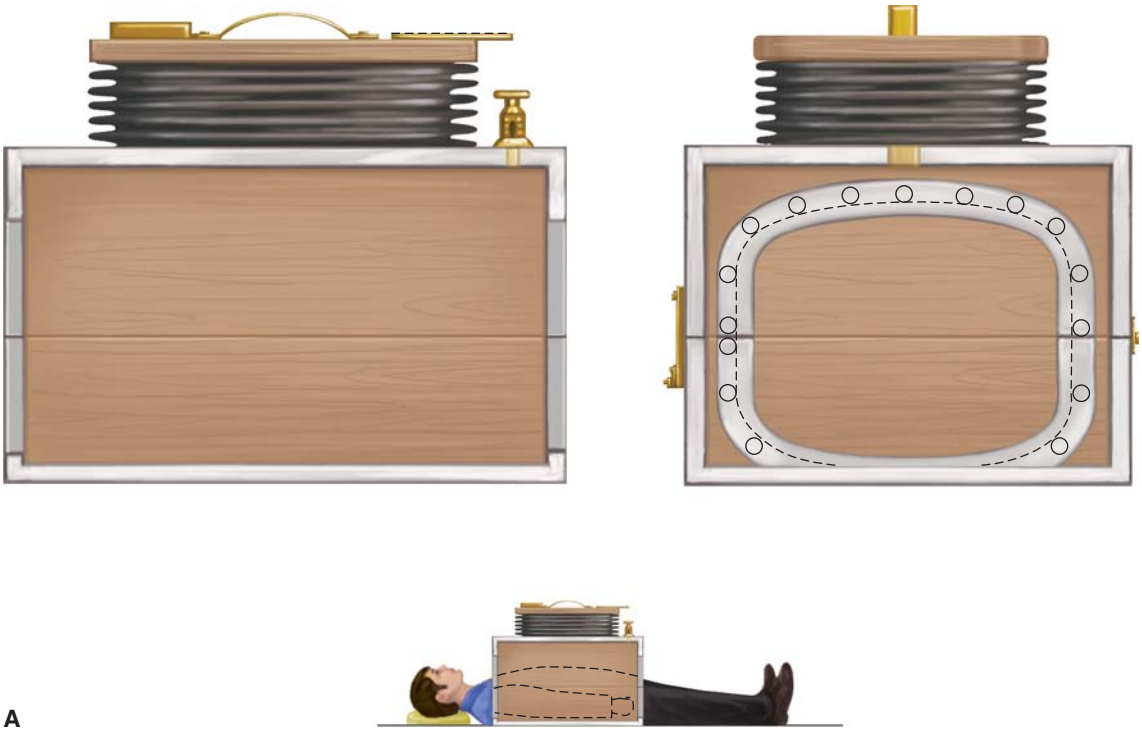
Positive-Pressure Ventilation

IN THE PHYSIOLOGY LABORATORY

Although positive-pressure ventilation was disavowed by clinicians, throughout the middle to late 1800s, physiologists relied increasingly on positive-pressure ventilation in animal experiments. Hering and Breuer used this technique to examine how alterations in lung volume influenced the vagi in 1868.[87] Bert, in his studies on blood oxygen and carbon dioxide content, wrote of giving animals sufficient curare to induce total paralysis and of providing artificial ventilation through a tracheostomy tube in 1878. A bellows with a graduated handle for controlling tidal volume proved to be quite effective in these experiments (Fig. 1-27).[15] Pflüger[26] and Head[88] described complex experiments in which cuffed tubes were used to ventilate isolated portions of the lung. Bowditch wrote of a simple but reliable volume-cycled ventilator used for animal studies as a standard piece of laboratory equipment at Harvard in 1879 (Fig. 1-28).[89]

IN THE OPERATING ROOM

The reintroduction of positive-pressure ventilation into clinical medicine occurred in two stages. Initially, positive-pressure ventilation was used in the operating room



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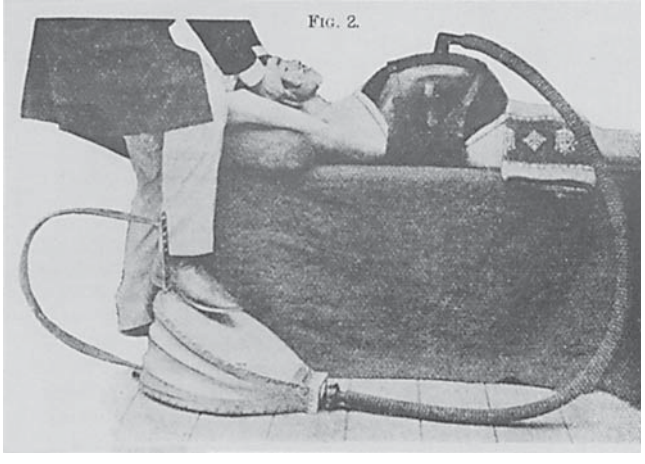


B

FIGURE 1-22 **A.** Eisenmenger's earlier version of his cuirass shell. (Used, with permission, from Emerson JH. *Evolution of Iron Lungs.* Cambridge, MA: JH Emerson; 1978:fig. 5.) **B.** The more sophisticated version described in 1904. A foot bellows allows positive and negative pressure to assist expiration and inspiration, respectively. This device is quite similar to chest shells still in use today. (Eisenmenger R. Apparatus for maintaining artificial respiration. *Lancet.* 1904;1:515.)

around the turn of the twentieth century. There was a clear and pressing need for positive-pressure ventilation to facilitate thoracic surgery. From the time of Galen, it was appreciated that opening the thorax invariably caused fatal pneumothorax. Vesalius had shown that positive-pressure ventilation could keep an animal's lungs inflated and the animal alive during these operations, but this lesson seems to have been forgotten. Consequently, lung surgery in the nineteenth century was limited to rare cases of draining lung abscesses and bronchiectatic or tuberculous cavities. Although pneumonectomy had been performed successfully in animals by 1881,[90,91] between 1880 and 1920 the mortality rate for thoracic surgery remained high, and these procedures were performed infrequently.[90,92] By 1896, Quénu and Longuet realized that to have success in thoracic operations, one had "to maintain a difference in pressure between the intra-alveolar air and the surrounding air." The surgeon could choose either to "lower the extra thoracic pressure, the intrapulmonary tension remaining the same, making it necessary…to operate in a relative vacuum, or to increase the intrabronchial pressure."[93] Only after positive-pressure ventilation had become a well-established technique during surgery was it applied to nonoperative patients, beginning in the 1950s.

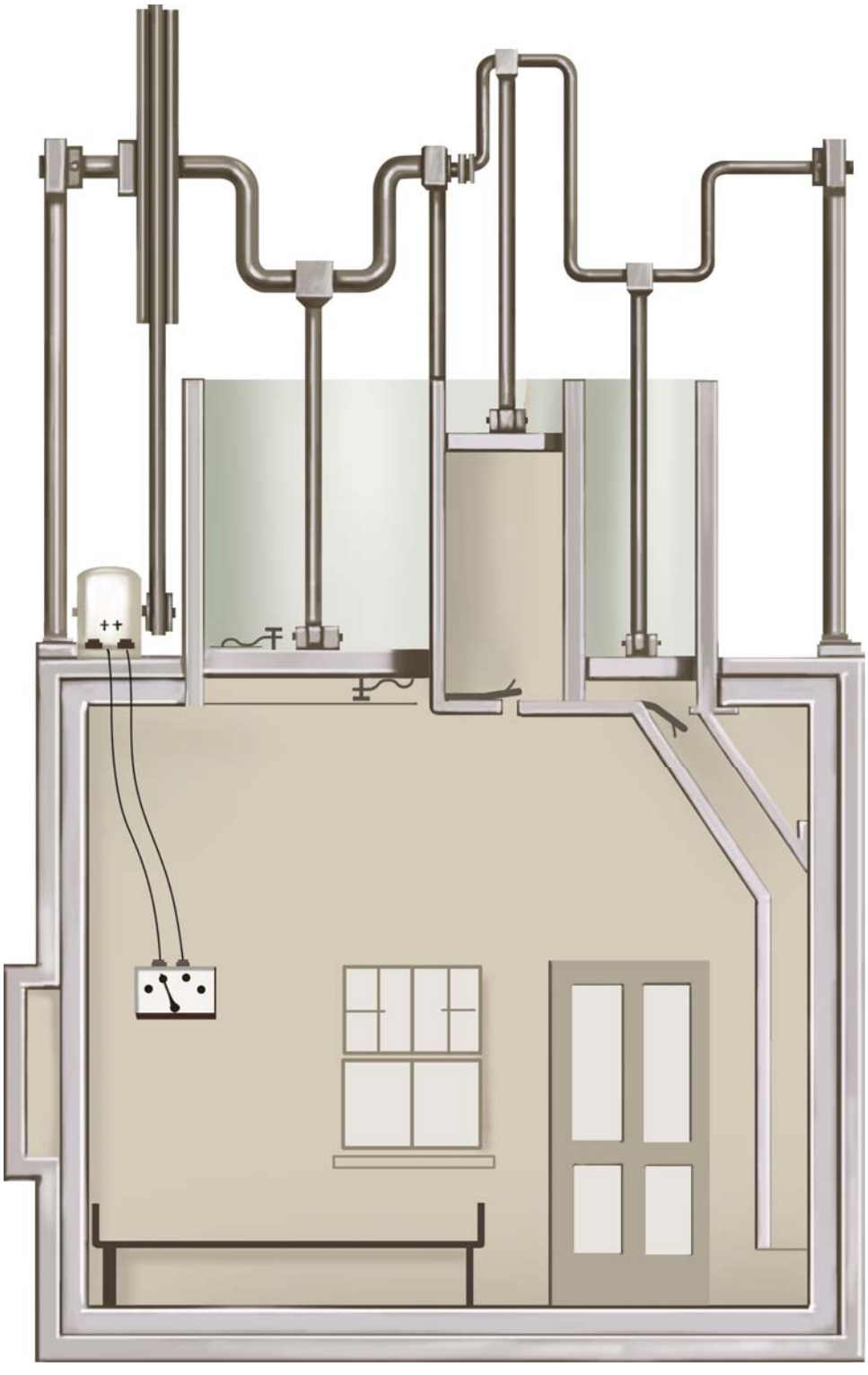


FIGURE 1-23 A negative-pressure respirator room, patented by Lord in 1908, provided optimal access to the patient for the nursing staff. (Used, with permission, from Emerson JH. *Evolution of Iron Lungs.* Cambridge, MA: JH Emerson; 1978:fig. 8.)

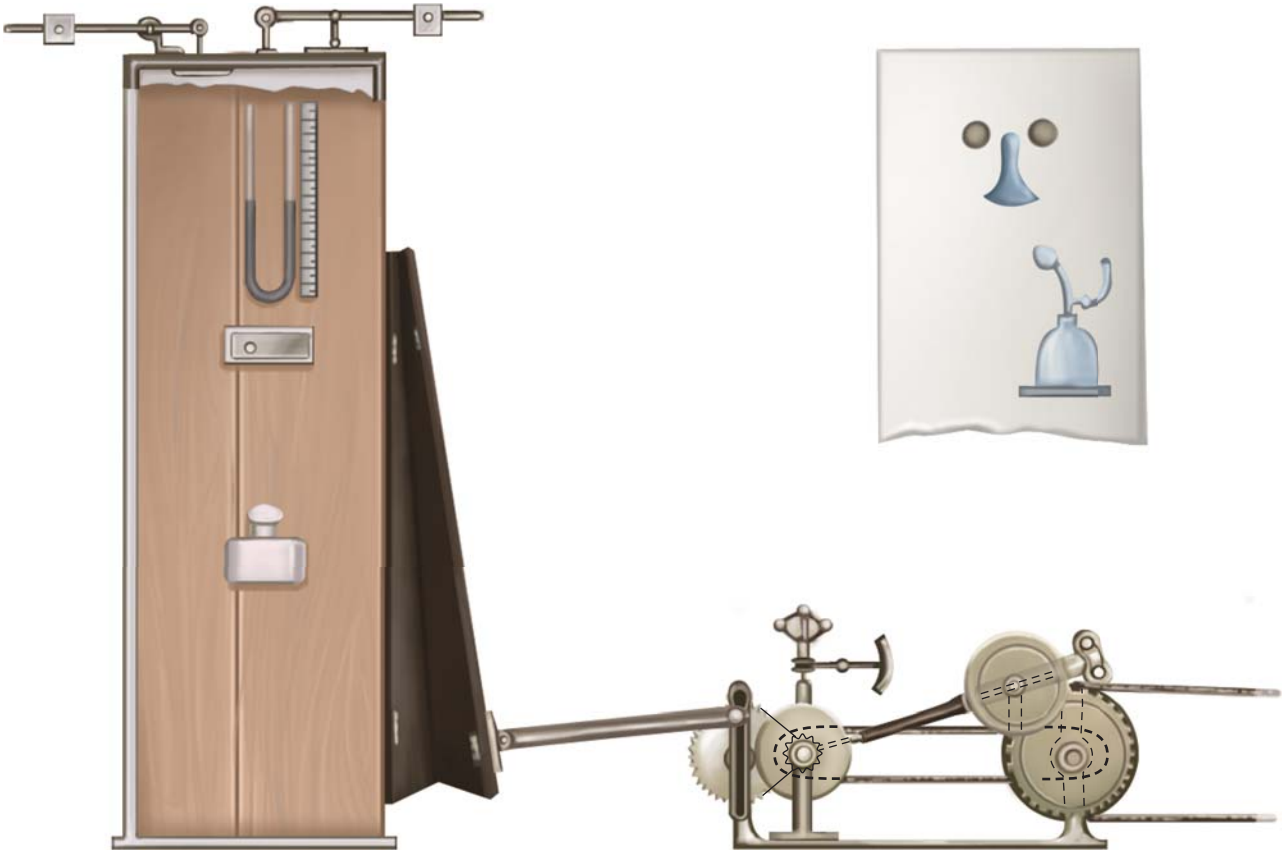


FIGURE 1-24 Severy's negative-pressure ventilator obliged the patient to stand but had a remarkable set of electromagnetic controls and pulleys for adjusting pressure changes within the box. (Used, with permission, from Emerson JH. *Evolution of Iron Lungs.* Cambridge, MA: JH Emerson; 1978: fig. 9.)

Tracheal Intubation

The obvious way to increase intrabronchial pressure would be to follow Vesalius's example by placing a tube in the trachea and inflating the lungs with a bellows. Positive-pressure ventilation had been well standardized in the physiology laboratory. Although techniques to cannulate the trachea had been developed in the late eighteenth century, translaryngeal intubation still was viewed skeptically by many physicians until the early 1900s.[94] Physicians only became reassured about the usefulness of translaryngeal intubation through work on controlling the airway. The most compelling reason for airway control always had been upper-airway obstruction. Tracheostomy historically was a well-known method of gaining access to the airway in such situations. Indirect references to this technique can be found in such ancient texts as the *Rig Veda*, written between 2000 and 1000 BC, and *Eber's Papyrus*, from about 1550 BC. Alexander the Great reputedly performed a tracheostomy with his sword in 400 BC on a soldier who was choking on a bone.[95] According to Frost[96] and McClelland,[97] Asclepiades of Bithynia was the first surgeon to perform tracheostomy routinely, around 100 BC. The Roman Antyllos also was noted for his skill in this procedure in 340 AD.[96] Although few surgeons were reported to have performed this procedure during the Dark Ages, Brasavola reintroduced the technique to the medical community in 1546. In 1833, Trousseau clearly demonstrated the lifesaving value of tracheostomy for managing upper-airway obstruction with his report on 200 of these operations for diphtheria.[96,97]

A small number of pioneering physicians experimented with techniques and devices to cannulate the trachea through either the nose or the mouth (translaryngeal intubation) in the late eighteenth century as a practical alternative to tracheostomy for managing upper-airway obstruction. Depaul, who succeeded Chaussier at the maternity hospital in Paris, successfully modified Chaussier's tubes for managing neonatal respiratory distress.[73] Bouchut used a silver truncated cone, "a little smaller than a thimble," to dilate the larynx in two children with diphtheria in1858.[98] Although transiently successful, Trousseau discouraged this approach and confirmed tracheotomy as the preferred approach. MacEwen of Glasgow used translaryngeal intubation to manage a small number of patients with upper

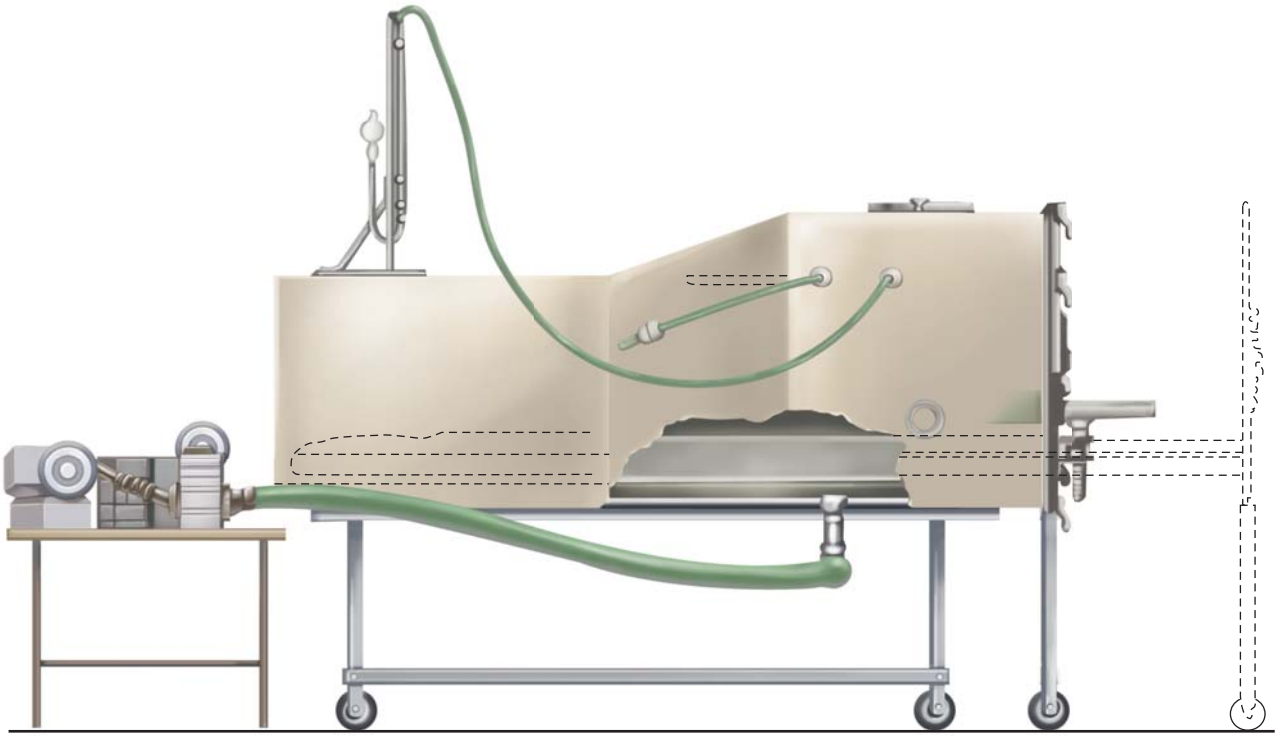


FIGURE 1-25 The Drinker-Shaw iron lung, developed in 1928, had a sliding bed and a close-fitting rubber collar for sealing the patient's neck. The patient's head protruded from the device at the right and rested on a flat support. (Used, with permission, from Emerson JH. *Evolution of Iron Lungs.* Cambridge, MA: JH Emerson; 1978:fig. 13.)

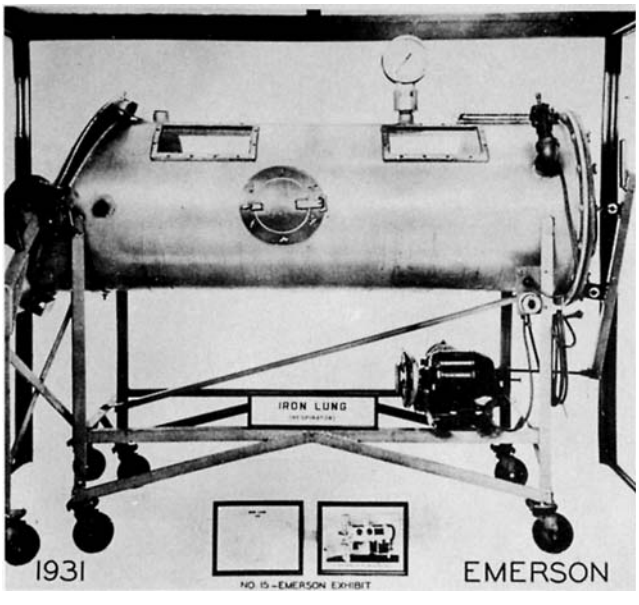


FIGURE 1-26 The Emerson tank respirator, built in 1931, used a bellows device to change pressure (hand pumps also were available in case of electricity failure), was less cumbersome and expensive than the Drinker-Shaw iron lung, and was easily opened and closed for nursing care. (Used, with permission, from Emerson JH. *Evolution of Iron Lungs.* Cambridge, MA: JH Emerson; 1978:fig. 15.)

airway obstruction and probably diphtheria in 1880.[99] O'Dwyer of New York proved to be the most persistent advocate of intralaryngeal tubes for managing upper airway obstruction. He was appointed to the medical staff of a foundling home in 1872. At that time the leading cause of infant mortality was diphtheria of the larynx. Even with tracheotomy, the survival rates for this condition were abysmal. O'Dwyer worked from 1880 to 1885 on developing a device for intubating the larynx, but his initial experience with a bivalved device proved unsuccessful. Despite

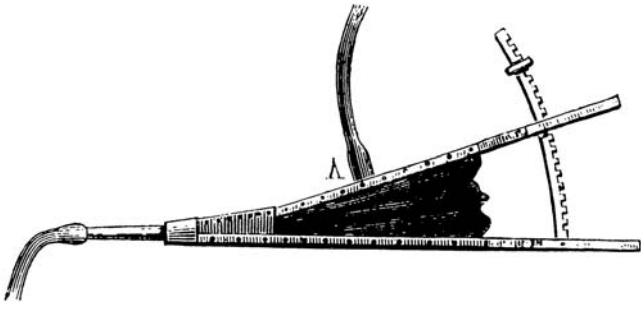


FIGURE 1-27 A bellows with graduated handle for controlling tidal volume was used by Bert to ventilate paralyzed animals in 1878. (Used, with permission, from Bert.[15])

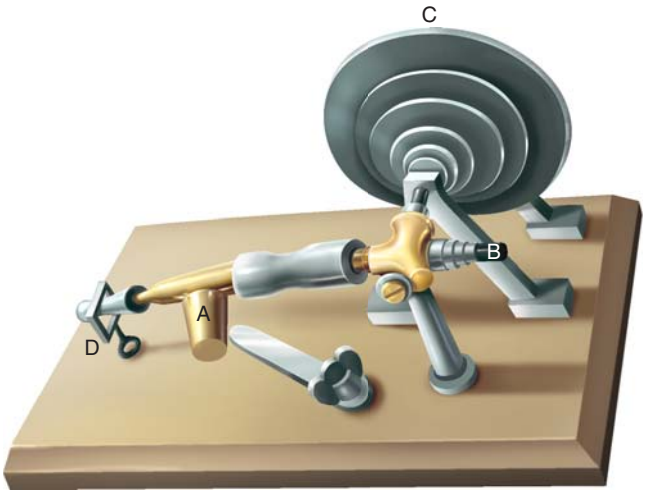


FIGURE 1-28 The volume-cycled ventilator used in the Harvard Physiology Department in 1870s. Air from a bellows or tromp enters *A* and passes to the animal through *B*. The respiratory rate is determined by adjusting the driving band on cone *C*. The amount of air entering the animal is determined by screw clamp *D*, which permits air to escape. (Used, with permission, from Bowditch HP. Physiological apparatus in use at the Harvard Medical School. *J Physiol*. 1879–1880;2:202.)

initial skepticism by the medical community about this technique, O'Dwyer persevered and later developed a more successful, simple, open-tube approach.[100–102] O'Dwyer, through his efforts over years and experience in hundreds of patients, should be recognized as the first physician to effectively advocate the use of translaryngeal intubation for managing upper-airway obstruction.[98]

Tracheal Anesthesia

As clinicians began to appreciate the value of translaryngeal intubation for managing upper-airway obstruction, anesthetists slowly began to grasp how useful this technique might be for administering anesthesia in the operating room. Ether anesthesia had first been used during an operation by Morton in 1846.[103] Snow, in 1858, gave rabbits chloroform vapor through a tracheostomy tube.[104] Trendelenburg apparently adapted this method for use in patients during operations on the mouth and larynx. A practical problem limiting these operations at the time was aspiration of blood into the lungs during the procedure. Trendelenburg solved this problem by devising a cuffed tracheostomy tube for sealing the airway in 1869 (Fig. 1-29).[73] With this cuffed tracheostomy tube in place, inhalational anesthesia could only be given practically through the tube itself. MacEwen's original work on translaryngeal intubation for upper-airway obstruction included one case in which successful anesthesia given through the tube allowed surgical removal of a pharyngeal tumor.[98] Maydl of Prague and Eisenmenger of Vienna both described cases of upper-airway surgery in 1893 using endotracheal anesthesia.[105]

Tuffier and Hallion, in 1896, ventilated animal lungs through a translaryngeal tube to prevent collapse during surgery.[106] Doyen improved their techniques.[107] Fell was well aware of the use of forced respiration, using a bellows to administer positive-pressure ventilation through a tracheotomy tube, from animal experiments, but had never heard hint of this technique possibly being useful in humans. He realized, though, that forced respiration might be a practical method for managing patients with respiratory paralysis from opiate overdose.[108] Fell considered that "if the respirations could be kept up by suitable means for a sufficient time to permit the elimination of the poison, life might be saved. He reported use of this technique in both opiate and anesthetic drug overdose.[109] O'Dwyer modified Fell's device so that it could be attached to a translaryngeal tube, and soon the Fell-O'Dwyer apparatus for mechanical ventilation was marketed. Matas realized that if anesthesia

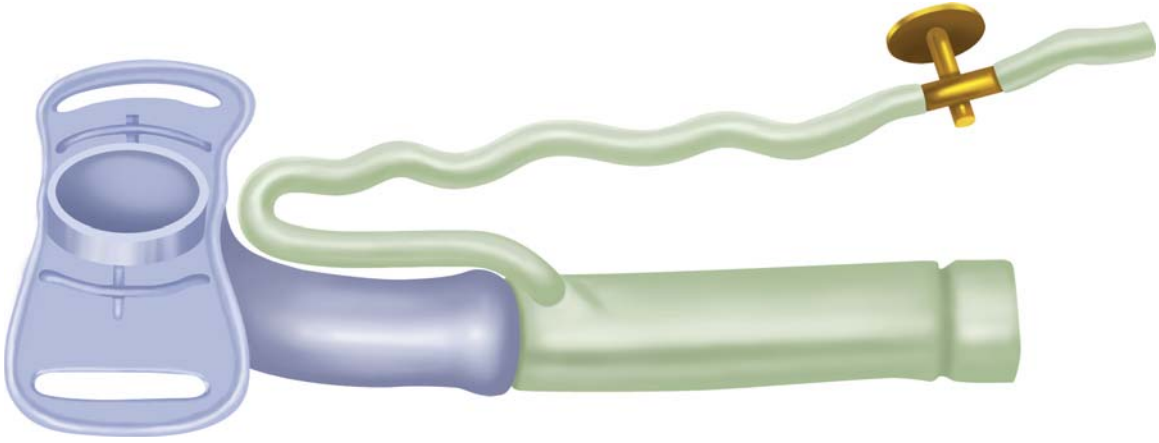


FIGURE 1-29 Trendelenburg first used this type of tracheostomy tube with inflatable cuff to prevent aspiration during operations on the mouth and larynx in 1869. (Used, with permission, from Lomholt N. A new tracheostomy tube: I. cuff with controlled pressure on the tracheal mMucous membrane. *Acta Anaesthesiol Scand.* 1967;11(3):312.)

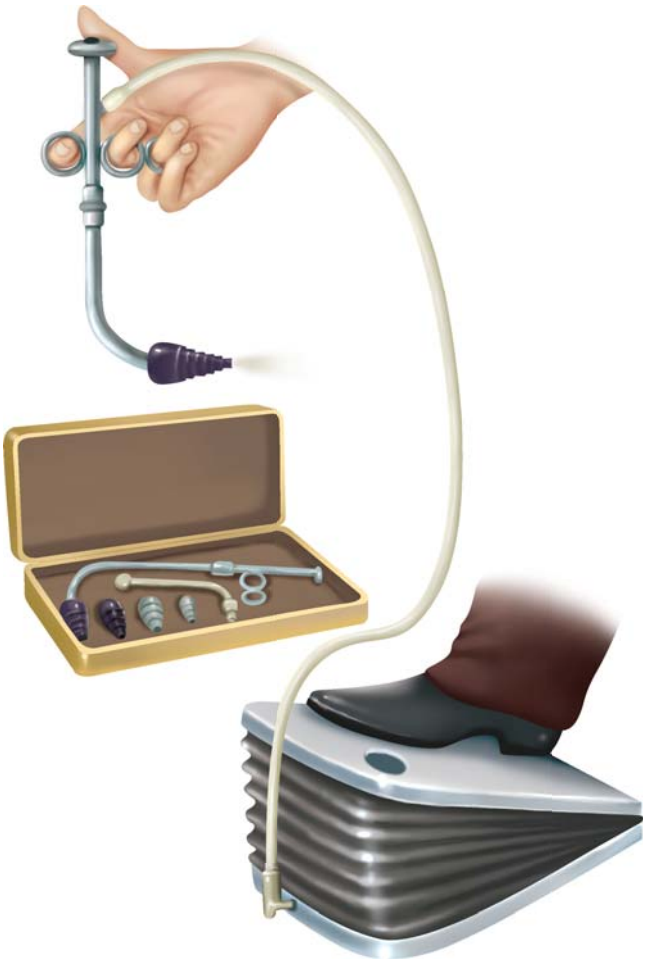


FIGURE 1-30 The Fell-O' Dwyer apparatus with modifications by Matas for delivering anaesthesia. (Used, with permission, from Matas R. Intralaryngeal insufflation. *JAMA*. 1900;34:1468–1473.)

could be administered readily through the apparatus, the Fell-O'Dwyer ventilator would be well suited for managing intrathoracic surgery. Matas modified this ventilator successfully and indicated that the new machine indeed was effective (Fig. 1-30).[107,110]

The interest in translaryngeal intubation for administering anesthesia and facilitating positive-pressure ventilation was stuttering at first. Kuhn apparently used this technique regularly and with great success. He experimented extensively with both the size and position of the tracheal tube, even using separate tubes for inhalation and exhalation.[111] In 1909, Meltzer and Auer modified this technique. Instead of using a tracheal tube that nearly approximated the diameter of the trachea and allowing the patients to inhale and exhale through that same tube, these physiologists used a narrow-bore tube. Air was blown into the lung through the tube and allowed to escape from the lung between the external wall of the tube and the trachea. This technique was referred to as *endotracheal insufflation.*[112] Ellsberg was the first to use endotracheal insufflation on a patient,[113] but others criticized the technique. Meyer disparagingly called Meltzer's insufflation method the "blowpipe apparatus." Meyer cited numerous concerns (e.g., risks of aspiration through the tube; incomplete control of airway pressure, especially when closing the chest; unreliable administration of anesthesia; and difficulties placing the tracheal tube correctly) and concluded that endotracheal insufflation was not suitable for thoracic surgery.[94]

Differential Pressure

Around 1904, Sauerbruch devised a working model of a cabinet that generated negative pressure around the lung. Sauerbruch built a small airtight operating room with the patient's body and the surgeon inside. The patient's head extended out of the room. By applying suction to this room, differential pressure was created across the pleural surface, atmospheric pressure within the bronchial tree, and negative pressure outside the lung (Fig. 1-31).[64] Meyer built a much larger version of a negative-pressure apparatus. The entire operating room was subjected to suction, and a small chamber was built within the operating room to enclose the patient's head and the anesthetist. This chamber either could be kept at atmospheric pressure or could subjected to positive pressure (Fig. 1-32).[114]

Surgeons also had the option of using devices that employed positive pressure without intubation to inflate

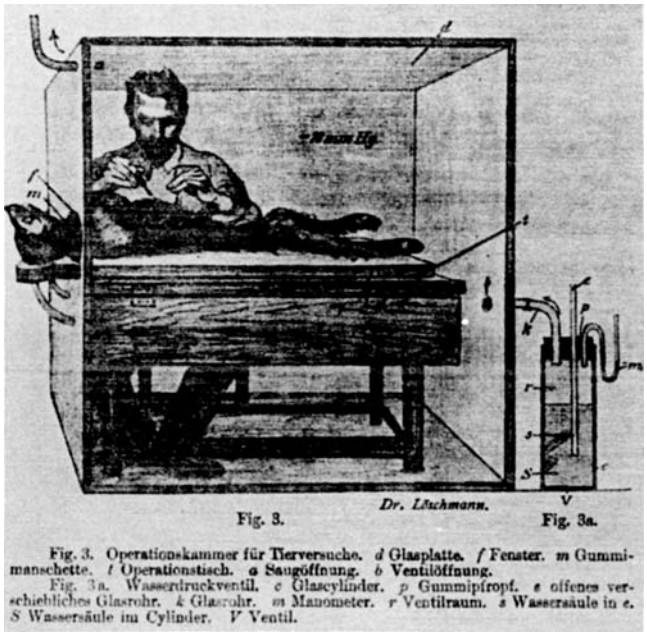
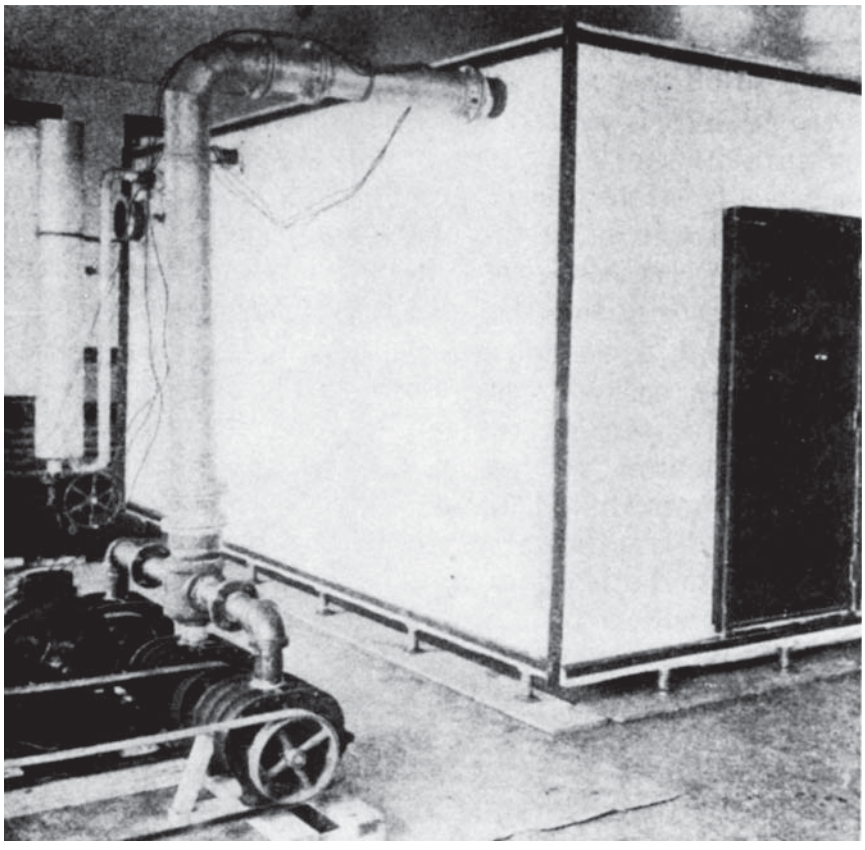


Fig. 3. Operationskammer für Tierversuche. *d* Glasplatte. *f* Fenster. *m* Gummimanschette. *l* Operationstisch. *a* Saugöffnung. *b* Ventilöffnung.
Fig. 3a. Wasserdruckventil. *c* Glascylinder. *p* Gummipfropf. *e* offenes verschiebliches Glasrohr. *k* Glasrohr. *m* Manometer. *r* Ventilraum. *s* Wassersäule in *e*. *S* Wassersäule im Cylinder. *V* Ventil.

FIGURE 1-31 The differential-pressure cabinet developed by Sauerbruch placed the surgeon inside a small chamber. Suction was applied to this chamber. With the animal's (in this case) or patient's head outside the chamber, the intrabronchial pressure remained at effective sea level. This differential pressure maintained lung inflation when the thorax was open. (Used, with permission, from Morch.[64])



A

B

FIGURE 1-32 A larger version of the differential-pressure cabinet was constructed by Meyer. **A.** The large chamber, shown from an outside view on the left, has suction applied to it. Inside this chamber, the patient is placed on a table with the patient's head inserted into a smaller chamber. Within this smaller chamber (**B**), kept at positive pressure, resides the anesthetist. (Used, with permission, from Meyer W. Pneumonectomy with the aid of differential air pressure. *JAMA*. 1909;77:1984.)

the lungs. Brauer is credited as devising the first positive-pressure cabinet in 1904. This apparatus was large enough for the patient's head to fit inside. Positive pressure in the cabinet would be transmitted to the lungs during the patient's respiratory efforts.[64,115–117] Modifications of the positive-pressure cabinet were put forth by Murphy,[115] Green,[116] and Green and Janeway (Fig. 1-33).[117] As an alternative to cabinets, other surgeons used face masks and helmets to supply positive-pressure ventilation (Fig. 1-34).[118–120]

Several factors favored the endotracheal insufflation method for both anesthesia and lung inflation during thoracic operations. The differential-pressure chambers were either large and cumbersome or small and confining, and all were expensive. A device for endotracheal insufflation, which was portable and easy to use, was built in 1910 by Elsberg for less than $100,[121] although more complex devices also were built (Fig. 1-35). The positive-pressure cabinets limited access to the patient's head during the procedure. Positive-pressure masks were not reliable in maintaining lung inflation. Techniques and devices for facilitating translaryngeal intubation were being developed quickly. Dorrance[122] described a simple endotracheal tube made of flexible rubber with an inflatable cuff at its distal end. Janeway developed the first modern laryngoscope, an invaluable aid for

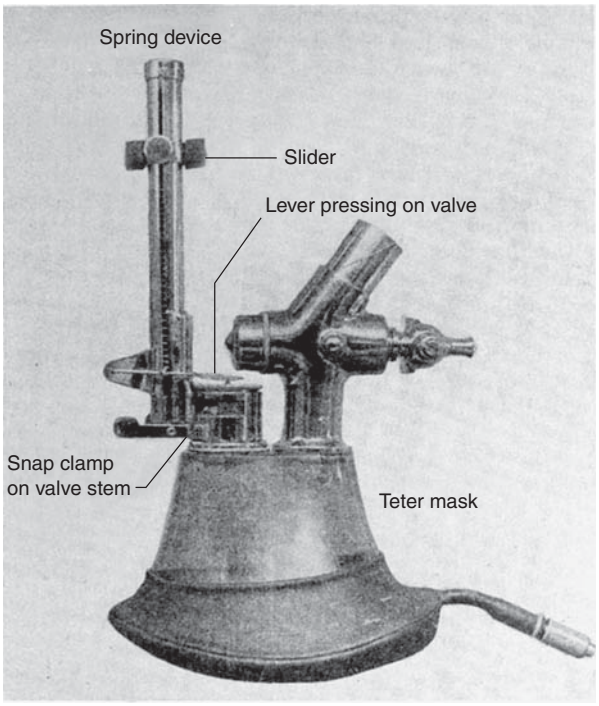
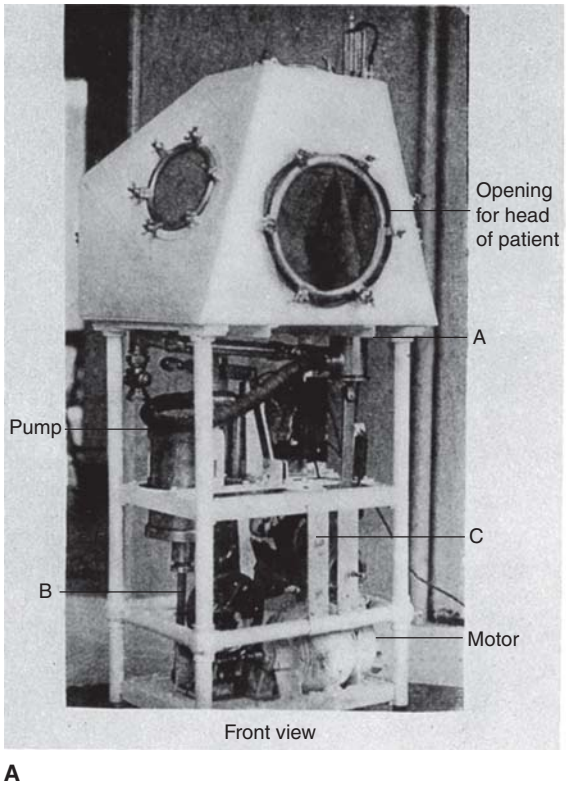
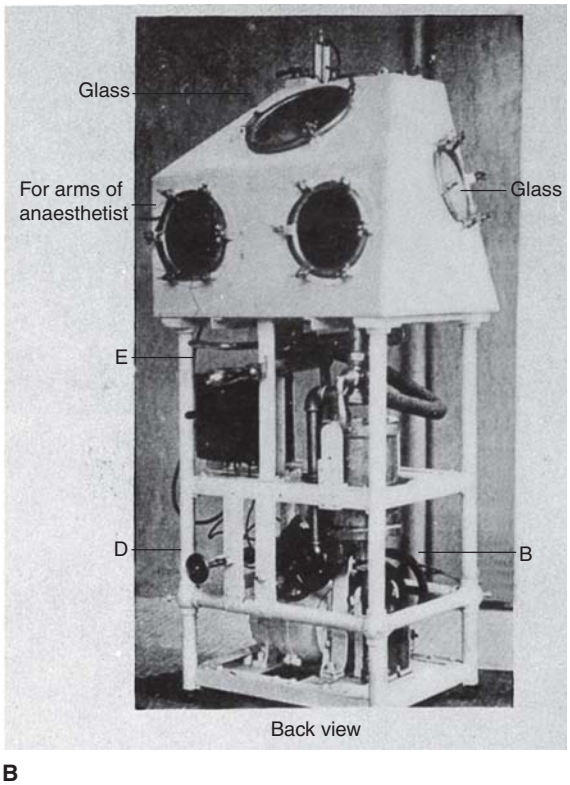


FIGURE 1-34 A positive-pressure mask used by Bunnell in 1912. (Used, with permission, from Bunnell S. The use of nitrous oxide and oxygen to maintain anesthesia and positive pressure for thoracic surgery. *JAMA*. 1912;58:836.)



A



B

FIGURE 1-33 Green and Janeway proposed this positive-pressure chamber in 1910. The patient's head is inserted into the chamber (**A**). The anesthetist's arms also can reach into the chamber (**B**). (Used, with permission, from Green NW, Janeway HH. Artificial respiration and intrathoracic esophageal surgery. *Ann Surg*. 1910;52:58–66.)

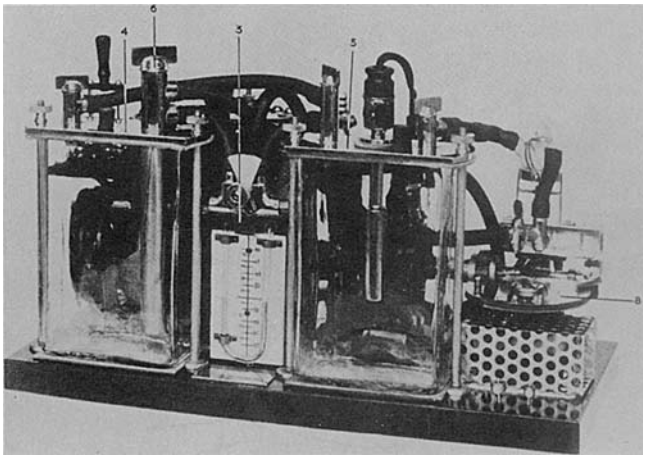


FIGURE 1-35 A sophisticated and complex ventilator built by Janeway in 1912. (Used, with permission, from Janeway HH. An apparatus for the intratracheal insufflation. *Ann Surg*. 1912;56:328–330.)

translaryngeal intubation.[64] Jackson was instrumental in providing clear guidelines for performing translaryngeal intubation.[123] With these developments, endotracheal insufflation became firmly established, and new devices for anesthesia and ventilation by insufflation were developed quickly.[124,125] Many other devices for positive-pressure ventilation, including the "pulmotor" portable resuscitator, were devised in the early 1900s.[64]

Translaryngeal Intubation

By World War I, endotracheal intubation had become an invaluable method for enabling extensive plastic facial reconstructions. However, anesthetists began to express dissatisfaction with the insufflation technique for anesthesia and ventilation. Insufflation did not protect from aspiration, especially during upper-airway operations. In these procedures, pharyngeal packing to prevent aspiration required placement of two tubes, one for insufflation and the other for exhalation. Placement of two tubes was technically difficult. Anesthetists would much prefer to use a cuffed tracheal tube, which, of course, was not feasible with insufflation. Anesthetists were finding that nitrous oxide was a better anesthetic agent than chloroform or ether, but it was very expensive to administer by insufflation. Periodic deflations of the lung usually were required, with insufflation to ensure adequate carbon dioxide removal. As a consequence of these problems with insufflation, Magill and Rowbotham returned to Matas's old "inhalation" method. They used a tracheal tube large enough to allow both inhalation and exhalation. A balloon cuff could be attached to the outer distal end of the tube to prevent aspiration.[105,126,127] Rowbotham also was instrumental in popularizing nasotracheal intubation.[128] A number of cleverly designed machines were produced before World War II that could be used to administer anesthesia and artificial ventilation via positive-pressure rhythmic "insufflation"(ventilation) through these large-diameter tubes.[64,129,130] By 1934, Guedel and Treweek described apneic anesthesia, or purposely giving enough anesthesia to cause complete respiratory paralysis. Artificial respiration by rhythmic bag ventilation adequately supported the patient during apnea. This technique provided the "quiet" field necessary for abdominal and thoracic surgery.[131]

Further favoring the use of translaryngeal intubation was recognition of retained pulmonary secretions as a cause of postoperative morbidity and mortality. As pointed out by Jackson in 1911, "when tracheal and bronchial secretions are in excess of the amount required properly to moisten the inspired air, they become a menace to life unless removed."[132] Postoperative atelectasis, attributed to retention of thick bronchial secretions and inhibition of coughing, was first described in 1928.[133] Bronchoscopy and intratracheal suctioning were the earliest techniques advised for removing secretions,[132,134,135] but it became apparent that easy access to the tracheobronchial tree for repeated suctioning might be necessary in difficult cases. Tracheostomy was recommended as early as 1932 specifically for this problem in polio patients,[136,137] and later for patients with a variety of surgical problems.[138–141] Physicians soon realized that suctioning through a large tube placed translaryngeally might be just as effective as through a tracheotomy tube. In the 1940s, case reports began to appear describing the successful and prolonged use of translaryngeal intubation for tracheobronchial toilet.[142–144] Modification of tracheal tubes to include "Murphy eyes" at the tips probably has reduced the likelihood that these tubes would become occluded by mucus.[145]

For the Nonoperative Patient

The second stage of the reintroduction of positive-pressure ventilation into clinical practice involved nonoperative patients and occurred dramatically in the 1950s. There had been isolated reports of physicians using positive-pressure ventilation for purely mechanical problems before this time. Bert describes a positive-pressure chamber built by Jourdanet in the 1870s (Fig. 1-36) and used for a variety of mechanical problems.[15] Williams wrote of treating pulmonary disease with a pneumatic differentiation chamber in 1885. The patients were placed within a cabinet, and the air in this cabinet was exhausted by suction. Simultaneously, "antiseptic air charged with remedial agents" was administered to the patient's mouth. The reduced pressure around the thorax and atmospheric pressure applied to the lungs were thought to dilate the lungs beneficially. Remarkable improvements were described for a wide variety of lung disorders with this device.[146] Fell used a bellows ventilator to manage respiratory depression secondary to opiate overdose in the late 1880s.[108] A remarkable series of studies described the use of positive-pressure respiration for the treatment of pulmonary edema.[147–149] The emphasis of these studies was not to assist respiration—forced

FIGURE 1-36 Jourdanet used this positive-pressure chamber to treat patients with a wide variety of disorders in the 1870s. (Used, with permission, from Bert.[15])

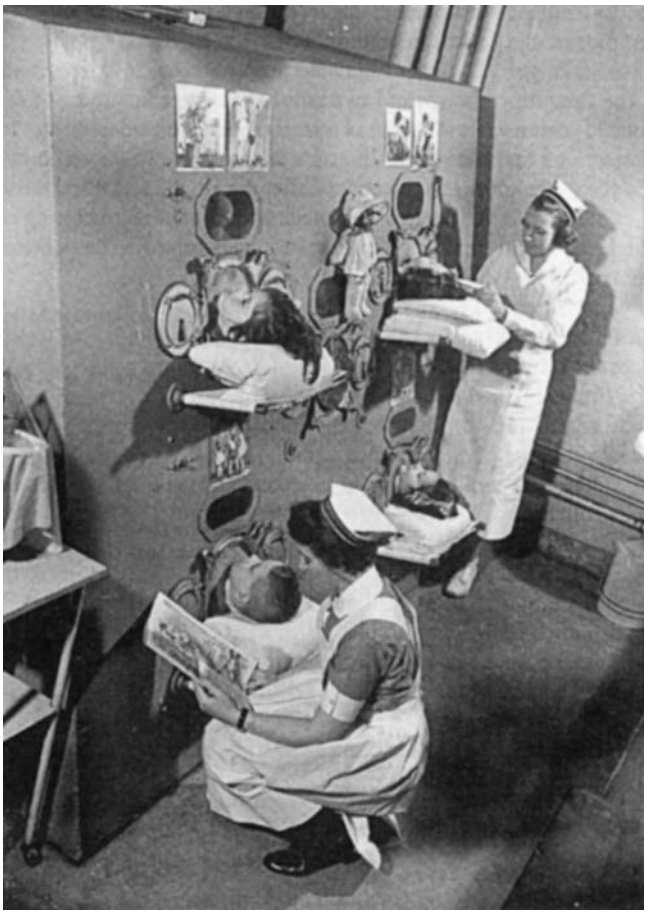


FIGURE 1-37 Young patients with respiratory paralysis from polio being treated in an "iron lung." (Photograph by Hansel Mieth, courtesy Time Life Pictures, Getty Images, 1938.)

respiration by intubation was felt to be unjustifiable[147]—but to use positive pressure to counterbalance the backward pressure on the pulmonary capillaries.[149] The widespread use of positive-pressure ventilation did not begin, however, until its value was demonstrated dramatically during a polio epidemic in Copenhagen in 1952.

PARALYTIC POLIO

A series of polio epidemics had swept across Europe and the United States in the 1930s and 1940s. Respiratory paralysis secondary to poliomyelitis was an infrequent but feared complication. Even with the best management techniques using iron lungs and cuirass ventilators (Fig. 1-37), the mortality rate for polio-induced respiratory paralysis probably was approximately 85%.[64] In the late summer of 1952, an epidemic struck Copenhagen. Of the first thirty-one patients admitted to Blegdamshospital, Copenhagen's hospital for communicable diseases, during this epidemic with respiratory paralysis, twenty-seven died within 3 days. Out of desperation, Henry Lassen, the chief physician and epidemiologist, called the freelance anesthetist Bjorn Ibsen for consultative advice. After reviewing the medical records and autopsy results, Ibsen made two startling conclusions. First, he felt that in the fatal cases there was insufficient atelectasis within the lungs to make adequate ventilation impossible. Second, he suggested that the increased blood levels of total CO_2 did not reflect metabolic alkalosis, as was generally believed, but rather acute respiratory acidosis. Ibsen's observations about respiratory acidosis were derived directly from work he had performed measuring exhaled carbon dioxide levels in the operating theater. Ibsen, as the anesthetist, had noted that exhaled carbon dioxide levels fluctuated during the course of surgery and could be compensated by more vigorous bag ventilation. Most importantly, when exhaled carbon dioxide levels increased, the patients in the operating theater had developed clammy skin and high blood pressure, similar signs to those found in the paralytic polio patients just before death. Based on these observations, Ibsen suggested inadequate ventilation as the cause of death and advised tracheostomy to allow the operative techniques of positive-pressure ventilation.

Lassen was not convinced; the iron lung and cuirass respirators had reliably provided adequate ventilation in the past. Lassen argued that it was unlikely that positive-pressure ventilation would save paralytic polio patients if the underlying disease process actually included extensive brainstem involvement.[150]

As a counterargument, Ibsen cited recent experience in the United States with a positive-pressure valve capable of providing mechanical positive-pressure ventilation to polio patients. These valves were developed as a result of intense interest by the U.S. Air Force during World War II in using positive pressure to increase altitude tolerance in pilots.[151,152] The unique attribute of these valves, such as the pneumatic balance respirator (PBR), was their ability to convert a continuous positive pressure into intermittent positive pressure. Intermittent positive-pressure breathing was applied in the late 1940s to a variety of medical problems and found to be effective in providing artificial ventilation to an apneic person;[153–155] in managing acute pulmonary edema, acute asthma, and postoperative patients with poor respiratory excursion;[154] possibly in improving oxygenation in various lung diseases;[156] and in administering medications by nebulization[157]. The Bennett valve was adapted as a positive-pressure respirator attachment for the standard tank respirator during the 1948 Los Angeles poliomyelitis epidemic (Fig, 1-38). The PBR supplied intermittent positive-pressure breaths in synchrony with the tank respirator's inspiratory negative-pressure phase.[158] Use of the PBR along with the tank respirator significantly reduced the case-fatality rate of respiratory paralysis associated with polio.[159]

Lassen eventually agreed to a trial of Ibsen's theory. The thirty-second patient with respiratory paralysis admitted to Blegdamshospital was the poignant case of a 12-year-old girl. When her condition deteriorated, Ibsen asked a surgeon to perform a tracheostomy, and a cuffed tracheal tube was introduced. During the procedure, the girl became comatose. Ibsen initially was unable to ventilate her effectively. He assumed that retained secretions were the problem, and he suctioned her. Her condition deteriorated further, and many physicians observing the trial began to leave, assuming that the outcome would be fatal. In this desperate situation, Ibsen decided to paralyze the girl. She collapsed immediately, and Ibsen finally was able to ventilate her adequately.

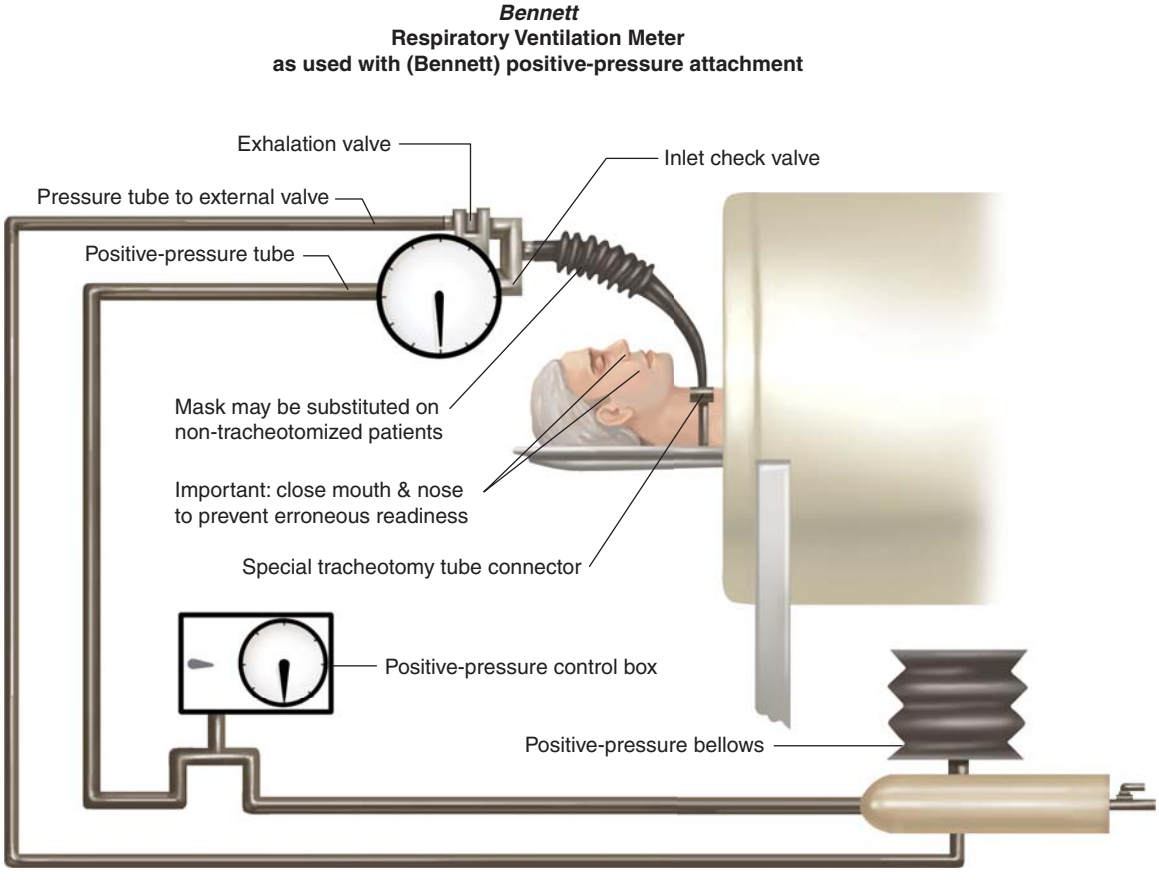


FIGURE 1-38 A schematic of the Bennett positive-pressure valve used via a tracheostomy tube in a patient in an iron lung. (Used, with permission, from Bower AG, Bennett VR, Dillon JB, Axelrod B. Investigation on the care and treatment of poliomyelitis patients. *Ann West Med Surg.* 1950;4:567.)

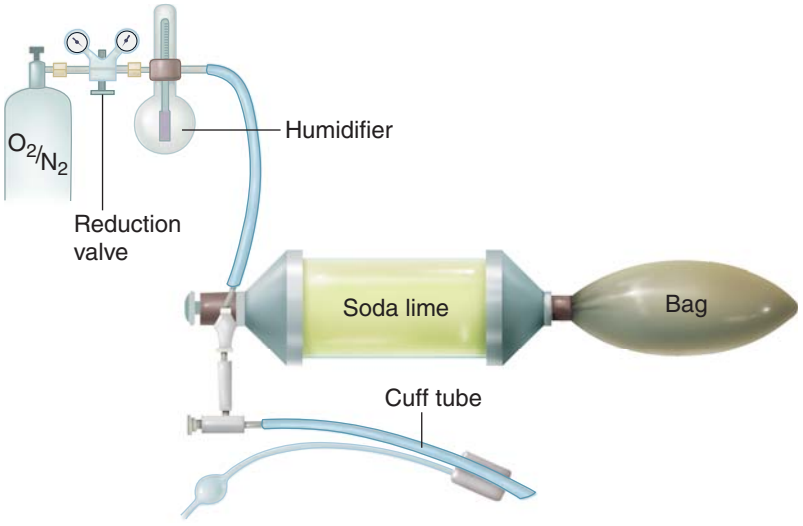


FIGURE 1-39 This hand ventilator was used in the Copenhagen polio epidemic of 1952 by hundreds of "ventilators" (i.e., medical students, technicians, volunteers, and others) to save many lives. (Lassen HCA. A preliminary report on the 1952 epidemic of poliomyelitis in Copenhagen with special reference to the treatment of acute respiratory insufficiency. *Lancet.* 1953;1:37–41.)

Her condition improved immediately.[150] Eventually, arterial blood-gas levels confirmed Ibsen's suspicions about respiratory acidosis as the cause of death in the previous patients, and positive-pressure ventilation proved successful in substantially reducing the mortality rates from paralytic polio. The only drawback was the equipment available (Fig. 1-39). Only bag ventilation was possible. During the remainder of the epidemic, it is estimated that 1500 medical and dental students worked around the clock providing bag ventilation by hand to help support these patients.[160,161]

The Copenhagen experience provided the impetus for a revolution in the medical care of patients with respiratory failure. First, it confirmed the value of positive-pressure ventilation and demonstrated the need for practical mechanical ventilators. Second, by encouraging the grouping of acutely ill patients in certain sections of the hospital and the organization of intensive care for these patients, it led the way for the later development of intensive-care units.[160,161] Third, Ibsen realized that provisions had to be made for resuscitating acutely ill patients in small outlying towns and transporting them to specialized centers.[162] Accordingly, mobile teams were formed with expertise in performing translaryngeal intubation and tracheotomy. After intubation and stabilization, patients could be transferred secondarily. This was obviously the precursor of our present emergency medical system.

OTHER DISEASES WITH INADEQUATE VENTILATION

Although the results using positive-pressure ventilation for the respiratory paralytic form of polio were remarkable, application of this technique to other medical problems was slow. Extensive work in pulmonary emphysema and chronic bronchitis had confirmed that in severe cases ventilatory failure was accompanied by high carbon dioxide levels and low oxygen levels. Supplemental oxygen alone seemed to worsen the situation.[163] Sporadic reports described the use of mechanical ventilation for treating this problem. Usually used were body respirators,[163–167] but occasionally either intermittent positive-pressure breathing via a pneumatic balance respirator[164] or hand ventilation[166,167] was used transiently. By 1961, Munck had collected a total of forty-two case reports describing some form of mechanical ventilation for exacerbations of chronic obstructive pulmonary disease (COPD) with successful outcomes in thirty-one.[168] Munck's group was the first to rely strictly on positive-pressure ventilation through a tracheotomy tube to treat patients with COPD in acute respiratory crises. Their methods emphasized reliance on monitoring arterial blood oxygen, carbon dioxide, and pH levels. The average duration of treatment in their series was 24 days. They emphasized that mechanical ventilation provides a fair chance of "tiding patients with diffuse chronic lung disease over an episode of life-threatening respiratory failure—and of obtaining a reasonable recovery," provided there is some historical evidence of pulmonary reserve.[168]

Many other groups throughout the 1960s and early 1970s found that positive-pressure ventilation through either a translaryngeal tube or tracheostomy was an effective method of managing acute exacerbations of COPD.[169–178] Conservative treatment, including the use of controlled levels of supplemental oxygen, antibiotics, bronchodilators, and respiratory stimulants, was useful for treating some patients with acute ventilatory failure complicating chronic lung disease,[179,180] but it was soon recognized that in severe cases with either coma or deteriorating arterial blood-gas values,

endotracheal intubation and mechanical ventilation provided the most appropriate alternative.[181]

In 1951, Nilsson recognized the value of translaryngeal intubation for controlling the airway in patients with barbiturate poisoning.[182] He later emphasized that artificial respiration via a mechanical ventilator is essential when barbiturate poisoning causes apnea or respiratory insufficiency.[183] Avoiding the potentially stigmatizing tracheotomy scar also was an important consideration in patients prone to depression. Bjork pioneered the use of positive-pressure respirator treatment in postoperative thoracic surgery patients. Initially, he was conservative in his approach and postponed tracheotomy until the patient was in severe respiratory failure. By the late 1950s, however, he was performing elective tracheotomy after pulmonary resections and cardiovascular surgery and providing "prophylactic" positive-pressure ventilation to prevent atelectasis and to minimize "heavy respiratory work." He believed that any patient with a small cardiopulmonary reserve, who could become exhausted rapidly following major surgery, would benefit from this approach.[184–187] As these principles were established in thoracic surgery, they were also applied to patients with, for example, crush injury of the chest, pulmonary edema, renal failure, tetanus, pneumonia, or peritonitis. The best results were obtained when respirator treatment was initiated early in the acute illness and not when chances for recovery were nil.[188]

Modern Respirators

Providing mechanical ventilation on a widespread basis could only be achieved with reliable respirators. Morch built the first clinically proven volume ventilator during World War II in Denmark for use in the operating room. Because of the war, pistons and cylinders for this ventilator were made from discarded sewer pipes.[64] As a direct result of the 1952 polio epidemic in Denmark, Bang constructed a mechanical respirator. Manual ventilation of patients with respiratory paralysis was possible in Copenhagen because of the availability of medical students. In Skive, where Bang practiced, medical students were not available, and Bang's respirator was a practical necessity. Fortunately, it worked.[189,190] The Engstrom respirator, built for the same reasons, proved to be hugely successful for managing poliomyelitis patients.[191] This volume-cycled respirator also was used by Bjork in his outstanding work in postoperative respiratory care. By 1954, a number of modern automatic respirators had been developed in Europe.[192] Morch was instrumental in bringing the concept of positive-pressure ventilation across the Atlantic to America.[64,193] The incorporation of this technique into standard medical practice apparently was slower in the United States than in Scandinavia.[64] Tank respirators still were used routinely in the United States until the 1960s,[194,195] although the benefits of endotracheal intubation and positive-pressure ventilation were slowly being appreciated.[194,196] Since the 1950s, an enormous number of practical ventilators have been introduced for everyday use. This was paralleled by a significant increase in the number of patients receiving mechanical ventilation in American hospitals throughout the 1960s. Pontoppidan found a fivefold increase in artificial respiration cases at the Massachusetts General Hospital between 1960 and 1968.[197]

Intensive Care

Organizing the "intensive care" that patients with ventilatory failure required was a substantial logistical problem. The Danes had congregated respiratory patients in special units. By the middle to late 1960s, widespread experience had accumulated with intensive care units specifically designed for managing patients requiring sophisticated respiratory care and mechanical ventilation.[198–202] By the 1970s, several centers reported impressive reductions in mortality rate through reliance on the intensive care unit approach.[203–205]

Adequacy of Ventilation

Until arterial blood-gas machines became available commercially, physicians had to rely on laborious and exacting methods of measuring blood oxygen and carbon dioxide levels. Astrup and others emphasized that measuring Pa_{O_2}, Pa_{CO_2}, and pH should be the ultimate goal for determining how well the respirator actually was ventilating the patient.[206,207] By 1957, it was realized that intermittent positive-pressure breathing was not always effective in reducing hypercapnia in emphysema. In fact, the more severe the obstructive lung disease, the less effective pressure-cycled respirators seemed to be in producing hyperventilation.[208] Conversely, pressure-cycled respirators easily could overventilate a patient and convert a dangerous acidosis into an equally dangerous alkalosis.[209] The issue of pulmonary encephalopathy secondary to hypercapnia was of serious concern to physicians,[210] as was the realization that mechanical ventilation could be followed by paradoxical central nervous system acidosis.[211,212]

Supplemental oxygen had been used to treat numerous medical ailments since Priestley and Scheele had identified "pure air" in the 1770s. By the beginning of the twentieth century, the physiologic benefits of oxygen therapy were better understood, and physicians became more interested in using oxygen specifically to treat respiratory disorders. The intravenous injection of oxygen was advocated by Tunnicliffe and Stebbing in 1916,[213] but attracted little interest. Haldane devised an apparatus for supplying controlled amounts of oxygen[214] that was used on soldiers exposed to suffocating gases during World War I. Because patients with pneumonia had low blood-oxygen levels, Meakins used the Haldane apparatus to treat hypoxic patients with pneumonia.[215] Stadie constructed and used

an oxygen chamber for treating pneumonia in 1922.[216,217] Barach administered oxygen through tents, nasal catheters, and mouth funnels in 1926.[218] Physicians believed that oxygen was useful in reducing the mortality rate in pneumonia but did not understand why it was effective.[219,220] The belief that oxygen treatment was beneficial unfortunately led to its indiscriminant use. It was not appreciated that supplemental oxygen given to a patient with COPD who had an acute ventilatory crisis with hypercapnia could result in paradoxic hypoventilation and worsened respiratory acidosis. Campbell played a leading role in recognizing this problem and devising a device, the venturi mask, for administering oxygen in a controlled fashion with a reduced risk of carbon dioxide retention.[221–223]

Just as oxygen use generally was believed to be beneficial for treating respiratory disorders, the use of oxygen was incorporated routinely into many early mechanical ventilators. This approach was justified in some cases because oxygen requirements to achieve adequate arterial oxygenation often were surprisingly high.[224] Mean inspired oxygen levels in the early respirators, however, could not be regulated accurately. Substantial and occasionally dangerous variations in inspired oxygen levels were found when ventilators were compared directly.[225–227] Nash and coworkers pointed out the potential gravity of this problem when they linked, for the first time in humans, diffuse alveolar damage (or the *respirator lung syndrome*) with the prolonged use of ventilators delivering a high inspired oxygen concentration.[228]

As an interesting aside, Frumin and coworkers found that insertion of an expiratory resistance increased arterial oxygen levels in anesthetized, paralyzed, artificially ventilated humans.[229] Manipulation of airway pressure by immersion of the exhalation limb from a tracheotomy tube 1 to 4 cm under water had been shown previously to improve ventilation in patients with multiple rib fractures.[230] These simple measures for increasing airway pressure, termed variously the *positive expiratory pressure plateau,*[231] *continuous positive airway pressure,*[232,233] and later, *positive end-expiratory pressure,* were to prove enormously successful in improving oxygenation in patients with both adult and infant respiratory distress syndromes.

Quality Control of Ventilators

As the need for ventilators, gas cylinders, connectors, oxygen-delivery masks, and myriad other types of respiratory equipment increased, the number of manufacturers producing this equipment proliferated. Quality control among manufacturers varied and manufacturers produced equipment of various size specifications, making integration of breathing circuits difficult. Anesthesiologists were particularly concerned with these problems because of the difficulties they had encountered in establishing universal color codes for anesthetic gas cylinders during World War II. Carbon dioxide cylinders in Britain were painted green, but U.S. oxygen cylinders also were painted green. Inevitably, when U.S. and British anesthesiologists worked together, cylinders were filled with the wrong gas and deaths occurred.[234–236]

The American Society for Anesthetists (ASA) organized a Committee on Standardization of Anesthetic and Resuscitating Equipment, charged with forging a consensus on manufacturing standards for this type of equipment. The ASA, in 1955, approved financial support for the American National Standards Committee Z79 on Anesthesia and Respiratory Equipment to operate under the umbrella of American National Standards Institute (ANSI). Members of this committee included representatives of various medical specialties and principal manufacturers of anesthesia and respiratory equipment. Committee Z79 effectively developed standards for a wide range of respiratory equipment. Under the Medical Device Amendments of 1976, the Food and Drug Administration (FDA) was charged with regulatory responsibility for the safety and efficacy of medical devices. The FDA had a significant impact on refining the standards established by Committee Z79. In 1983, the relationship between ANSI and Committee Z79 was terminated for financial and liability reasons. At that time, the ASA agreed to transfer this committee's sponsorship to the American Society for Testing Materials (ASTM). The committee's name was then changed to F29.[236]

Numerous problems are encountered with positive-pressure ventilation. Concern about accidental disconnections from the ventilator led to alarm systems being developed. Adequate humidification of the ventilator air supply had to be ensured.[192] The risk of nosocomial pneumonia was not understood initially. Vigilant attention to sterilization of respiratory equipment, proper suctioning technique, and minimization of stagnant water in tubing and humidification sources was advised to reduce the risk of "ventilator lung."[198] There was considerable debate for decades over whether translaryngeal intubation was preferred over tracheotomy for patients requiring prolonged mechanical ventilation. Although this subject is still controversial, a consensus conference in 1986 recommended translaryngeal intubation as the preferred initial choice for obtaining airway control in most patients needing artificial respiration. Secondary tracheotomy could be deferred for up to 20 days or longer depending on the individual situation.[237]

Weaning

An intriguing problem developed as the use of positive-pressure ventilation became more widespread. Once patients were placed on a mechanical ventilator, how were they to be "weaned" eventually from such respiratory support? This question actually had two components: How could the physician determine when a patient was ready to be weaned? What methods could be used to facilitate the weaning process? Numerous criteria have been advocated as reasonable indicators that patients are weaning

candidates.[238–240] Similarly, numerous techniques have been proposed as useful modalities for maximizing the chances for a successful weaning process. Modifications of ventilator technology in the 1970s led to the proposal of such methods as intermittent mandatory ventilation[241,242] and mandatory minute volume[243] as alternatives to the standard T-piece method of weaning.[244–246] Although many physicians express strong preferences for one weaning modality over another,[247] it has never been shown clearly that modalities such as intermittent mandatory ventilation hasten the weaning process.[248,249] Whether more recently introduced technological advances in ventilator techniques, such as pressure-support and pressure-control ventilation, will improve the weaning process is unclear.

CONCLUSION

A rich and complex weave of discoveries in many different scientific and technical areas has brought us to the early 1990s, a time during which physicians have been trained to rely routinely on mechanical ventilation for managing all manner of acute, serious illnesses. Only 40 years ago, cadres of medical and dental students manually ventilated polio patients with respiratory paralysis, and at the turn of the twentieth century, a foot-operated bellows for mechanical ventilation was a remarkable innovation. In the late eighteenth century, the concept of using a bellows and translaryngeal tube for resuscitating the apparently drowned was just being introduced, and in the sixteenth century, Vesalius was forced to make a pilgrimage to the Holy Land to atone for the sin of restarting a Spanish nobleman's heart by inflating his lungs. The debt we owe to the many pioneers who have contributed to the advances in the field of mechanical ventilation is humbling, just as the hope for future unforeseeable developments in this field is enthralling.

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II

PHYSICAL BASIS OF MECHANICAL VENTILATION

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2

CLASSIFICATION OF MECHANICAL VENTILATORS AND MODES OF VENTILATION

Robert L. Chatburn

A good ventilator classification scheme describes how ventilators work in general terms, but with enough detail so that one particular model can be distinguished from others. It facilitates description by focusing on key attributes in a logical and consistent manner. A clear description allows us to quickly assess new facts in relation to our previous knowledge. Learning the operation of a new ventilator or describing it to others then becomes much easier. Understanding how the ventilator operates, we can then anticipate appropriate ventilator management strategies for particular clinical situations. The classification system described in this chapter is based on previously published work.[1–7]

A ventilator is simply a machine, a system of related elements designed to alter, transmit, and direct energy in a predetermined manner to perform useful work. We put energy into the ventilator in the form of electricity (energy = volts × amps × time) or compressed gas (energy = pressure × volume). That energy is transmitted or transformed (by the ventilator's drive mechanism) in a predetermined manner (by the control circuit) to augment or replace the patient's muscles in performing the work of breathing. Thus to understand mechanical ventilators in general, we must first understand their basic functions: (a) power input, (b) power transmission or conversion, (c) control scheme, and (d) output. This simple format can be expanded to add as much detail as desired (Table 2-1).

A discussion of input power sources and power conversion and transmission is beyond the scope of this chapter; these topics have been treated elsewhere.[7,8] The chapter does, however, explore in detail control schemes and ventilator modes because these directly affect patient management.

CONTROL SYSTEM

Models of Patient–Ventilator Interaction

To understand how a machine can be controlled to replace or supplement the natural function of breathing, we need to first understand something about the mechanics of breathing itself. The study of mechanics deals with forces, displacements, and the rate of change of displacement. In physiology, force is measured as pressure (pressure = force/area), displacement as volume (volume = area × displacement), and the relevant rate of change as flow [average flow = Δvolume/Δtime; instantaneous flow ($\dot{V}$) = dv/dt, the derivative of volume with respect to time]. Specifically, we are interested in the *pressure* necessary to cause a *flow* of gas to enter the airway and increase the *volume* of the lungs.

The study of respiratory mechanics is essentially the search for simple but useful models of respiratory system mechanical behavior. Figure 2-1 illustrates the process by which the respiratory system is represented first by a graphical model, and then by a mathematical model based on the graphical model. Pressure, volume, and flow are measurable

TABLE 2-1: OUTLINE OF VENTILATOR CLASSIFICATION SYSTEM

I. Input
  A. Pneumatic
  B. Electri
    1. AC
    2. DC (battery)

II. Power conversion and transmission
  A. External compressor
  B. Internal compressor
  C. Output control valves

III. Control scheme
  A. Control circuit
    1. Mechanical
    2. Pneumatic
    3. Fluidic
    4. Electric
    5. Electronic
  B. Control variables
    1. Pressure
    2. Volume
    3. Time
  C. Phase variables
    1. Trigger
    2. Target
    3. Cycle
    4. Baseline
  D. Modes of ventilation
    1. Control variable
    2. Breath sequence
    3. Targeting schemes

IV. Output
  A. Pressure waveforms
    1. Rectangular
    2. Exponential
    3. Sinusoidal
    4. Oscillating
  B. Volume waveforms
    1. Ascending ramp
    2. Sinusoidal
  C. Flow waveforms
    1. Rectangular
    2. Ascending ramp
    3. Descending ramp
    4. Sinusoidal

V. Alarms
  A. Input power alarms
    1. Loss of electric power
    2. Loss of pneumatic power
  B. Control circuit alarms
    1. General systems failure
    2. Incompatible ventilator settings
    3. Warnings (e.g., inverse inspiratory-to-expiratory timing ratio)
  C. Output alarms (high/low conditions)
    1. Pressure
    2. Volume
    3. Flow
    4. Time
      a. Frequency
      b. Inspiratory time
      c. Expiratory time
    5. Inspired gas
      a. Temperature
      b. FI_{O_2}

variables in the mathematical model that change with time over the course of one inspiration and expiration. The relation among them is described by the *equation of motion for the respiratory system.*[9] The derivation of this equation stems from a force-balance equation that is an expression of Newton's third law of motion (for every action, there is an equal and opposite reaction):

$$P_{TR} = P_E + P_R \quad (1)$$

where P_{TR} is the transrespiratory pressure (i.e., pressure at the airway opening minus pressure at the body surface), P_E is the pressure caused by elastic recoil (elastic load), and P_R is the pressure caused by flow resistance (resistive load).

Transrespiratory pressure can have two components, one generated by the ventilator (P_{vent}) and one generated by the respiratory muscles (P_{mus}). Elastic recoil pressure is the product of elastance (E = Δpressure/Δvolume) and volume. Resistive pressure is the product of resistance (R = Δpressure/Δflow) and flow. Thus, Eq. (1) can be expanded to yield the following equation for inspiration:

$$P_{vent} + P_{mus} = EV + R\dot{V} \quad (2)$$

The combined ventilator and muscle pressure causes volume and flow to be delivered to the patient. (Of course, muscle pressure may subtract rather than add to ventilator pressure in the case of patient–ventilator dyssynchrony, in which case both volume and flow delivery are reduced.) Pressure, volume, and flow are functions of time and are called *variables.* They are all measured relative to their values at end-expiration. Elastance and resistance are assumed to remain constant and are called *parameters.*

For passive expiration, both ventilator and muscle pressure are absent, so Eq. (2) becomes

$$-R\dot{V} = EV \quad (3)$$

The negative sign on the left side of the equation indicates flow in the expiratory direction. This equation also shows that passive expiratory flow is generated by the energy stored in the elastic compartment (i.e., lungs and chest wall) during inspiration.

Equation (2) shows that if the patient's respiratory muscles are not functioning, muscle pressure is zero, and the ventilator must generate all the pressure for inspiration. On the other hand, a ventilator is not needed for normal spontaneous breathing (i.e., vent pressure = 0). Between those two extremes, an infinite number of combinations of muscle pressure (i.e., patient effort) and ventilator pressure are possible under the general heading of "partial ventilator support." The equation of motion also gives the basis for defining an *assisted* breath as one for which ventilator pressure rises above baseline during inspiration or falls below baseline during expiration.

Control Variables

In the equation of motion, the mathematical form of any of the three variables (i.e., pressure, volume, or flow as functions of time) can be predetermined, making it the independent variable and making the other two the dependent variables. We now have a theoretical basis for classifying ventilators as pressure, volume, or flow controllers. Thus, during pressure-controlled ventilation, pressure is the independent variable and may take the form of, say, a step function (i.e., a rectangular pressure waveform). The shapes of the volume and flow waveforms for a passive respiratory system (P_{mus} = 0) then depends on the shape of the pressure waveform as well as the parameters of resistance and compliance. On the other hand, during volume-controlled ventilation, we can specify the shape of the volume waveform making flow-dependent and pressure-dependent variables. The same reasoning applies to a flow controller. Notable exceptions are interpulmonary percussive ventilation, and high-frequency

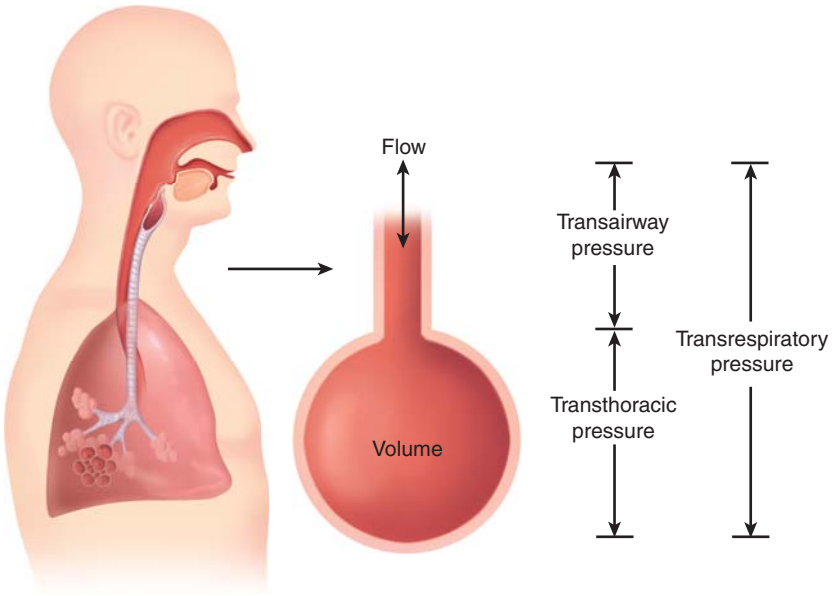

FIGURE 2-1 The respiratory system is often modeled as a single flow resistance (representing the endotracheal tube and the airways) connected to an elastic chamber (representing the lungs and chest wall). Flow through the airways is generated by transairway pressure (pressure at the airway opening minus pressure in the lungs). Expansion of the elastic chamber is generated by transthoracic pressure (pressure in the lungs minus pressure on the body surface). Transrespiratory pressure (pressure at the airway opening minus pressure on the body surface) is the sum of these two pressures and is the total pressure required to generate inspiration. The "airway-pressure" gauge on a positive-pressure ventilator displays transrespiratory pressure.

oscillatory ventilation, both of which control only the duration of flow pulses; the resulting airway pressure pulses along with actual inspiratory flows and volumes depend on the instantaneous values of respiratory system impedance. Because neither pressure, volume, nor flow in the equation of motion are predetermined, we would classify this type of device as a "time controller."

It follows from the preceding discussion that any conceivable ventilator can control only one variable at a time: pressure, volume, or flow. Because volume and flow are inverse functions of one another, we can simplify our discussion and consider only pressure and volume as *control variables*. I discuss later in "Modes of Ventilation" exactly how ventilator control systems work. We will see that it is possible for a ventilator to switch quickly from one control variable to another, not only from breath to breath, but even during a single inspiration.

Phase Variables

Because breathing is a periodic event, the ventilator must be able to control a number of variables during the respiratory cycle (i.e., the time from the beginning of one breath to the beginning of the next). Mushin et al[10] proposed that this time span be divided into four phases: the change from expiration to inspiration, inspiration, the change from inspiration to expiration, and expiration. This convention is useful for examining how a ventilator starts, sustains, and stops an inspiration and what it does between inspirations. A particular variable is measured and used to start, sustain, and end each phase. In this context, pressure, volume, flow, and time are referred to as *phase variables*.[11] Figure 2-2 shows the criteria for determining phase variables.

Trigger Variable

All ventilators measure one or more variables associated with the equation of motion (i.e., pressure, volume, flow, or time). Inspiration is started when one of these variables reaches a preset value. Thus, the variable of interest is considered an initiating, or *trigger*, variable. Time is a trigger variable when the ventilator starts a breath according to a set frequency independent of the patient's spontaneous efforts. Pressure is the trigger variable when the ventilator senses a drop in baseline pressure caused by the patient's inspiratory effort and begins a breath independent of the set frequency. Flow or volume are the trigger variables when the ventilator senses the patient's inspiratory effort in the form of either flow of volume into the lungs.

Flow triggering reduces the work the patient must perform to start inspiration.[12] This is so because work is proportional to the volume the patient inspires times the change in baseline pressure necessary to trigger. Pressure triggering requires some pressure change and hence an irreducible amount of work to trigger. With flow or volume triggering, however, baseline pressure need not change, and theoretically, the patient need do no work on the ventilator to trigger.

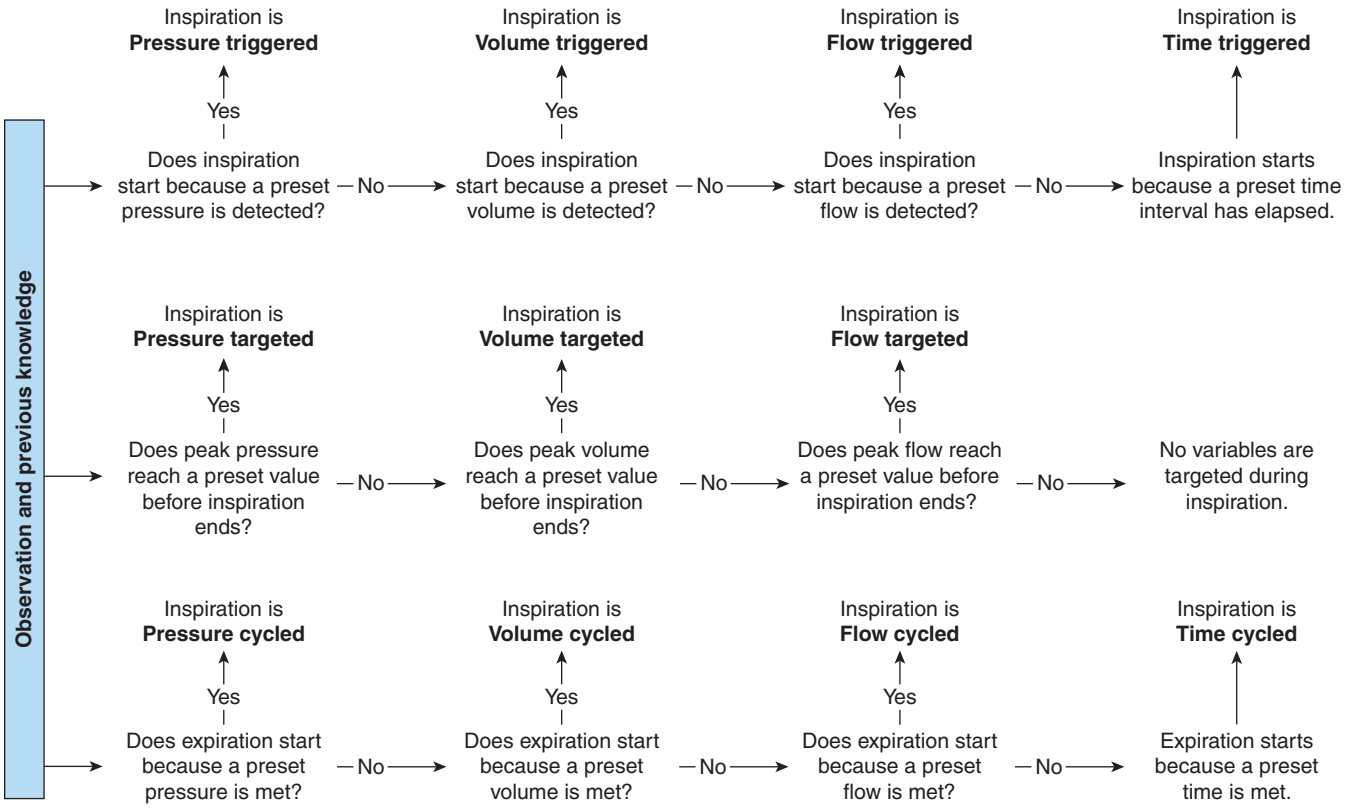

FIGURE 2-2 Criteria for determining the phase variables during a ventilator-assisted breath.

The patient effort required to trigger inspiration is determined by the ventilator's *sensitivity* setting. Some ventilators indicate sensitivity qualitatively ("min" or "max"). Alternatively, a ventilator may specify a trigger threshold quantitatively (e.g., 5 cm H_2O below baseline). Once the trigger variable signals the start of inspiration, there is always a short delay before flow to the patient starts. This delay is called the *response time* and is secondary to the signal-processing time and the mechanical inertia of the drive mechanisms. It is important for the ventilator to have a short response time to maintain optimal synchrony with patient inspiratory effort.

Target Variable

Here *target* means restricting the magnitude of a variable during inspiration. A *target variable* is one that can reach and maintain a preset level *before* inspiration ends (i.e., it does not end inspiration). Pressure, flow, or volume can be target variables and actually all can be active for a single breath (e.g., using the P_{max} feature on a Dräger ventilator). Note that time cannot be a target variable because specifying an inspiratory time would cause inspiration to end, violating the preceding definition. Astute readers may notice that in the past I have used the term *limit* where here I have used *target.* This was done to be consistent with the International Standards Organization's use of the term *limit* as applying to alarm situations only.

Clinicians often confuse target variables with cycle variables. To *cycle* means "to end inspiration." A cycle variable always ends inspiration. A target variable does not terminate inspiration; it only sets an upper bound for pressure, volume, or flow (Fig. 2-3).

Cycle Variable

The inspiratory phase always ends when some variable reaches a preset value. The variable that is measured and used to end inspiration is called the *cycle variable.* The cycle variable can be pressure, volume, flow, or time. Manual cycling is also available on some ventilators.

When a ventilator is set to pressure cycle, it delivers flow until a preset pressure is reached, at which time inspiratory flow stops and expiratory flow begins. The most common application of pressure cycling on mechanical ventilators is for alarm settings.

When a ventilator is set to volume cycle, it delivers flow until a preset volume has passed through the control valve. By definition, as soon as the set volume is met, inspiratory flow stops and expiratory flow begins. If expiration does not begin immediately after inspiratory flow stops, then an inspiratory hold has been set, and the ventilator is, by definition,

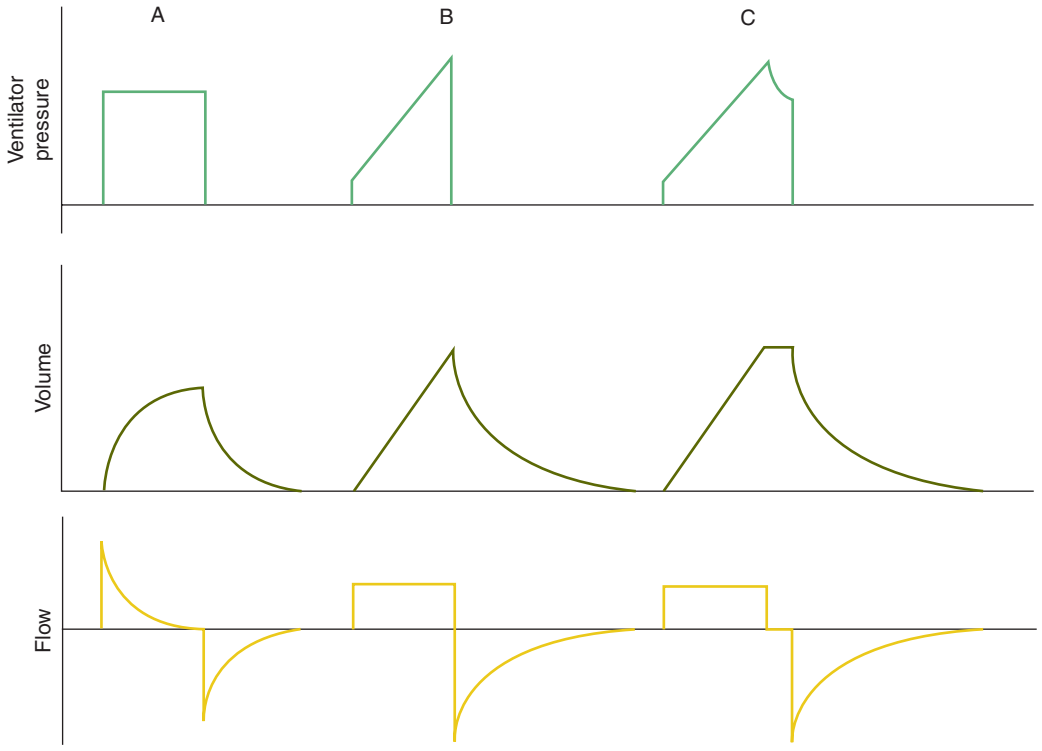

FIGURE 2-3 This figure illustrates the distinction between the terms *target* and *cycle.* **A.** Inspiration is pressure-targeted and time-cycled. **B.** Flow is targeted, but volume is not, and inspiration is volume-cycled. **C.** Both volume and flow are targeted, and inspiration is time-cycled. (Reproduced, with permission, from Chatburn.[6])

time cycled (see Fig. 2-3). Note that the volume that passes through the ventilator's output control valve is never exactly equal to the volume delivered to the patient because of the volume compressed in the patient circuit. Some ventilators use a sensor at the Y-connector (such as the Dräger Evita 4 with the neonatal circuit) for more accurate tidal volume measurement. Others measure volume at some point inside the ventilator, and the operator must know whether the ventilator compensates for compressed gas in its tidal volume readout.

When a ventilator is set to flow cycle, it delivers flow until a preset level is met. Flow then stops, and expiration begins. The most frequent application of flow cycling is in the pressure-support mode. In this mode, the control variable is pressure, and the ventilator provides the flow necessary to meet the inspiratory pressure target. In doing so, flow starts out at a relatively high value and decays exponentially (assuming that the patient's respiratory muscles are inactive after triggering). Once flow has decreased to a relatively low value (such as 25% of peak flow, typically preset by the manufacturer), inspiration is cycled off. Manufacturers often set the cycle threshold slightly above zero flow to prevent inspiratory times from getting so long that patient synchrony is degraded. On some ventilators, the flow-cycle threshold may be adjusted by the operator to improve patient synchrony. Increasing the flow-cycle threshold decreases inspiratory time and vice versa.

Time cycling means that expiratory flow starts because a preset inspiratory time interval has elapsed.

Baseline Variable

The baseline variable is the parameter controlled during expiration. Although pressure, volume, or flow could serve as the baseline variable, pressure control is the most practical and is implemented by all modern ventilators. Baseline or expiratory pressure is always measured and set relative to atmospheric pressure. Thus, when we want baseline pressure to equal atmospheric pressure, we set it to zero. When we want baseline pressure to exceed atmospheric pressure, we set a positive value, called *positive end-expiratory pressure* (PEEP).

MODES OF VENTILATION

The general goals of mechanical ventilation are to promote safety, comfort, and liberation (Table 2-2).[1] Specific objectives under these goals include ensuring adequate gas exchange, avoiding ventilator induced lung injury, optimizing patient-ventilator synchrony, and minimizing the duration of ventilation. The preset pattern of patient-ventilator interaction designed to achieve these objectives is referred to as a *mode* of ventilation. Specifically, a mode can be classified according to the outline in Table 2-3.[2]

TABLE 2-2: GOALS AND OBJECTIVES OF MECHANICAL VENTILATION

1. Promote safety
   a. Optimize ventilation–perfusion of the lung
      i. Maximize alveolar ventilation
      ii. Minimize shunt
   b. Optimize pressure–volume curve
      i. Minimize tidal volume
      ii. Maximize compliance
2. Promote comfort
   a. Optimize patient–ventilator synchrony
      i. Maximize trigger–cycle synchrony
      ii. Minimize auto-PEEP
      iii. Maximize flow synchrony
      iv. Coordinate mandatory and spontaneous breaths
   b. Optimize work demand versus work delivered
      i. Minimize inappropriate shifting of work from ventilator to patient
3. Promote liberation
   a. Optimize the weaning experience
      i. Minimize adverse events
      ii. Minimize duration of ventilation

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TABLE 2-3: OUTLINE OF MODE CLASSIFICATION SYSTEM

1. Primary control variable
   a. Pressure
   b. Volume
2. Breath sequence
   a. Continuous mandatory ventilation (CMV)
   b. Intermittent mandatory ventilation (IMV)
   c. Continuous spontaneous ventilation (CSV)
3. Primary targeting scheme
   a. Set-point
   b. Dual
   c. Servo
   d. Adaptive
   e. Optimal
   f. Intelligent
4. Secondary targeting scheme
   a. Set-point
   b. Servo
   c. Adaptive
   d. Optimal
   e. Intelligent

Control Variable

I have already mentioned that pressure, volume, or flow can be controlled during inspiration. When discussing modes I will refer to inspiration as being pressure-controlled or volume-controlled. Ignoring flow control is justified because when the ventilator controls volume directly (i.e., using a volume-feedback signal), flow is controlled indirectly, and vice versa (i.e., mathematically, volume is the integral of flow, and flow is the derivative of volume).

There are clinical advantages and disadvantages to volume and pressure control. To keep within the scope of this chapter, we can just say that volume control results in a more stable minute ventilation (and hence more stable blood gases) than pressure control if lung mechanics are unstable. On the other hand, pressure control allows better synchronization with the patient because inspiratory flow is not constrained to a preset value. Although the ventilator must control only one variable at a time during inspiration, it is possible to begin a breath-in pressure control and (if certain criteria are met) switch to volume control or vice versa (referred to as dual targeting, described in "Targeting Schemes" below).

Breath Sequence

The *breath sequence* is the pattern of mandatory or spontaneous breaths that the mode delivers. A *breath* is a positive airway flow (inspiration) relative to baseline, and it is paired (by size) with a negative airway flow (expiration), both associated with ventilation of the lungs. This definition excludes flow changes caused by hiccups or cardiogenic oscillations. It allows, however, the superimposition of, for example, a spontaneous breath on a mandatory breath or vice versa. The flows are paired by size, not necessarily by timing. In airway pressure-release ventilation, for example, there is a large inspiration (transition from low pressure to high pressure) possibly followed by a few small inspirations and expirations, followed finally by a large expiration (transition from high pressure to low pressure). These comprise several small spontaneous breaths superimposed on one large mandatory breath. During high-frequency oscillatory ventilation, in contrast, small mandatory breaths are superimposed on larger spontaneous breaths.

A *spontaneous breath,* in the context of mechanical ventilation, is a breath for which the patient determines both the timing and the size. The start and end of inspiration may be determined by the patient, independent of any machine settings for inspiratory time and expiratory time. That is, the patient both triggers and cycles the breath. On some ventilators, the patient may make short, small spontaneous efforts during a longer, larger mandatory breath, as in the case of *airway pressure-release ventilation.* It is important to make a distinction between spontaneous breaths and assisted breaths. An *assisted breath* is one for which the ventilator does some work for the patient, as indicated by an increase in airway pressure (i.e., P_{vent}) above baseline during inspiration or below baseline during expiration. For example, in the *pressure-support mode,* each breath is assisted because airway pressures rise to the *pressure-support* setting above PEEP (i.e., $P_{vent} > 0$). Each breath is also spontaneous because the patient both triggers and cycles the breath. The patient may cycle the breath in the *pressure-support* mode by actively exhaling, but

even if the patient is passive at end-inspiration, the patient's resistance and compliance determine the cycle point and thus the size of the breath for a given *pressure-support* setting. In contrast, for a patient on continuous positive airway pressure, each breath is spontaneous but unassisted. Breaths are spontaneous because the patient determines the timing and size of the breaths without any interference by the ventilator. Breaths during continuous positive airway pressure are not assisted because airway pressure is controlled by the ventilator to be as constant as possible (i.e., $P_{vent} = 0$). Understanding the difference between assisted and unassisted spontaneous breaths is very important clinically. When making measurements of tidal volume and respiratory rate for calculation of the rapid-shallow breathing index, for example, the breaths must be *spontaneous* and *unassisted.* If they are assisted (e.g., with pressure support), an error of 25% to 50% may be introduced.

A *mandatory breath* is any breath that does not meet the criteria of a spontaneous breath, meaning that the patient has lost control over the timing and/or size. Thus, a mandatory breath is one for which the start or end of inspiration (or both) is determined by the ventilator, independent of the patient; that is, the machine triggers and/or cycles the breath. It is possible to superimpose a short mandatory breath on top of a longer spontaneous breath, as in the case of high-frequency oscillatory ventilation.

Having defined spontaneous and mandatory breaths, there are three possible breath sequences, designated as follows:

- *Continuous spontaneous ventilation (CSV).* All breaths are spontaneous.
- *Intermittent mandatory ventilation (IMV).* Spontaneous breaths are permitted between mandatory breaths. When the mandatory breath is triggered by the patient, it is commonly referred to as *synchronized IMV.* Because the trigger variable can be specified in the description of phase variables, I will use IMV instead of synchronized IMV to designate general breath sequences.
- *Continuous mandatory ventilation (CMV).* Spontaneous breaths are not permitted between mandatory breaths, as the intent is to provide a mandatory breath for every patient inspiratory effort. CMV originally meant that every breath was mandatory. The development of the "active exhalation valve," however, made it possible for the patient to breathe spontaneously during a mandatory pressure-controlled breath on some ventilators. In fact, it was always possible for the patient to breathe spontaneously during pressure-controlled mandatory breaths on infant ventilators. *The key distinction between CMV and IMV is that with CMV, the ventilator attempts to deliver a mandatory breath every time the patient makes an inspiratory effort* (unless a mandatory breath is already in progress). This means that during CMV, if the operator decreases the ventilator rate, the level of ventilator support is unaffected as long as the patient continues making inspiratory efforts. With IMV, the rate setting directly affects the number of mandatory breaths and hence the level of ventilator support. Thus, CMV is normally viewed as a method of "full ventilator support," whereas IMV is usually viewed as a method of partial ventilator support. Of course, actual "full ventilatory support" can only be achieved if the patient is making no inspiratory efforts, for example, is paralyzed, but the term is often used loosely to mean supplying as much support as possible for a given patient condition.

Given the two ways to control inspiration (i.e., pressure and volume) and the three breath sequences (i.e., CMV, IMV, or CSV), there are five possible breathing patterns; volume control (VC)-CMV, VC-IMV, pressure control (PC)-CMV, PC-IMV, PC-CSV (see Table 2-2). VC-CSV is not possible because volume control implies that inspiration ends after a preset tidal volume is delivered, hence violating the patient cycling criterion of a spontaneous breath.

Targeting Schemes

Targeting schemes are feedback control systems used by mechanical ventilators to deliver specific ventilatory patterns.[1] The targeting scheme is a key component of a mode classification system. Before we can describe specific targeting schemes used by ventilators, we must first appreciate the basic concepts of engineering control theory.

The term *closed-loop control* refers to the use of a feedback signal to adjust the output of a system. Ventilators use closed-loop control to maintain consistent pressure and flow waveforms in the face of changing patient/system conditions. This is accomplished by using the output as a feedback signal that is compared to the operator-set input. The difference between the two is used to drive the system toward the desired output. For example, pressure-control modes use airway pressure as the feedback signal to control gas flow from the ventilator. Figure 2-4 is a schematic of a general

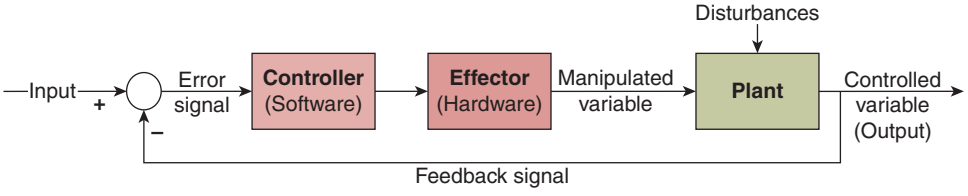


FIGURE 2-4 Generalized control circuit (see text for explanation). The "plant" in a control circuit for mechanical ventilation is the patient. (Reproduced with permission from Chatburn RL. Mireles-Cabodevila E, Closed loop control of mechanical ventilation. *Respir Care.* 2011;56(1): 85–98.)

control system. The input is a reference value (e.g., operator preset inspiratory pressure) that is compared to the actual output value (e.g., instantaneous value of airway pressure). The difference between those two values is the error signal. The error signal is passed to the controller (e.g., the software control algorithm). The controller converts the error signal into a signal that can drive the effector (e.g., the hardware) to cause a change in the manipulated variable (e.g., inspiratory flow). The relationship between the input and the output of the controller is called the transfer function in control theory. Engineers need to understand the transfer function in terms of complex mathematical equations. Clinicians, however, need only understand the general operation of the function in terms of how the mode affects the patient's ventilatory pattern, and we will use that frame of reference in defining targeting schemes. The "plant" in Figure 2-4 refers to the process under control. In our case, the plant is the patient and the delivery circuit connecting the patient to the ventilator. The plant is the source of the "noise" that causes problems with patient–ventilator synchrony. At one extreme, a paralyzed patient and an intact delivery circuit pose little challenge for a modern ventilator to deliver a predetermined ventilatory pattern, and thus synchrony is not an issue. At the opposite extreme is a patient with an intense, erratic respiratory drive and a delivery circuit with leaks (e.g., around an uncuffed endotracheal tube) making patient–ventilator synchrony virtually impossible. The challenge for both clinicians and engineers is to develop technology and procedures for dealing with this wide range of circumstances.

The plant alters the manipulated variable to generate the feedback signal of interest as the control (output) variable. Continuing with the example above, the manipulated variable is flow, but the feedback control variable is pressure (i.e., ventilator flow times plant impedance equals airway pressure), as in pressure-control modes.

Closed-loop control can also refer to the use of feedback signals to control the overall pattern of ventilation, beyond a single breath, such as the use of end-tidal carbon dioxide tension as a feedback signal to control minute ventilation.

The process of "setting" or adjusting a ventilation mode can be thought of as presetting various target values, such as tidal volume, inspiratory flow, inspiratory pressure, inspiratory time, frequency, PEEP, oxygen concentration, and end-tidal carbon dioxide concentration. The term *target* is used for two reasons. First, just like in archery, a target is aimed at but not necessarily hit, depending on the precision of the control system. An example is setting a target value for tidal volume and allowing the ventilator to adjust the inspiratory pressure over several breaths to finally deliver the desired value. In this case, we could more accurately talk about delivering an average target tidal volume over time.

The second reason for using *target* is because the term *control* is overused and we need it to preserve some fundamental conventions regarding modes such as *volume control* versus *pressure control.* From this use of the term *target,* we can logically refer to the control system transfer function (relationship between the input and the output of the controller) as a targeting scheme. The history of these schemes clearly shows an evolutionary trend toward increasing levels of automation. In fact, we can identify three groups of targeting schemes based on increasing levels of autonomy: manual, servo, and automatic. Manual targeting schemes require the operator to adjust all the target values. Servo targeting schemes are unique in that there are no static target values; rather, the operator sets the parameters of a mathematical model that drives the ventilator's output to follow a dynamic signal (like power steering on an automobile). Automatic targeting schemes enable the ventilator to set some or all of the ventilatory targets, using either mathematical models of physiologic processes or artificial-intelligence algorithms.

The basic concept of closed-loop control has evolved into at least six different ventilator targeting schemes (set-point, dual, servo, adaptive, optimal, and intelligent). These targeting schemes are the foundation that makes possible several dozen apparently different modes of ventilation. Once we understand how these control types work, many of the apparent differences are seen to be similarities. We then avoid a lot of the confusion surrounding ventilator marketing hype and begin to appreciate the true clinical capabilities of different ventilators.

SET-POINT

In set-point targeting, the operator sets specific target values and the ventilator attempts to deliver them (Fig. 2-5). The simplest examples for volume-control modes are tidal volume and inspiratory flow. For pressure-control modes, the operator may set inspiratory pressure and inspiratory time or cycle threshold.

DUAL

As it relates to mechanical ventilation, volume control means that inspired volume, as a function of time, is predetermined by the operator before the breath begins. In contrast, pressure control means that inspiratory pressure as a function of time is predetermined. "Predetermined" in this sense means that either pressure or volume is constrained to a specific mathematical form. In the simple case where either pressure or flow are preset constant values (e.g., set-point targeting, as explained above), we can say that they are the independent

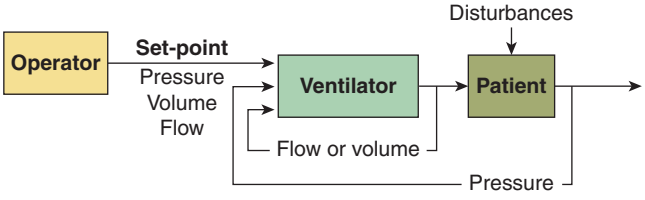


FIGURE 2-5 Set-point targeting. (Reproduced, with permission, from Chatburn RL. Computer control of mechanical ventilation. *Respir Care.* 2004;49:507–515.)

variables in the equation of motion. The equation of motion for the respiratory system is a general mathematical model of patient–ventilator interaction:

$$P(t) = EV(t) + R\dot{V}(t) \quad (4)$$

where $P(t)$ is inspiratory pressure as a function of time (t), E is respiratory-system elastance, $V(t)$ is volume as a function of time, R is respiratory-system resistance, and $\dot{V}$ is flow as a function of time. Thus, for example, if pressure is the independent variable, then both volume and flow are dependent variables, indicating pressure control. If volume is the independent variable, then pressure is the dependent variable, indicating volume control. Because volume is the integral of flow, if $\dot{V}$ is predetermined, then so is $V(t)$. Therefore, for simplicity, we include the case of flow being the independent variable as a form of volume control.

Only one variable (i.e., pressure or volume) can be independent at any moment, but a ventilator controller can switch between the two during a single inspiration. When this happens, the targeting scheme is called dual set-point control or dual targeting. There are two basic ways that ventilators have implemented dual targeting. One way is to start inspiration in volume control and then switch to pressure control if one or more preset thresholds are met (e.g., a desired peak airway pressure target). An example of such a threshold is the operator-set P_{max} in volume control on the Dräger Evita XL ventilator. The other form of dual targeting is to start inspiration in pressure control and then switch to volume control (e.g., if a preset tidal volume has not been met when flow decays to a preset value). This was originally described as "volume-assured pressure-support ventilation,"[13] but is currently only available as a mode called "Volume Control Assist Control with Machine Volume" in the CareFusion Avea ventilator.

Dual targeting is an attempt to improve the synchrony between patient and ventilator. This can be seen in the equation of motion if a term representing the patient inspiratory force (muscle pressure or P_{mus}) is added:

$$P(t) = EV(t) + RV(t) - P_{mus}(t) \quad (5)$$

With set-point targeting in volume control modes, volume and flow are preset. Therefore, if the patient makes an inspiratory effort (i.e., $P_{mus}(t) > 0$), then the equation dictates that transrespiratory-system pressure, $P(t)$, must fall. Because work is the result of both pressure and volume delivery (i.e., work = $\int Pdv$), if pressure decreases, the work the ventilator does on the patient decreases and hence we have asynchrony of work demand on the part of the patient versus work output on the part of the ventilator.

With set-point pressure control, transrespiratory pressure is preset. Consequently, if the patient makes an inspiratory effort, both volume and flow increase. With constant pressure and increased volume, work per liter for the breath stays constant. Although this gives better work synchrony than does volume control, it is not ideal. Nevertheless, merging of volume and pressure control using a dual targeting scheme provides the safety of a guaranteed minimum tidal volume with the patient comfort of flow synchrony provided by pressure control.

SERVO

The term *servo* was coined by Joseph Farcot in 1873 to describe steam-powered steering systems. Later, hydraulic "servos" were used to position antiaircraft guns on warships. Servo control specifically refers to a control system that converts a small mechanical motion into one requiring much greater power, using a feedback mechanism. As such, it offers a substantial advantage in terms of creating ventilation modes capable of a high degree of synchrony with patient breathing efforts. That is, ventilator work output can be made to match patient work demand with a high degree of fidelity. We apply the name *servo control* to targeting schemes in which the ventilator's output automatically follows a varying input. This includes proportional-assist ventilation (PAV; Fig. 2-6),[14] automatic tube compensation (ATC),[15] and neurally adjusted ventilatory assist (NAVA),[16] in which the airway pressure signal not only follows but amplifies signals that are surrogates for patient effort (i.e., volume, flow, and diaphragmatic electrical signals). Note that the term *servo control* has been loosely used since it was coined to refer to any type of general feedback control mechanism, but I am using it in a very specific manner, as it applies to ventilator targeting schemes.

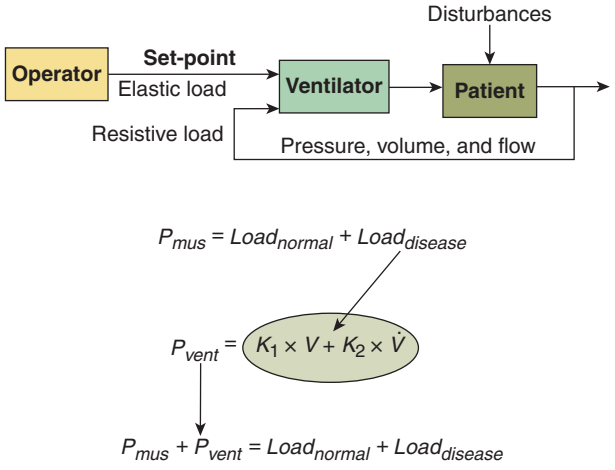


FIGURE 2-6 Servo targeting is the basis for the proportional-assist mode. In this mode, the operator sets targets for elastic and resistive unloading. The ventilator then delivers airway pressure in proportion to the patient's own inspiratory volume and flow. When the patient's muscles have to contend with an abnormal load secondary to disease, proportional assist allows the operator to set amplification factors (K_1 and K_2) on the feedback volume and flow signals. By amplifying volume and flow, the ventilator generates a pressure that supports the abnormal load, freeing the respiratory muscles to support only the normal load caused by the natural elastance and resistance of the respiratory system. (Reproduced, with permission, from Chatburn RL. Computer control of mechanical ventilation. *Respir Care.* 2004;49:507–515.)

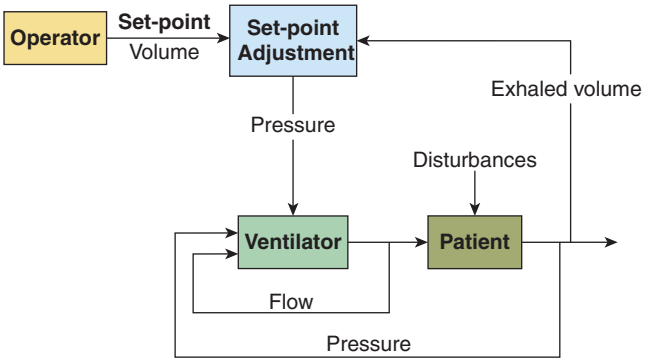


FIGURE 2-7 Adaptive targeting. Notice that the operator has stepped back from direct control of the within-breath parameters of pressure and flow. Examples of adaptive targeting are pressure-regulated volume control (PRVC) on the Siemens ventilator and autoflow on the Dräger Evita 4 ventilator. (Reproduced, with permission, from Chatburn RL. Computer control of mechanical ventilation. *Respir Care.* 2004;49: 507–515.)

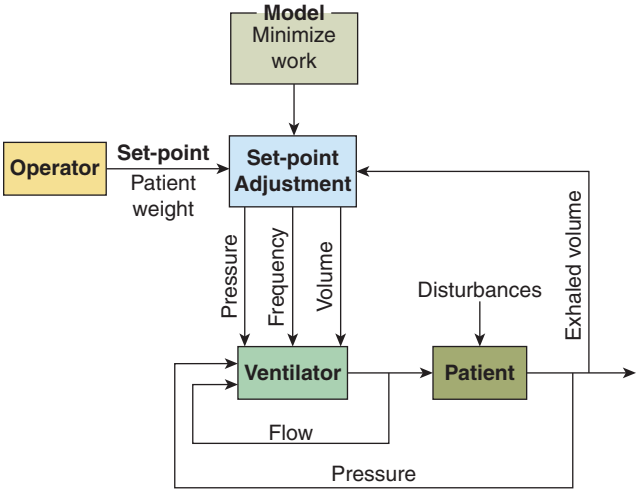


FIGURE 2-8 Optimal targeting. A static mathematical model is used to optimize some performance parameter, such as work of breathing. The only commercially available form of optimal targeting is the adaptive-support ventilation (ASV) mode on the Hamilton Galileo ventilator. (Reproduced, with permission, from Chatburn RL. Computer control of mechanical ventilation. *Respir Care.* 2004;49:507–515.)

ADAPTIVE

An adaptive targeting scheme involves modifying the function of the controller to cope with the fact that the system parameters being controlled are time varying. As it applies to mechanical ventilation, adaptive targeting schemes allow the ventilator to set some (or conceivably all) of the targets in response to varying patient conditions. Modern intensive care unit ventilators may use adaptive flow targeting as a more accurate way to deliver volume control modes than set-point targeting. For example, the Covidien PB 840 ventilator automatically adjusts inspiratory flow between breaths to compensate for volume compression in the patient circuit and thus achieving an average target tidal volume equal to the operator-set value.[17] Aside from this application of adaptive targeting, there are four distinct approaches to basic adaptive targeting, which are represented by the mode names *pressure-regulated volume control* (inspiratory pressure automatically adjusted to achieve an average tidal volume target, Fig. 2-7), *mandatory rate ventilation* (inspiratory pressure automatically adjusted to maintain a target spontaneous breath frequency), *adaptive flow/adaptive I-time* (inspiratory time and flow automatically adjusted to maintain a constant inspiratory time-to-expiratory time ratio of 1:2), and *mandatory minute ventilation* (automatic adjustment of mandatory breath frequency to maintain a target minute ventilation).

OPTIMAL

Optimal targeting is an advanced form of adaptive targeting.[18] Optimal targeting in this context means that the ventilator controller automatically adjusts the targets of the ventilatory pattern to either minimize or maximize some overall performance characteristic (Fig. 2-8). Adaptive-support ventilation (ASV) on the Hamilton ventilators is the only commercially available mode to date that uses optimal targeting. This targeting scheme was first described by Tehrani in 1991[20] and was designed to minimize the work rate of breathing, mimic natural breathing, stimulate spontaneous breathing, and reduce weaning time.[20] The operator inputs the patient's weight. From that, the ventilator estimates the required minute alveolar ventilation, assuming a normal dead space fraction. Next, an optimum frequency is calculated based on work by Otis et al[21] that predicts a frequency resulting in the least mechanical work rate:[20]

$$f = \frac{-1 + \sqrt{1 + 4\pi^2 RC_E \left(\frac{MV - fV_D}{V_D}\right)}}{2\pi^2 RC_E} \qquad (6)$$

where MV is predicted minute ventilation (L/min) based on patient weight and the setting for percent of predicted MV to support, V_D is predicted dead space (L) based on patient weight, RC_E is the expiratory time constant calculated as the slope of the expiratory flow volume curve and f is the computed optimal frequency (breaths/min). The target tidal volume is calculated as MV/f. The ASV controller uses the Otis equation to set the tidal volume (Fig. 2-8). As with simple adaptive pressure targeting, the inspiratory pressure within a breath is controlled to achieve a constant value and between breaths the inspiratory pressure is adjusted to achieve a target tidal volume. Unlike simple adaptive pressure targeting, however, the target is not set by the operator; instead, it is estimated by the ventilator in response to changes in respiratory-system mechanics and patient effort. Individual pressure-targeted breaths may be mandatory (time triggered and time cycled) or spontaneous (flow triggered and flow cycle).

ASV adds some expert rules that put safety limits on frequency and tidal volume delivery and reduce the risk of auto-PEEP. In that sense, this mode may be considered an intelligent targeting scheme, or more appropriately, a hybrid system (i.e., using a mathematical model and artificial intelligence).

INTELLIGENT

Intelligent targeting systems are another form of adaptive targeting schemes that use artificial-intelligence techniques.[22] The most convincing proof of the concept was presented by East et al,[23] who used a rule-based expert system for ventilator management in a large, multicenter, prospective, randomized trial. Although survival and length of stay were not different between human and computer management, computer control resulted in a significant reduction in multiorgan dysfunction and a lower incidence and severity of lung overdistension injury. The most important finding, however, was that *expert knowledge can be encoded and shared successfully with institutions that had no input into the model.* Note that the expert system did not control the ventilator directly, but rather made suggestions for the human operator. In theory, of course, the operator could be eliminated.

There is only one ventilator mode commercially available to date in the United States with a targeting scheme that relies entirely on a rule-based expert system (Fig. 2-9). That mode is SmartCare/PS on the Dräger Evita XL ventilator. This mode is a specialized form of pressure support that is designed for true (ventilator led) automatic weaning of patients. The SmartCare/PS controller uses predefined acceptable ranges for spontaneous breathing frequency, tidal volume, and end-tidal carbon dioxide tension to automatically adjust the inspiratory pressure to maintain the patient in a "respiratory zone of comfort."[23]

The SmartCare/PS system divides the control process into three steps. The first step is to stabilize the patient within the "zone of respiratory comfort" defined as combinations of tidal volume, respiratory frequency, and end tidal CO_2 values defined as acceptable by the artificial-intelligence program. There are different combinations depending on whether the patient has chronic obstructive pulmonary disease or a neuromuscular disorder. The second step is to progressively decrease the inspiratory pressure while making sure the patient remains in the "zone." The third step tests readiness for extubation by maintaining the patient at the lowest level of inspiratory pressure. The lowest level depends on the type of artificial airway (endotracheal tube vs. tracheostomy tube), the type of humidifier (heat and moisture exchanger vs. a heated humidifier), and the use of automatic tube compensation. Once the lowest level of inspiratory pressure is reached, a 1-hour observation period is started (i.e., a spontaneous breathing trial) during which the patient's breathing frequency, tidal volume, and end-tidal CO_2 are monitored. Upon successful completion of this step, a message on the screen suggests that the clinician "consider separation" of the patient from the ventilator. This method for automatic weaning reduces the duration of mechanical ventilation and intensive care unit length of stay in a multicenter randomized controlled trial.[24,25] The advantage of artificial intelligence, however, may be less noticeable in environments where natural intelligence is plentiful. Rose et al recently concluded that "Substantial reductions in weaning duration previously demonstrated were not confirmed when the SmartCare/PS system was compared to weaning managed by experienced critical care specialty nurses, using a 1:1 nurse-to-patient ratio. The effect of SmartCare/PS may be influenced by the local clinical organizational context."[26]

The ultimate in ventilator targeting system to date is the artificial neural network (Fig. 2-10).[27] Again, this experimental system does not control the ventilator directly but acts as a decision-support system. What is most interesting is that *the neural network is capable of learning,* which offers significant advantages over static mathematical models and even expert rule-based systems.

Neural nets are essentially data-modeling tools used to capture and represent complex input–output relationships. A neural net learns by experience the same way a human brain does, by storing knowledge in the strengths of internode connections. As data-modeling tools, they have been used in many business and medical applications for both diagnosis and forecasting.[28] A neural network, like an animal brain, is made up of individual neurons. Signals (action potentials) appear at the unit's inputs (synapses). The effect of each signal may be approximated by multiplying the signal by some number or weight to indicate the strength of the signal. The weighted signals then are summed to produce

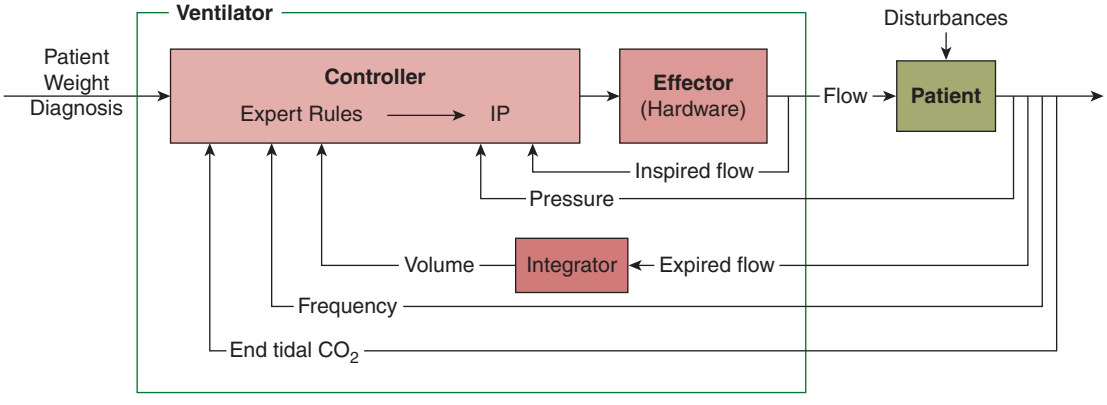


FIGURE 2-9 An intelligent targeting system for automatically adjusting pressure support levels (e.g., SmartCare/PS). IP, inspiratory pressure. (Reproduced, with permission, from Chatburn RL, Mireles-Cabodevila E. Closed loop control of mechanical ventilation. *Respir Care.* 2011;56(1):85–98.

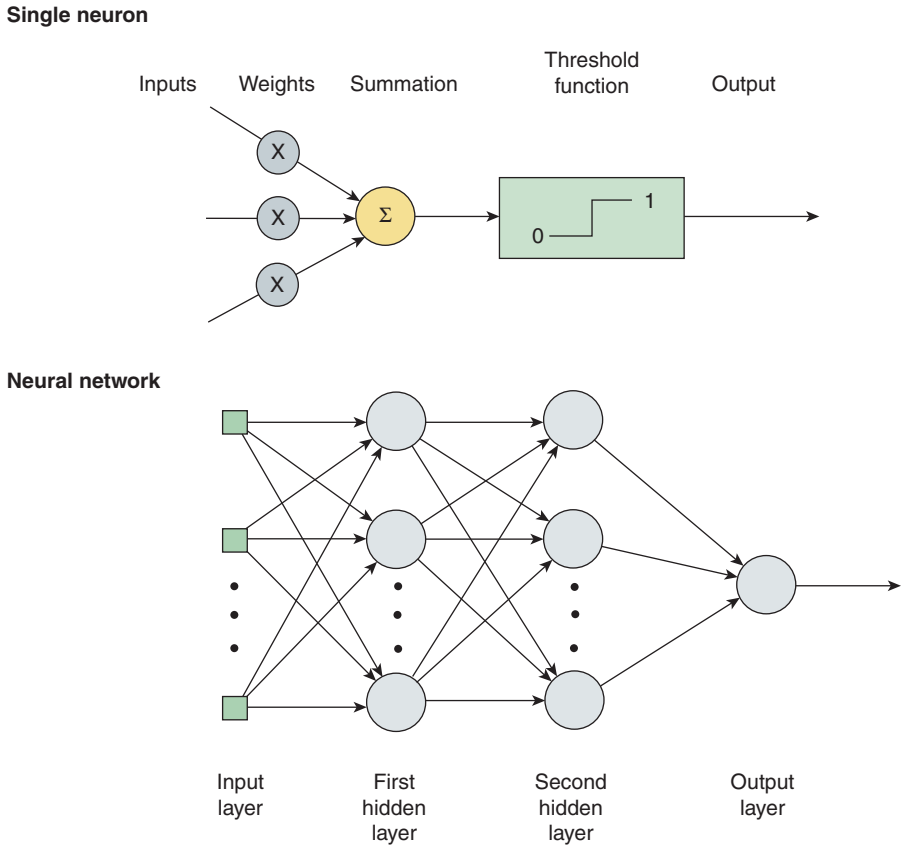


FIGURE 2-10 Neural network structure. A single neuron accepts inputs of any value and weights them to indicate the strength of the synapse. The weighted signals are summed to produce an overall unit activation. If this activation exceeds a certain threshold, the unit produces an output response. A network is made up of layers of individual neurons. (Reproduced, with permission, from Chatburn RL. Computer control of mechanical ventilation. *Respir Care.* 2004;49:507–515.)

an overall unit activation. If this activation exceeds a certain threshold, the unit produces an output response. Large numbers of neurons can be linked together in layers (see Fig. 2-10). The nodes in the diagram represent the summation and transfer processes. Note that each node contains information from all neurons. As the network learns, the weights change, and thus the values at the nodes change, affecting the final output.

In summary, ventilator control schemes display a definite hierarchy of evolutionary complexity. At the most basic level, control is focused on what happens within a breath. We can call this *manual control,* and there is a very direct need for operator input of static set-points. The next level up is what we can call *automatic control.* Here, set-points are dynamic in that they may be adjusted automatically over time by the ventilator according to some model of desired performance. The operator is somewhat removed in that inputs are entered at the level of the model and take effect over several breaths instead of at the level of individual breath control. Finally, the highest level so far is what might be considered *intelligent control.* Here, the operator can be eliminated altogether. Not only dynamic set-points but also dynamic models of desired performance are permitted. There is the possibility of the system learning from experience so that the control actually spans between patients instead of just between breaths.

Mode Classification

When Mushin et al wrote the classic book on automatic ventilation of the lungs,[10] the emphasis was on classifying ventilators and there were very few modes on each device. These devices have undergone a tremendous technological evolution during the intervening years. As a result, there are now more than 170 names of modes on ventilators in the United States alone, with as many as two dozen available on a single device. The proliferation of names makes education of end users very difficult, potentially compromising the quality of patient care. In addition, although there may be more than 170 mode names, these are not uniquely different modes. Consequently, the emphasis today in describing ventilators must be on classifying modes, shifting awareness from names to tags. Much has been written on the subject,[2,5,29–31] and this section gives a brief overview of the development and application of a ventilator mode taxonomy.

You can easily appreciate the motivation for classifying modes, just as we do animals or plants (or cars or drugs) because of their large number and variety. The logical basis for a mode taxonomy, however, is not apparent without some consideration. This basis has become a teaching system I have developed and tested and is founded on ten simple constructs (or aphorisms), each building on the previous one to yield a practical taxonomy. These aphorisms summarize many of the ideas discussed previously in this chapter, and there is even some evidence that they are recognized internationally by clinicians.[32] In simplified form, the aphorisms are as follows:

1. *A **breath** is one cycle of positive flow (inspiration) and negative flow (expiration).* The purpose of a ventilator is to assist breathing. Therefore, the logical start of a taxonomy is to define a breath. Breaths are defined such that during mechanical ventilation, small artificial breaths may be superimposed on large natural breaths or vice versa.
2. *A breath is **assisted** if pressure rises above baseline during inspiration or falls during expiration.* A ventilator assists breathing by doing some portion of the work of breathing. This occurs by delivering volume under pressure.
3. *A ventilator assists breathing using either **pressure control** (PC) or **volume control** (VC).* The equation of motion is the fundamental model for understanding patient–ventilator interaction and hence modes of ventilation. The equation is an expression of the idea that only one variable can be predetermined at a time; pressure or volume (flow control is ignored for simplicity and for historical reasons, and because controlling flow directly will indirectly control volume and vice versa).
4. *Breaths are classified according to the criteria that **trigger** (start) and **cycle** (stop) inspiration.* A ventilator must know when to start and stop flow delivery for a given breath. Because starting and stopping inspiratory flow are critical events in synchronizing patient–ventilator interaction, and because they involve uniquely different operator-influenced factors, they are distinguished by giving them different names.
5. *Trigger and cycle criteria can be either patient or machine initiated.* A major design consideration in creating modes is the ability to synchronize breath delivery with patient demand and at the same time to guarantee breath delivery if the patient is apneic. Therefore, understanding patient–ventilator interaction means understanding the difference between machine and patient trigger and cycle events.
6. *Breaths are classified as **spontaneous** or **mandatory** based on both the trigger and cycle criteria.* A spontaneous breath arises without apparent external cause. Thus, it is patient triggered and patient cycled. Any machine involvement in triggering or cycling leads to a mandatory breath. Note that the definition of a spontaneous breath is independent of the definition of an assisted or unassisted breath.
7. *Ventilators deliver only three basic **breath sequences**: CMV, IMV, and CSV.* The two breath classifications logically lead to three possible breath sequences that a mode can deliver. CSV implies all spontaneous breaths; IMV allows spontaneous breaths to occur between mandatory breaths and CMV does not.
8. *There are only five basic **ventilatory patterns**: VC-CMV, VC-IMV, PC-CMV, PC-IMV, and PC-CSV.* All modes can be categorizes by these five patterns. This provides enough practical detail about a mode for most clinical purposes.
9. *Within each ventilatory pattern there are several variations that can be distinguished by their **targeting scheme(s)**.* When comparing modes or evaluating the capability of a ventilator, more detail is required than just the ventilatory pattern. Modes with the same pattern can be distinguished by describing the targeting schemes they use. There are at present only six basic targeting schemes: set-point, dual, servo, adaptive, optimal, and intelligent.
10. *A **mode of ventilation** is classified according to its control variable, breath sequence, and targeting scheme(s).* A practical taxonomy of ventilatory modes is based on just four levels of detail: the control variable (pressure or volume), the breath sequence (CMV, IMV, or CSV), the targeting scheme used for primary breaths (CMV and CSV), and, if applicable, secondary breaths (IMV).

In teaching these constructs to respiratory therapists and physicians, most educators would agree that knowing a concept and applying it are two different skills. As with any taxonomy, learning the definitions and mastering the heuristic thinking required to actually categorize specific cases requires further guidance and some practice. Say, for example, your task is to compare the capabilities of two major intensive care unit ventilator models for a large capital purchase. Memorizing the ten aphorisms may not translate into the ability to classify the modes offered on these two ventilators as a basis for comparison. To facilitate that skill, I created the three tools shown in Figures 2-11 and 2-12 and in Table 2-4. Using these tools you can create a simple spreadsheet that defines and compares the modes on any number of ventilators. Table 2-5 is an example of such a table for the Covidien PB 840 ventilator and the Dräger Evita XL ventilator. When implemented as a spreadsheet with built-in data-sorting functions, the table becomes a database with several major uses:

1. A "Rosetta Stone" that can be used to translate from mode name to mode classification and vice versa. In this way modes can be identified that are functionally identical but have different proprietary names.
2. A tool for engineers to describe performance characteristics of individual named modes. Information like this should be available to users in the ventilator's manual.
3. A system for clinicians to compare and contrast the capabilities of various modes and ventilators.
4. A paradigm for educators to use in teaching the basic principles of mechanical ventilation.

One can imagine the utility of an expanded database containing the classification of all modes on all commercially available ventilators.

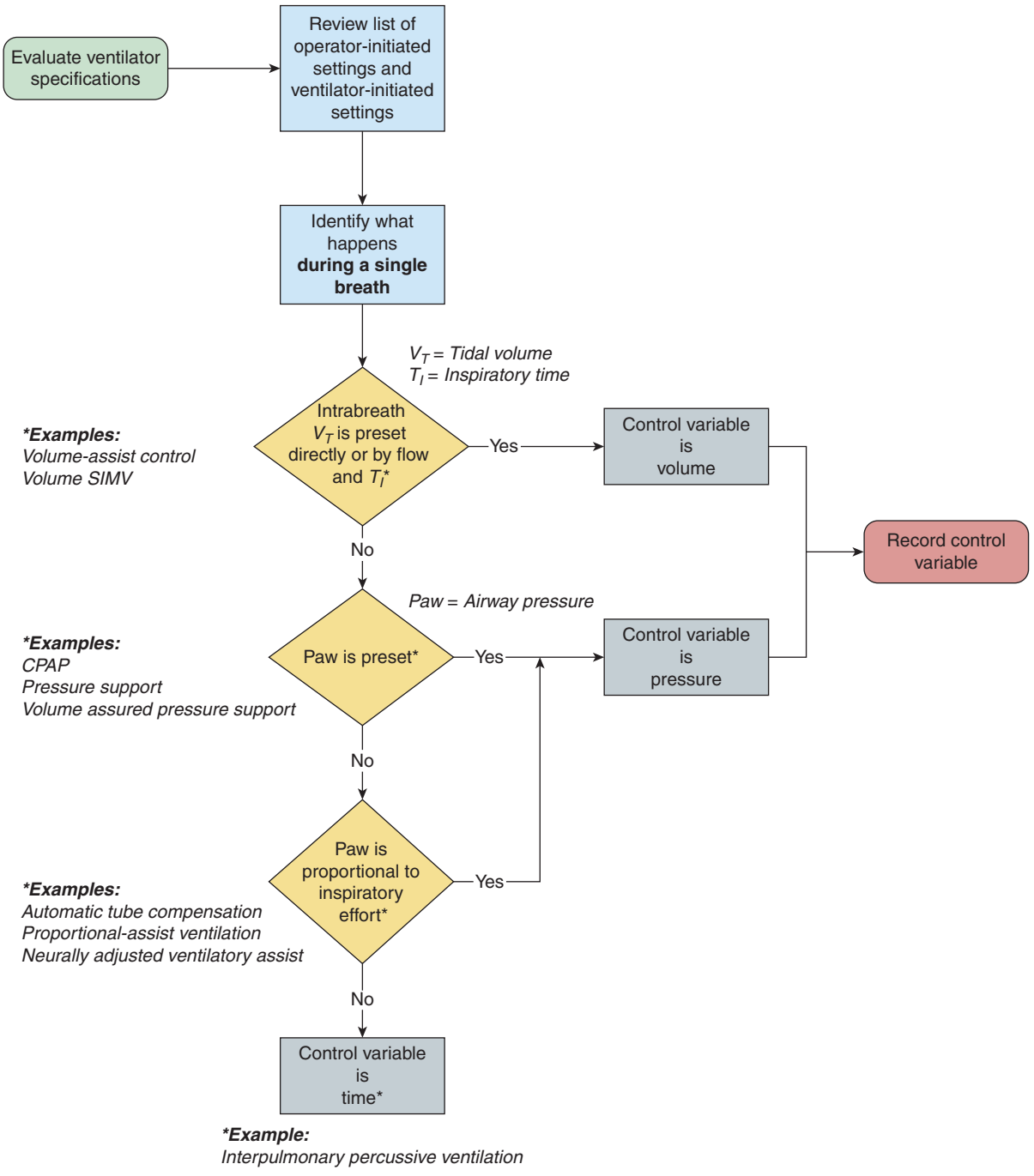


FIGURE 2-11 Algorithm for determining the control variable when classifying a mode. *SIMV,* synchronized intermittent mandatory ventilation. (Copyright 2011 by Mandu Press Ltd. and reproduced with permission.)

VENTILATOR ALARM SYSTEMS

As with other components of ventilation systems, ventilator alarms have increased in number and complexity. Fortunately, the classification system I have been describing can be expanded to include alarms as well (see Table 2-1).

MacIntyre[33] has suggested that alarms also be categorized by the events that they are designed to detect. Level 1 events include life-threatening situations, such as loss of input power or ventilator malfunction (e.g., excessive or no flow of gas to the patient). The alarms in this category should be mandatory (i.e., not subject to operator

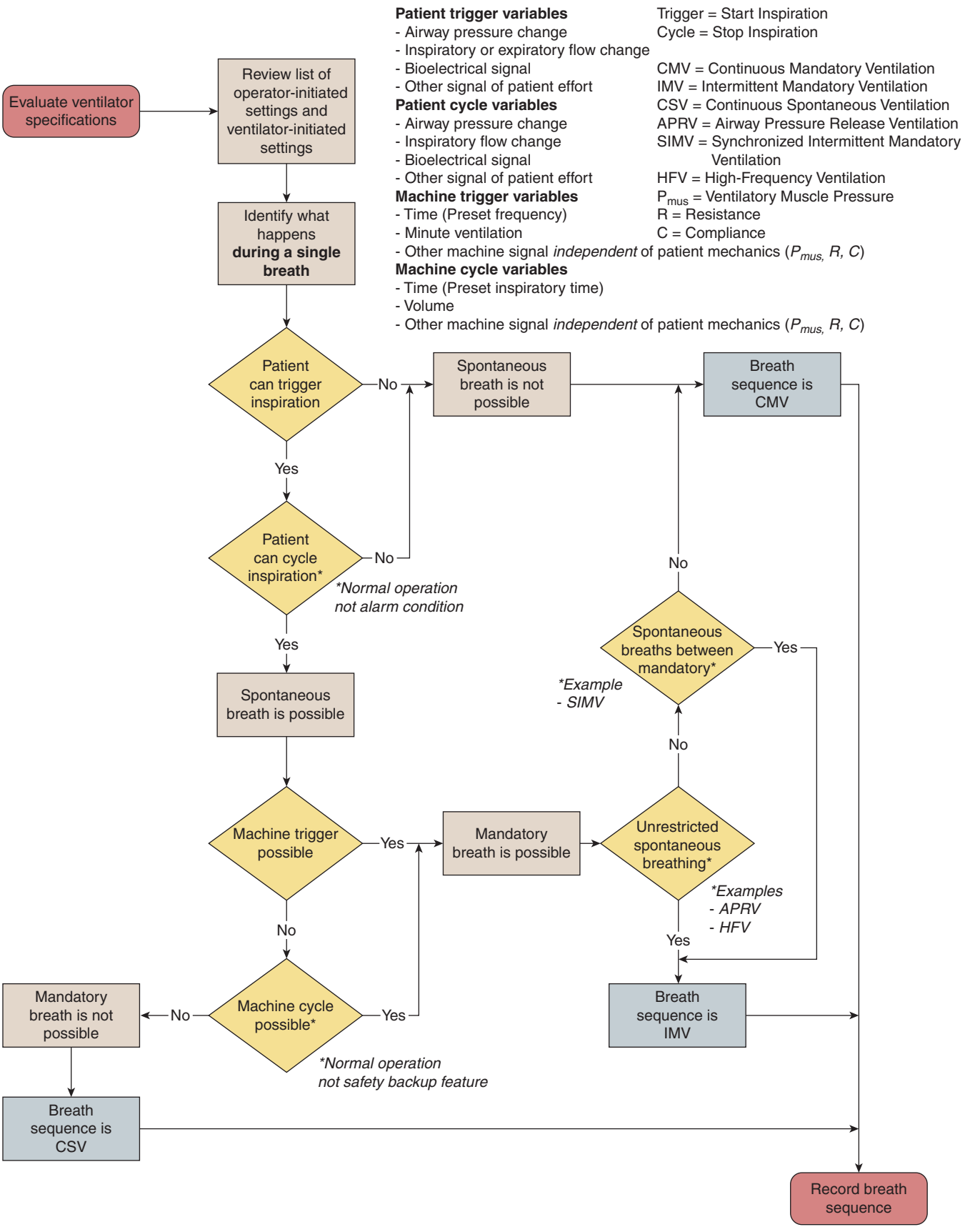
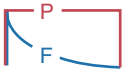
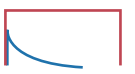
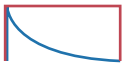
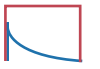
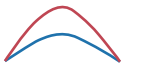
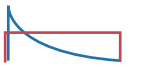
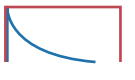
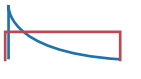
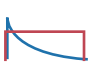
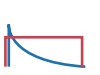


FIGURE 2-12 Algorithm for determining the breath sequence when classifying a mode. (Copyright 2011 by Mandu Press Ltd. and reproduced with permission.)

TABLE 2-4: EXPLANATION OF HOW TARGETING SCHEMES TRANSFORM OPERATOR INPUTS INTO VENTILATOR OUTPUTS

#	Control Variable	Target Scheme	Explanation	Example Mode Name	Predetermined Inputs: WB Target	Predetermined Inputs: Cycle	Predetermined Inputs: BB Target	Ventilator Output: + Impedance	Ventilator Output: − Impedance
1	P	Set-point	Peak airway pressure is independent of impedance	PC SIMV	P	T			
2	P	Set-point	Peak airway pressure is independent of impedance	Pressure support	P	F			
3	P	Set-point	Peak airway pressure is independent of impedance	Automatic resuscitator	F	P			
4	V	Set-point	Tidal volume is independent of impedance	VC A/C	F	T			
5	P	Dual P-F	Same as #1 if secondary target not activated	VAPS	P,F	V			
6	V	Dual F-P	Same as #4 if secondary target not activated	CMV + Pressure Limited	F,P	V			
7	P	Servo	Pressure is automatically proportional to inspiratory effort Effort is represented by patient:		Percent Support	F			
			flow	ATC					
			volume and flow	PAV+					
8	P	Servo	Pressure is authomatically proportional to inspiratory effort represented by diaphgram EMG	NAVA	$\frac{\text{cm } H_2O}{\mu v}$	NA			
9	P	Adaptive	Same as #1 within a breath plus volume target between breaths	PRVC	NA	T	Volume		
10	P	Optimal	Same as #9 plus algorithm to minimize inspiratory work rate	ASV	NA	F	%MV Frequency Volume		
11	P	Intelligent	Same as #9 plus volume, PCO_2 and frequency targets using artificial intelligence algorithms	Smart Care/PS	NA	NA	Frequency Volume $P_{ET}CO_2$		

P, pressure; *V*, volume; *F*, flow; *T*, time; *R*, resistance; *E*, elastance; *MV*, minute volume; *Edi*, electrical activity of diaphragm; *WB Target*, within-breath preset parameters of the pressure, volume, or flow waveform; *BB Target*, between breath targets modify WB targets or overal ventiltory pattern; *Cycle*, end of inspiration; *NA,* not available as operator preset, ventilator determines value if applicable.

low impedance, low resistance and/or elastance;
high impedance, high resistance and/or elastance;

TABLE 2-5: SPREADSHEET EXAMPLE OF HOW MODES ON TWO COMMON ICU VENTILATORS WOULD BE CLASSIFIED

The spreadsheet could be sorted any number of ways (e.g., using AutoFilter drop-down dialogs) to compare the ventilators on various capabilities (e.g., all modes with adaptive pressure targeting). The spreadsheet also functions as a mode translator, giving the different proprietary names for identical modes.

			Order	Family	Genus	Species
					Primary Breath	Secondary Breath
Manufacturer	Model	Manufacturer's Mode Name	Primary Control Variable	Breath Sequence	Target Scheme	Target Scheme
Covidien	840	Volume Control Plus Assist Control	Pressure	CMV	adaptive	N/A
Covidien	840	Volume Support	Pressure	CSV	adaptive	N/A
Covidien	840	Volume Control Plus Synchronized Intermittent Mandatory Ventilation	Pressure	IMV	adaptive	set-point
Covidien	840	Volume Ventilation Plus Synchronized Intermittent Mandatory Ventilation	Pressure	IMV	adaptive	adaptive
Covidien	840	Tube Compensation	Pressure	CSV	servo	N/A
Covidien	840	Proportional Assist Plus	Pressure	CSV	servo	N/A
Covidien	840	Pressure Control Assist Control	Pressure	CMV	set-point	N/A
Covidien	840	Pressure Support	Pressure	CSV	set-point	N/A
Covidien	840	Spontaneous	Pressure	CSV	set-point	N/A
Covidien	840	Pressure Control Synchronized Intermittent Mandatory Ventilation	Pressure	IMV	set-point	set-point
Covidien	840	BiLevel	Pressure	IMV	set-point	set-point
Covidien	840	Volume Control/Assist Control	Volume	CMV	set-point	N/A
Covidien	840	Volume Control Synchronized Intermittent Mandatory Ventilation	Volume	IMV	set-point	set-point
Dräger	Evita XL	Mandatory Minute Volume with AutoFlow	Pressure	IMV	adaptive	set-point
Dräger	Evita XL	Continuous Mandatory Ventilation with AutoFlow	Pressure	CMV	adaptive	N/A
Dräger	Evita XL	Synchronized Intermittent Mandatory Ventilation with AutoFlow	Pressure	IMV	adaptive	set-point
Dräger	Evita XL	SmartCare	Pressure	CSV	intelligent	N/A
Dräger	Evita XL	Automatic Tube Compensation	Pressure	CSV	servo	N/A
Dräger	Evita XL	Pressure Controlled Ventilation Plus Assisted	Pressure	CMV	set-point	set-point
Dräger	Evita XL	Pressure Controlled Ventilation Plus Pressure Support	Pressure	IMV	set-point	set-point
Dräger	Evita XL	Airway Pressure Release Ventilation	Pressure	IMV	set-point	set-point
Dräger	Evita XL	Continuous Positive Airway Pressure/Pressure Support	Pressure	CSV	set-point	N/A
Dräger	Evita XL	Mandatory Minute Volume	Volume	IMV	adaptive	set-point
Dräger	Evita XL	Continuous Mandatory Ventilation with Pressure Limited Ventilation	Volume	CMV	dual	N/A
Dräger	Evita XL	Synchronized Intermittent Mandatory Ventilation with Pressure Limited Ventilation	Volume	IMV	dual	set-point
Dräger	Evita XL	Mandatory Minute Volume with Pressure Limited Ventilation	Volume	IMV	dual/ adaptive	set-point
Dräger	Evita XL	Continuous Mandatory Ventilation	Volume	CMV	set-point	N/A
Dräger	Evita XL	Synchronized Intermittent Mandatory Ventilation	Volume	IMV	set-point	set-point

CMV, continuous mandatory ventilation; *CSV,* continuous spontaneous ventilation; *IMV,* intermittent mandatory ventilation.

choice), redundant (i.e., multiple sensors and circuits), and noncanceling (i.e., alarm continues to be activated, even if the event is corrected, and must be reset manually). Level 2 events can lead to life-threatening situations if not corrected in a timely fashion. These events include such things as blender failure, high or low airway pressure, autotriggering, and partial patient circuit occlusion. They also may include suspicious ventilator settings such as an inspiratory-to-expiratory timing (I:E) ratio greater than 1:1. Alarms for level 2 events may not be redundant and may be self-canceling (i.e., alarm inactivated if event ceases to occur). Level 3 events are those that affect the patient–ventilator interface and may influence the level of support provided. Examples of such events are changes in patient compliance and resistance, changes in patient respiratory drive, and auto-PEEP. Alarm function at this level is similar to that of level 2 alarms. Level 4 events reflect the patient condition alone rather than ventilator function. As such, these events usually are detected by stand-alone monitors, such as oximeters, cardiac monitors, and blood-gas analyzers. Some ventilators, however, are able to incorporate the readings of a capnograph in their displays and alarm systems.

THE FUTURE

Almost 20 years ago, Warren Sanborn predicted that ventilators today would "… report the patient's metabolic state; manage oxygen delivery; calculate cardiac output, synchronize breath delivery with cardiac cycle to maximize cardiac output…and perform all these functions automatically or at least presenting consensus-based advisory messages to the practitioner…."[17] Some of these ideas were never developed commercially. Some were tried and abandoned. Some, have evolved beyond Warren's broad vision.

There are three basic ways to improve ventilators in the future. First, just like computer games, ventilators need to improve the operator interface constantly. Yet very little research has been done to call attention to problems with current displays.[34,35] We have come a long way from using a crank to adjust the stroke of a ventilator's piston to set tidal volume. The operator interface must provide for three basic functions: allow input of control and alarm parameters, monitor the ventilator's status, and monitor the ventilator–patient interaction status. We have a long way to go before the user interface provides an ideal experience with these functions.

Second, the weak link in the patient–ventilator system is the patient circuit. We buy a $35,000 ventilator with state-of-the-art computer control, and then we connect it to the patient (priceless) with a $1.98 piece of plastic tubing that is subject to filling with condensate from a heated humidifier whose design has not changed appreciably in 20 years. The resistance and compliance of the delivery circuit make flow control and volume delivery more difficult. It is like buying a Ferrari and putting wooden wheels on it. In the future, water vapor should be treated like any other desirable inhaled gas constituent (e.g., air, oxygen, helium, or nitric oxide) and metered from within the ventilator. The inspiratory part of the patient circuit should be a sterile, insulated, permanent part of the ventilator right up to the patient connection, which can be a disposable tip for cleaning purposes. The gas should be delivered under high pressure as a jet to provide not only conventional pressure, volume, and flow waveforms but also high-frequency ventilation. The jet also can be used to provide a counterflow PEEP effect, eliminating any need for an exhalation–valve system. The disposable tip could be designed to house disposable sensors and would be the only part of the circuit to be exposed to the patient's exhaled gas. If ventilator manufacturers saw themselves as providers of the entire system, instead of letting third parties deal in plastic connecting tubing, I think we would see a huge evolutionary step in ventilator performance, better patient outcomes, and potential savings in labor costs for providers.

Third, the most exciting area for development probably is in the intelligence that will be built into future ventilator control circuits. The real challenge in closed-loop control of ventilation is defining, measuring, and interpreting the appropriate feedback signals. If we stop to consider all the variables a human operator assesses, the problem looks insurmountable. Not only does a human consider a wide range of individual physiologic variables, but there are the more abstract evaluations of such things as metabolic, cardiovascular, and psychological states. Add to this the various environmental factors that may affect operator judgment, and we get a truly complex control problem (Fig. 2-13).

I would like to speculate now about a response to this challenge. The ideal control strategy would have to start out with basic tactical control of the individual breath. Next, we add longer-term strategic control that adapts to changing load characteristics. Mathematical models could provide the basic parameters of the mode, whereas expert rules would place limits to ensure lung protection.

Next, we sample various physiologic parameters and use fuzzy logic to establish the patient's immediate condition. This information is passed on to a neural network, which would then select the best response to the patient's condition.

The neural network ideally would have access to a huge database comprised of both human expert rules and actual patient responses to various ventilator strategies. This arrangement would allow the ventilator not only to learn from its interaction with the current patient but also to contribute to the database.

Finally, the database and this ventilator could be networked with other intelligent ventilators to multiply the learning capacity exponentially (Fig. 2-14). Whatever the future brings, it seems clear that ventilators will have more intelligence built in to increase patient safety and decrease the time required to provide care.

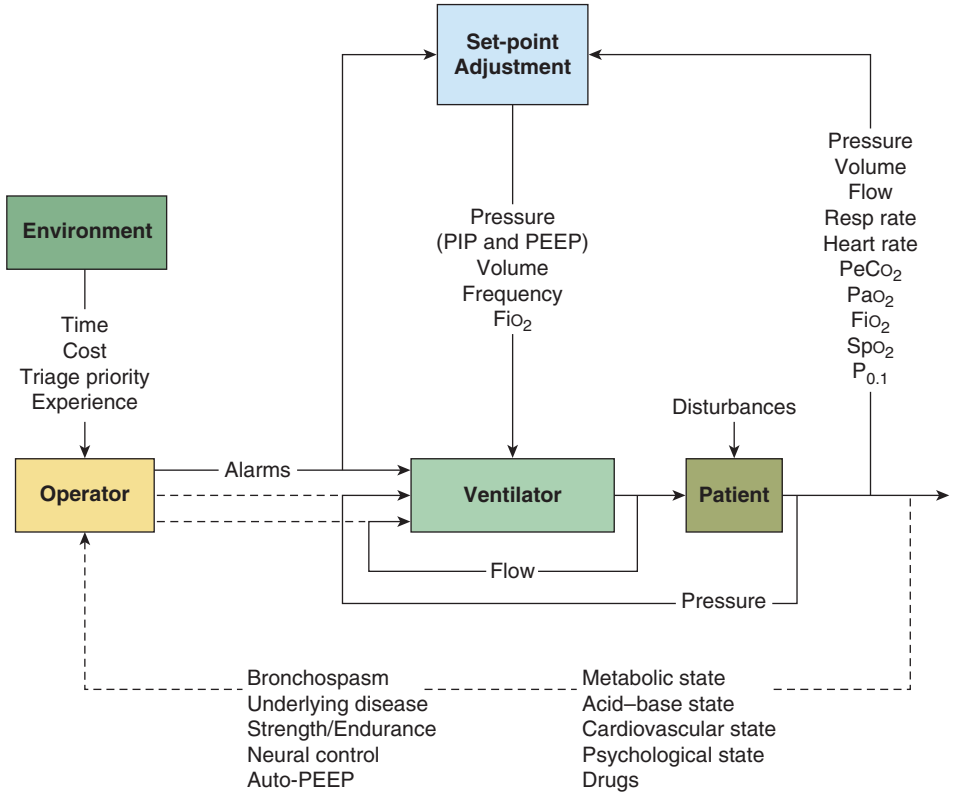


FIGURE 2-13 The challenge of total computer control of mechanical ventilation. *Solid arrows* depict signals that have been used at least experimentally. *Dotted arrows* represent potential feedback signals. (Reproduced, with permission, from Chatburn RL. Computer control of mechanical ventilation. *Respir Care.* 2004;49:507–515.)

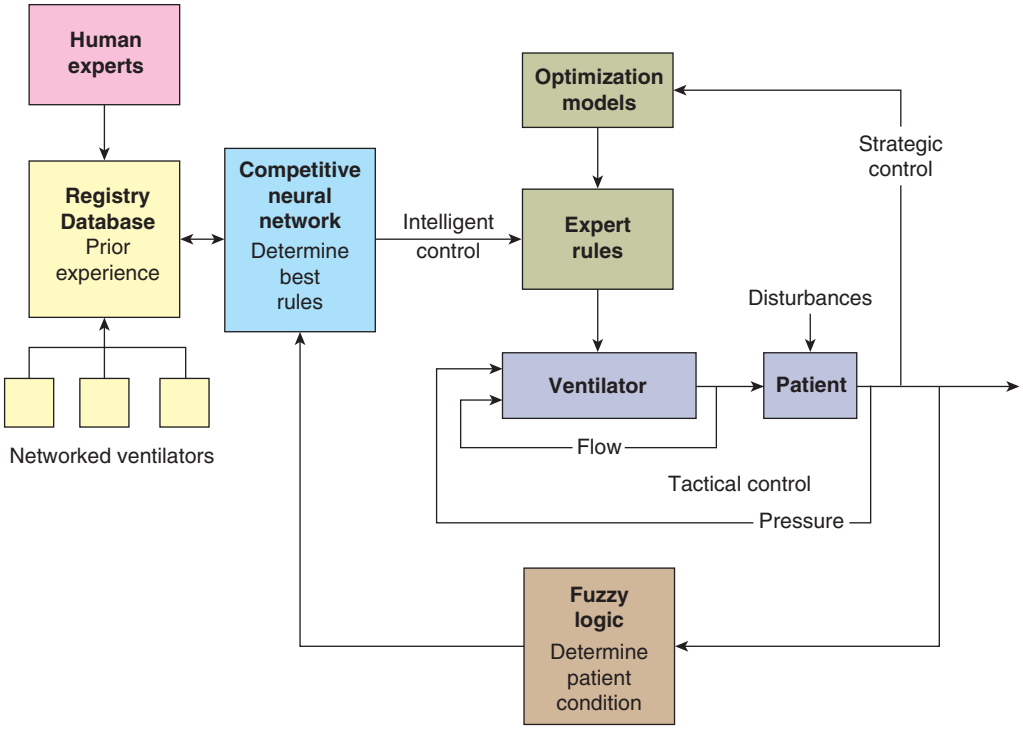


FIGURE 2-14 A potential approach to the challenge of fully automated control of mechanical ventilation. (Reproduced, with permission, from Chatburn RL. Computer control of mechanical ventilation. *Respir Care.* 2004;49:507–515.)

SUMMARY AND CONCLUSION

Mechanical ventilators have become so complex that a system of classification is necessary to communicate intelligently about them. The theoretical basis for this classification system is a mathematical model of patient–ventilator interaction known as the *equation of motion for the respiratory system*. From this model we deduce that as far as an individual inspiration is concerned, any conceivable ventilator can be classified as either a pressure, volume, or flow controller (and in rare cases, simply an inspiratory-expiratory time controller). An individual breath is shaped by the phase variables that determine how the breath is triggered (started), targeted (sustained), and cycled (stopped).

A *mode* of ventilation can be characterized using a four-level taxonomy: (a) control variable, that is, pressure or volume according to the equation of motion; (b) the breath sequence, that is, CMV, IMV, or CSV; (c) targeting scheme for primary breaths; and (d) targeting scheme for secondary breaths. The trend in ventilator targeting schemes has been from basic manual control (within-breath control requiring operator input of static set-points), to more advanced automatic control (between-breath control of set-points that are adjusted automatically by the ventilator with minimal operator input), to the highest level of intelligent control (in which the operator theoretically may be eliminated altogether in favor of artificial-intelligence systems capable of learning).

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3

BASIC PRINCIPLES OF VENTILATOR DESIGN

Robert L. Chatburn
Eduardo Mireles-Cabodevila

THE VENTILATOR AS A "BLACK BOX"

A mechanical ventilator is an automatic machine designed to provide all or part of the work the body must do to move gas into and out of the lungs. The act of moving air into and out of the lungs is called breathing, or, more formally, ventilation.

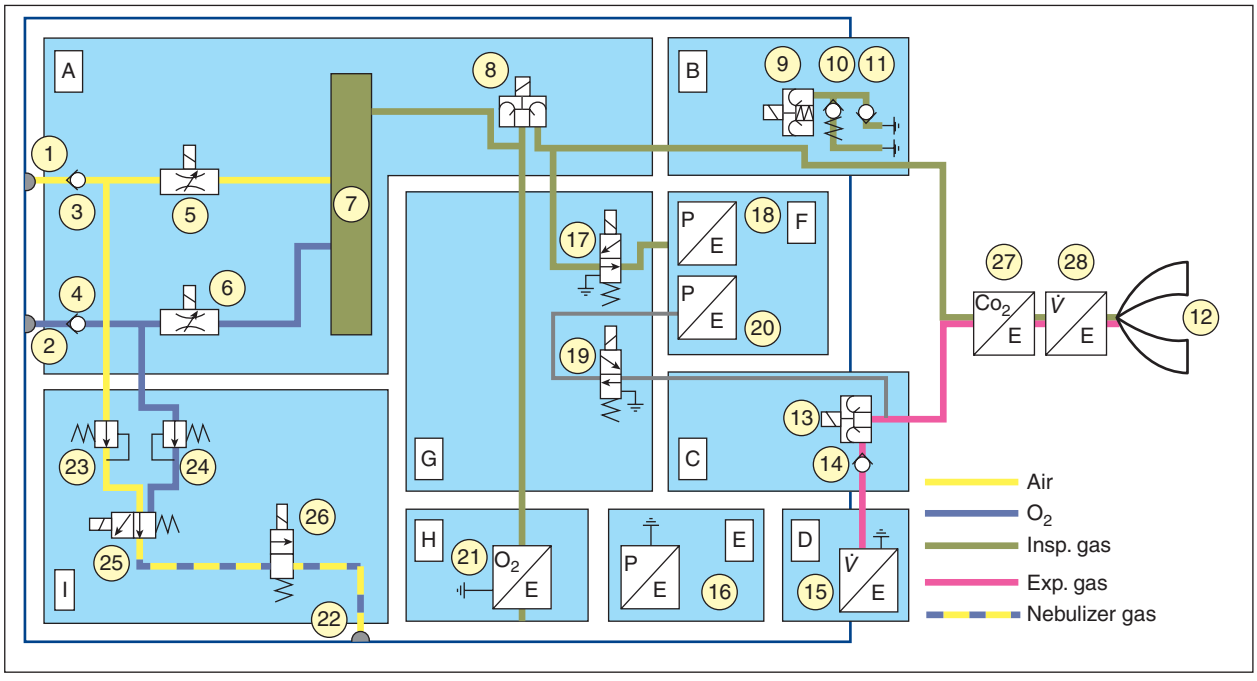
The simplest mechanical device we could devise to assist a person's breathing would be a hand-driven, syringe-type pump that is fitted to the person's mouth and nose using a mask. A variation of this is the self-inflating, elastic resuscitation bag. Both of these require one-way valve arrangements to cause air to flow from the device into the lungs when the device is compressed, and out from the lungs to the atmosphere as the device is expanded. These arrangements are not automatic, requiring an operator to supply the energy to push the gas into the lungs through the mouth and nose. Thus, such devices are not considered mechanical ventilators.

Automating the ventilator so that continual operator intervention is not needed for safe, desired operation requires three basic components:

1. A source of input energy to drive the device;
2. A means of converting input energy into output energy in the form of pressure and flow to regulate the timing and size of breaths; and
3. A means of monitoring the output performance of the device and the condition of the patient.

There was a time when you could take a handful of simple tools and do routine maintenance on your car engine. About that time the average clinician could also completely disassemble and reassemble a mechanical ventilator as a training exercise or to perform repairs. In those days (the late 1970s), textbooks[1] describing ventilators understandably paid much attention to the individual mechanical components and pneumatic schematics. In fact, this philosophy was reflected to some extent in previous editions of this book. Today, both cars and ventilators are incredibly complex mechanical devices controlled by multiple microprocessors running sophisticated software (Fig. 3-1). Figure 3-2 shows the pneumatic schematic of a current intensive care ventilator. All but the most rudimentary maintenance of ventilators is now the responsibility of specially trained biomedical engineers. Our approach to describing ventilator design has thus changed from a focus on individual components to a more generalized model of a ventilator as a "black box," that is, a device for which we supply an input and expect a certain output and whose internal operations are largely unknowable, indeed, irrelevant, to most clinical operators. What follows, then, is only a brief overview of the key design features of mechanical ventilators with an emphasis on input power requirements, transfer functions (pneumatic and electronic control systems), and outputs (pressure, volume, and flow waveforms). The rest of the chapter focuses on the interactions between the operator and the ventilator

FIGURE 3-1 Examples of commonly used intensive care ventilators: **A.** Dräger Infinity V500, **B.** Hamilton G5, **C.** Maquet Servo i, **D.** Covidien PB840. (Image with permission from Nellcor Puritan Bennett LLC, Boulder, Colorado, doing business with Covidien.)



1 Air gas inlet
2 O_2 gas inlet
3 Air nonreturn valve
4 O_2 nonreturn valve
5 Air metering valve
6 O_2 metering valve
7 Tank
8 Mixed gas metering valve
9 Safety valve
10 Emergency expiratory valve
11 Emergency breathing valve
12 Patient's lungs
13 Expiratory valve
14 Nonreturn valve
15 Expiratory flow sensor
16 Barometric pressure sensor
17 Calibration valve for inspiratory pressure sensor
18 Inspiratory pressure sensor
19 Calibration valve for expiratory pressure sensor
20 Expiratory pressure sensor
21 O_2 sensor
22 Nebulizer outlet
23 Air pressure regulator
24 O_2 pressure regulator
25 Nebulizer mixer valve
26 Nebulizer changeover valve
27 CO_2 sensor
28 Neonatal flow sensor (depending on the patient category)

FIGURE 3-2 Pneumatic schematic of the Dräger Infinity V500 intensive care ventilator. **A.** Gas-mixture and gas-metering assembly. Gas from the supply lines enters the ventilator via the gas-inlet connections for oxygen and air (*1,2*). Two nonreturn valves (*3,4*) prevent one gas from returning to the supply line of the other gas. Mixing takes place in the tank (*7*) and is controlled by two valves (*5,6*). Inspiratory flow is controlled by a third valve (*8*). **B.** Inspiratory unit consists of safety valve (*9*) and two nonreturn valves (*10,11*). In normal operation, the safety valve is closed so that inspiratory flow is supplied to the patient's lungs (*12*). During standby, the safety valve is open and enables spontaneous inspiration by the emergency breathing valve (*11*). The emergency expiratory valve (*10*) provides a second channel for expiration when the expiratory valve (*13*) is blocked. **C.** Expiratory unit consists of the expiratory valve (*13*) and a nonreturn valve (*14*). The expiratory valve is a proportional valve and is used to adjust the pressure in the patient circuit. In conjunction with the spring-loaded valve of the emergency air outlet (*10*), the nonreturn valve (*14*) prevents pendulum breathing during spontaneous breathing. **D.** Expiratory flow sensor. **E.** Barometric pressure sensor. Conversion of mass flow to volume, body temperature and pressure saturated (*BTPS*) requires knowledge of ambient pressure. **F.** Pressure measurement assembly. Pressure in the patient circuit is measured with two independent pressure sensors (*18,20*). **G.** Calibration assembly. The pressure sensors are regularly zero calibrated by connection to ambient pressure via the two calibration valves (*17,19*). **H.** Oxygen sensor. **I.** Medication nebulizer assembly. (Reproduced, with permission, from Dräger Medical AG & Co. KG. *V500 Operator's Manual*. Luebeck, Germany.)

(the operator interface), and between the ventilator and the patient (the patient interface).

Inputs

Mechanical ventilators are typically powered by electricity or compressed gas. Electricity, either from wall outlets (e.g., 100 to 240 volts AC, at 50/60 Hz) or from batteries (e.g., 10 to 30 volts DC), is used to run compressors of various types. Batteries are commonly used as the primary power source in the home-care environment but are usually reserved for patient transport or emergency use in hospitals. These sources provide compressed air for motive power as well as air for breathing. Alternatively, the power to expand the lungs is supplied by compressed gas from tanks, or from wall outlets in the hospital (e.g., 30 to 80 pounds per square inch [psi]). Some transport and emergency ventilators use compressed gas to power both lung inflation and the control circuitry. For these ventilators, knowledge of gas consumption is critical when using cylinders of compressed gas.

The ventilator is generally connected to separate sources of compressed air and compressed oxygen. In the United States, hospital wall outlets supply air and oxygen at 50 psi, although most ventilators have internal regulators to reduce this pressure to a lower level (e.g., 20 psi). This permits the delivery of a range of oxygen concentrations to support the needs of sick patients. Because compressed gas has all moisture removed, the gas delivered to the patient must be warmed and humidified so as to avoid drying out the lung tissue.

Conversion and Control

The input power of a ventilator must be converted to a predefined output of pressure and flow. There are several key systems required for this process. If the only power input is electrical, the ventilator must use a compressor or blower to generate the required pressure and flow. A compressor is a machine for moving a relatively low flow of gas to a storage container at a higher level of pressure (e.g., 20 psi). A blower is a machine for generating relatively larger flows of gas as the direct ventilator output with a relatively moderate increase of pressure (e.g., 2 psi). Compressors are generally found on intensive care ventilators whereas blowers are used on home-care and transport ventilators. Compressors are typically larger and consume more electrical power than blowers, hence the use of the latter on small, portable devices.

FLOW-CONTROL VALVES

To control the flow of gas from a compressor, ventilator engineers use a variety of flow-control valves, from very simple to very complex. The simplest valve is just a fixed orifice flow resistor that permits setting a constant flow to the external

FIGURE 3-3 CareFusion Infant Flow SiPAP device.

tubing that conducts the gas to the patient, called the *patient circuit*. Such devices are used in small transport ventilators and automatic resuscitators. Manually adjusted variable-orifice flow meters have been used in simple infant ventilators in the past (e.g., Bourns BP-200) and are currently used in the Infant Flow SiPAP device (CareFusion, Minneapolis, MN), as shown in Figure 3-3. The advent of inexpensive microprocessors in the 1980s led to development of digital control of flow valves that allow a great deal of flexibility in shaping the ventilator's output pressure, volume, and flow waveforms (Fig 3-4).[2] Such valves are used in most of the current generation of intensive care ventilators.

Directing flow from the source gas into the patient requires the coordination of the output flow-control valve and an expiratory valve or "exhalation manifold" (Fig. 3-5). In the simplest case, when inspiration is triggered on, the output control valve opens, the expiratory valve closes, and the only path left for gas is into the patient. When inspiration is cycled off, the output valve closes and the exhalation valve opens, flow from the ventilator ceases and the patient exhales out through the expiratory valve (see Fig. 3-2). The most sophisticated ventilators employ a complex interaction between the output flow-control valve and the exhalation valve, such that a wide variety of pressure, volume, and flow waveforms may be generated to synchronize the ventilator output with patient effort as much as possible.

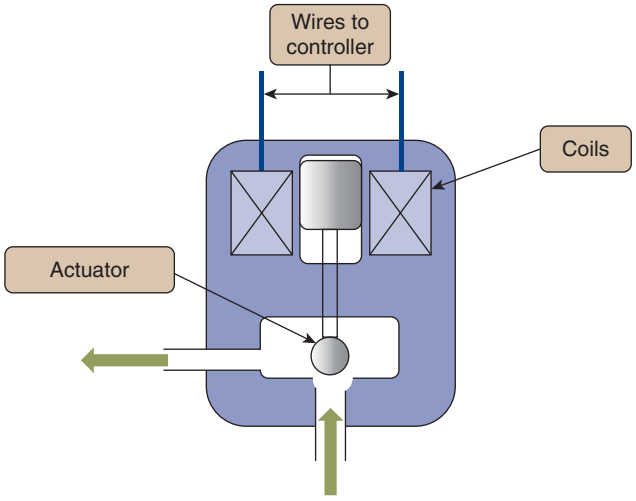


FIGURE 3-4 Schematic of an output flow-control valve.

FIGURE 3-6 Small, pneumatically powered transport ventilator using a pneumatic control system. (Reproduced, with permission, from CAREvent, O-Two Medical Technologies, Ontario, Canada.)

CONTROL SYSTEMS

In the simplest terms, the control system of a ventilator is comprised of components that generate the signals that operate the output valve and the exhalation manifold to obtain the desired output waveforms and modes of ventilation. Control systems may be based on mechanical, pneumatic, fluidic, or electronic components. Mechanical components include levers, pulleys, cams, and so on.[3] Pneumatic control circuits use gas pressure to operate diaphragms, jet entrainment devices, pistons, and other items. Use of lasers to create micro channels for gas flow has enabled miniaturization of ventilator control circuits that are powered entirely by gas pressure to create small, but sophisticated, ventilators for transport, such as the CAREvent (O-Two Medical Technologies) shown in Figure 3-6. Fluidic circuits are analogs of electronic logic circuits.[4] Just as an electronic logic circuit uses electricity, the fluidic circuit uses a very small gas flows to generate signals that operate switches and timing components. Both pneumatic and fluidic control systems are immune to failure from electromagnetic interference, such as around magnetic resonance imaging equipment. Examples of simple pneumatic and fluidic ventilator control circuits have been illustrated elsewhere.[5] By far, the majority of ventilators use electronic control circuits with microprocessors to manage the complex monitoring (e.g., from pressure and flow sensors) and control (valves) functions of modern ventilators used in almost every health care environment.

What makes one ventilator so different from another has as much to do with the control system software as it does with the hardware. The control software determines how the ventilator interacts with the patient; that is, the modes available. Thus, a discussion about control systems is essentially a discussion about mode capabilities and classifications. Chapter 2 describes the specific design principles of ventilator control systems in detail.

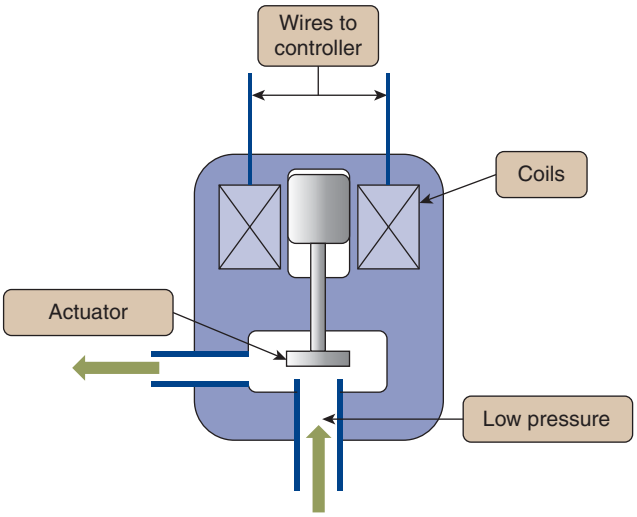


FIGURE 3-5 Schematic of an exhalation valve.

Outputs

Just as the study of cardiology involves the use of electrocardiograms and blood pressure waveforms, the study of mechanical ventilation requires an understanding of output waveforms. The waveforms of interest are the pressure, volume, and flow.

IDEALIZED PRESSURE, VOLUME, AND FLOW WAVEFORMS

Output waveforms are conveniently graphed in groups of three. The horizontal axis of all three graphs is the same and has the units of time. The vertical axes are in units of pressure, volume, and flow. For the purpose of identifying

characteristic waveform shapes, the specific baseline values are irrelevant. What is important is the relative magnitudes of each of the variables and how the value of one affects or is affected by the value of the others.

Figure 3-7 illustrates the typical waveforms available on modern ventilators. These waveforms are idealized; that is, they are precisely defined by mathematical equations and are meant to characterize the operation of the ventilator's control system. As such, they do not show the minor deviations, or "noise," often seen in waveforms recorded during actual ventilator use. This noise can be caused by a variety of extraneous factors such as vibration and flow turbulence. Of course, scaling of the horizontal and vertical axes can affect the appearance of actual waveforms considerably. Finally, the waveforms in Figure 3-7 do not show the effects of the resistance and compliance of the patient circuit.

No ventilator is an ideal pressure, volume, or flow controller, and ventilators are designed to only approximate a particular waveform. Idealized waveforms as shown in Figure 3-7 are, nevertheless, helpful because they are used commonly in other fields (e.g., electrical engineering), which makes it possible to use mathematical procedures and terminology that already have been established. For example, a standard mathematical equation is used to describe the most common ventilator waveforms for each control variable. This known equation may be substituted into the equation of motion, which is then solved to get the equations for the other two variables. Once the equations for pressure, volume, and flow are known, they are easily graphed. This is the procedure that was used to generate the graphs in Figure 3-7.

EFFECTS OF THE PATIENT CIRCUIT

The pressure, volume, and flow the patient actually receives are never precisely the same as what the clinician sets on the ventilator. Sometimes these differences are caused by instrument inaccuracies or calibration error. More commonly, the patient delivery circuit contributes to discrepancies between the desired and actual patient values. This is so because the patient circuit has its own compliance and resistance. Thus, the pressure measured inside a ventilator upstream of the patient always will be higher than the pressure at the airway opening because of patient circuit resistance. In addition, the volume and flow coming out of the ventilator's exhalation manifold will exceed those delivered to the patient because of the compliance of the patient circuit.

Exactly how the mechanical properties of the patient circuit affect ventilator performance depends on whether they are connected in series or in parallel with the patient. It turns out that the resistance of the patient circuit is connected in series whereas the compliance is modeled as a parallel connection. To understand this, we first make the simplifying assumption that we can examine the patient circuit's resistance separate from its compliance. It is intuitively obvious that the same flow of gas that comes from the ventilator travels through the circuit tubing as through the patient's airway opening. We also can see that the pressure drop across the patient circuit will be different from that across the respiratory system because they have different resistances. By a definition we borrow from electronics, when two circuit components share the same flow but have different pressure drops, they are connected in series. This

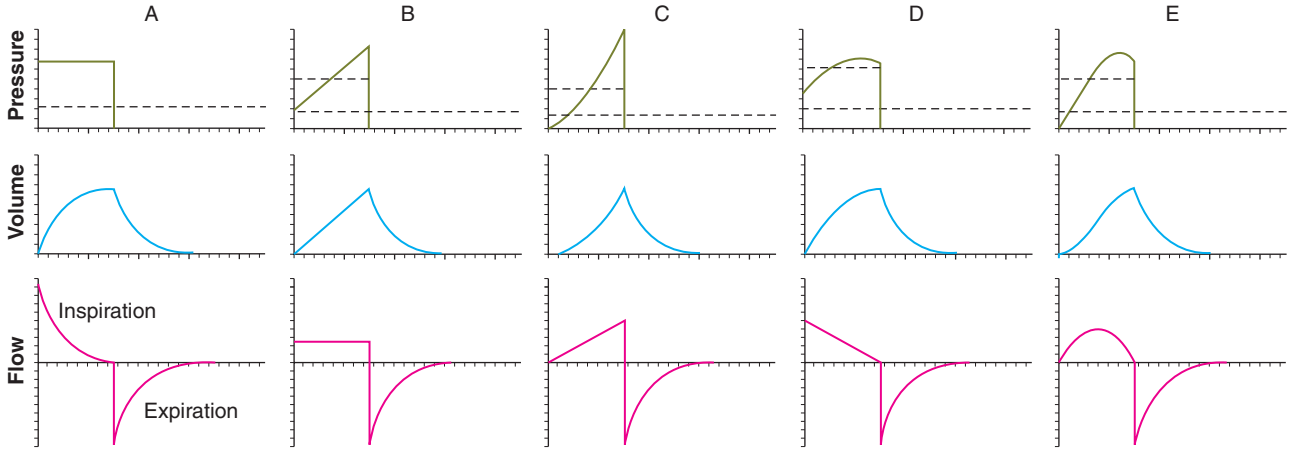


FIGURE 3-7 Idealized ventilator output waveforms. **A.** Pressure-controlled inspiration with a rectangular pressure waveform. **B.** Volume-controlled inspiration with a rectangular flow waveform. **C.** Volume-controlled inspiration with an ascending-ramp flow waveform. **D.** Volume-controlled inspiration with a descending-ramp flow waveform. **E.** Volume-controlled inspiration with a sinusoidal flow waveform. The *short dashed lines* represent mean inspiratory pressure, and the *long dashed lines* represent mean pressure for the complete respiratory cycle (i.e., mean airway pressure). Note that mean inspiratory pressure is the same as the pressure target in A. These waveforms were created as follows: (a) defining the control waveform using a mathematical equation (e.g., an ascending-ramp flow waveform is specified as flow = constant × time), (b) specifying the tidal volume for flow-control and volume-control waveforms, (c) specifying the resistance and compliance, (d) substituting the preceding information into the equation of motion for the respiratory system, and (e) using a computer to solve the equation for the unknown variables and plotting the results against time. (Reproduced, with permission, from Chatburn RL. *Fundamentals of Mechanical Ventilation.* Cleveland Heights, OH: Mandu Press; 2003:143.)

means that the patient circuit resistance, however small, adds to the total resistive load seen by the ventilator. Thus, in a volume-controlled breath, the peak inspiratory pressure is higher, and in a pressure-controlled breath, the tidal volume and peak flow are lower. In practice, the effect of patient circuit resistance is usually ignored because it is so much lower than the resistance of the respiratory system.

Now consider the patient circuit compliance. The effective compliance of the patient circuit is a combination of the tubing compliance and the compressibility of the gas inside it. As the ventilator delivers the breath to the patient, pressure at the airway opening rises relative to atmospheric pressure, which is the driving force for flow into the lungs. The patient circuit is connected between the ventilator and the airway, so the pressure it experiences across its walls is the same as that experienced by the respiratory system (remember that we are ignoring its resistance now, so we can ignore any pressure drop between the ventilator outlet and the airway opening). The volume change of the patient circuit tubing is different from that of the respiratory system because the compliance of the circuit is different. Because the patient circuit and the respiratory system fill with different volumes during the same inspiratory time, the flows they experience are different (remember that flow = volume ÷ time). Again borrowing a definition from electronics, if two circuit components share the same pressure drop but different flows, they are connected in parallel. Because they are in parallel, the two compliances are additive, so the total compliance is greater than either component.

Patient circuit compliance sometimes can be greater than respiratory system compliance and thus can have a large effect on ventilation. It must be accounted for either automatically by the ventilator or manually by increasing the tidal volume. For example, when ventilating neonates, patient circuit compliance can be as much as three times that of the respiratory system, even with small-bore tubing and a small-volume humidifier. Thus, when trying to deliver a preset tidal volume during volume-controlled ventilation, as little as 25% of the set volume will be delivered to the patient, with 75% compressed in the patient circuit. The compliance of the patient circuit can be determined by occluding the tubing at the patient *Y*, delivering a small volume under flow control (using zero positive end-expiratory pressure [PEEP]), and noting the resulting pressure. Using a short inspiratory hold will make it easier to read the pressure. Then compliance is calculated as before, by dividing the volume by the pressure. Once the patient circuit compliance is known, the set tidal volume can be corrected using the following equation:

$$V_{delivered} = \frac{V_{set}}{1+(C_{PC}/C_{RS})} \tag{1}$$

where $V_{delivered}$ is the tidal volume delivered to the patient, V_{set} is the tidal volume setting on the ventilator, C_{PC} is the patient circuit compliance, and C_{RS} is the respiratory system compliance.

We can get a more intuitive understanding of this equation if we put in some values. Suppose, for example, that we use the perfect patient circuit that has zero compliance. Substituting zero for C_{PC}, we get

$$\begin{aligned} V_{delivered} &= \frac{V_{set}}{1+(C_{PC}/C_{RS})} = \frac{V_{set}}{1+(0/C_{RS})} \\ &= \frac{V_{set}}{1+0} = \frac{V_{set}}{1} = V_{set} \end{aligned} \tag{2}$$

which shows that there is no effect on the delivered tidal volume. Suppose now that C_{PC} is as large as C_{RS} (i.e., $C_{PC} = C_{RS}$). Now we have

$$V_{delivered} = \frac{V_{set}}{1+(C_{PC}/C_{RS})} = \frac{V_{set}}{1+1} = \frac{V_{set}}{2} \tag{3}$$

in which case, half the volume from the ventilator goes to the patient, and the other half is compressed in the patient circuit. Some ventilators automatically compensate for gas lost to the patient circuit.[2]

The effect of the patient circuit is more troublesome during volume-controlled modes than during pressure-controlled modes. This is so because during volume control, the ventilator meters out a specific volume of gas, and unless it measures flow at the airway opening, it has no way of knowing how much goes to the patient and how much goes to the patient circuit. In contrast, during pressure-controlled modes, the ventilator simply meters out a set pressure change no matter where the gas goes. Because the respiratory system and the patient circuit compliance are in parallel, they both experience the same driving pressure (peak inspiratory pressure minus end-expiratory pressure), so tidal volume delivery is affected very little. The only effect might be that the patient circuit compliance may tend to increase the pressure rise time, which would tend to decrease peak flow and tidal volume slightly.

Another area where patient circuit compliance causes trouble is in the determination of auto-PEEP. There are several methods for determining auto-PEEP. One method to determine auto-PEEP during mechanical ventilation is to create an expiratory hold manually (i.e., delay the next inspiration) until static conditions prevail throughout the lungs (i.e., no flow anywhere in the lungs). The pressure at this time (total PEEP) minus the applied PEEP is an estimation of global auto-PEEP. Note that auto-PEEP may vary throughout the lungs depending on the distribution of lung disease and may not reflect pressure behind collapsed areas in patients with severe flow limitation. Auto-PEEP is an index of the gas trapped in the system at end expiration secondary to an insufficient expiratory time:

$$\text{measured auto-PEEP} = \frac{V_{trapped}}{C_{total}} \tag{4}$$

where $V_{trapped}$ is the volume of gas trapped in the patient and the patient circuit at end-expiration (above that associated with applied PEEP), and C_{total} is the total compliance of the

respiratory system and the patient circuit. The problem is that we want auto-PEEP to reflect the gas trapped in the patient, not in the circuit. If we know the compliances of the patient circuit and the respiratory system, we can correct the measured auto-PEEP as follows:

$$\text{true auto-PEEP} = \frac{C_{RS} + C_{PC}}{C_{RS}} \times \text{measured auto-PEEP} \quad (5)$$

where true auto-PEEP is that which exists in the lungs, measured auto-PEEP is the amount of end-expiratory pressure in equilibration with the lungs and the patient circuit, C_{RS} is the respiratory system compliance, and C_{PC} is the patient circuit compliance. If the ventilator displays auto-PEEP on its monitor, check the ventilator's operating manual to see whether or not the auto-PEEP calculation is corrected for patient circuit compliance. The larger C_{PC} is relative to C_{RS}, the larger will be the error. Again, the error will be most noticeable in pediatric and neonatal patients.

THE OPERATOR INTERFACE

The operator interaction with the ventilator mainly happens through the ventilator display. The display or interface has evolved in parallel with the ventilators. The key to this evolution are the technological advances in the last three decades.[2] The microprocessors, the digital displays, and the interactive screens have all permeated from other technological advances into the ventilator world. There are still remnants of the evolutionary process. In their initial ventilator generations, the interface had no or minimal manifestation of the interaction with the patient. The operator would enter the ventilator settings by using knobs or buttons that regulated simple functions (pressure, flow, or time). The results of these changes were evaluated in the patient clinical response, and occasionally through simple pressure analog displays. Some ventilators still use these type of displays (e.g., CareFusion 3100A high-frequency oscillator and Puritan Bennett LP-10, Fig. 3-8).

Most of the ventilators produced in the last decade have advanced displays, including liquid crystal displays and color touch screens with one or more multipurpose knobs or buttons. This allows the user to scroll through different menus and to select and activate the selections (e.g., Hamilton G5 ventilator, Fig. 3-9). The operator can customize the screen to the operator's needs. Current ventilators allow graphical displays of alarms, settings, respiratory system calculations, and measurements. The ventilator display evolution has not necessarily resulted in easier management of the ventilator. These advances brought issues with the amount of information displayed, the actions taken with that information, and the ease of use of certain interfaces.[6] As the level of sophistication has increased, we have been able to increase the number of ventilation parameters monitored. This requires a new level of training and understanding of human behavior. For example, a mode of ventilation may be preferentially chosen based on the amount of alarms it triggers,[7] or its ease of use.[6,8]

FIGURE 3-8 Puritan Bennett LP-10 home-care ventilator. (Image with permission from Nellcor Puritan Bennett LLC, Boulder, Colorado, doing business with Covidien.)

Operator Inputs

The operator input refers to parameters or settings entered by the operator of the ventilator. Each mode of ventilation has particular features, some of which can be adjusted by the operator. We describe here the most common adjustable parameters. The effect of each parameter on the lung is better understood under the light of the equation of motion (see Chapter 2).[9,10] A change of one parameter will lead to changes in others (i.e., in volume control, for the same respiratory characteristics changing the tidal volume will cause a change in peak airway pressure). Furthermore, knowing the basic construction and characteristics of a

FIGURE 3-9 G5 ventilator. (Reproduced with permission from Hamilton Medical, AG.)

mode of ventilation (volume vs. pressure control breaths) or the breath sequence (mandatory vs. spontaneous) will help understand how the setting will affect the ventilator output (see Chapter 2).

The operator input is presented below in the order that follows the progression of a breath; starting with the gas inhaled, to triggering, targeting, cycling, and baseline variables.

Inspired Gas Concentration

A mechanical ventilator has the capacity of delivering different mixtures of gas. Most ventilators allow the administration of specific concentrations of oxygen. A few allow the administration of helium, nitric oxide, or anesthesia gases.

OXYGEN

Oxygen is the most common gas administered to patients undergoing mechanical ventilation. The oxygen percentage in the inspired gas (FI_{O_2}) can be regulated in most ventilators by means of a direct adjustment of a specific control (21% to 100%). However, this is not true for all ventilators. For example, some home ventilators (e.g., LP-10 or the LTV 1150, Pulmonetic, CareFusion) use a connection to a low-pressure oxygen source to the ventilator or the patient circuit. The following formula can calculate the flow of oxygen to achieve a desired oxygen concentration:

$$O_2 \text{ required} = \frac{f \times V_T \times (\text{desired } FIo_2 - 0.21)}{0.79} \qquad (6)$$

where O_2 required is 100% oxygen flow in L/min, f is the breathing frequency in breaths/min, V_T is the tidal volume in liters and the FI_{O_2} is the patient O_2 concentration desired in decimal format (i.e., 30% = 0.3). An oxygen analyzer should be used to confirm the measurements. It must be recognized that changes in oxygen flow, breathing rate, or tidal volume will change the FI_{O_2}.

When transporting the critically ill patient, availability of oxygen supplies for the mechanically ventilated patient is crucial. Size and weight of cylinders makes transport difficult and presents an increased risk of fire. Branson et al. have described a solution using a portable oxygen concentrator (SeQual Eclipse II) paired with the Impact 754 and Pulmonetics LTV-1200 ventilators.[11]

For the rest of the current mechanical ventilators, the ventilator adjusts the mixture of air and oxygen to achieve the desired FIo_2. The mixing of air is achieved by an internal or external blender. A blender may use proportioning valves that regulate the flow of air and oxygen to a mixing changer (Fig. 3-10). It is similar to the mechanism used to mix hot and cold water in a shower—the more oxygen needed, the larger the opening for oxygen and the smaller it is for air. To work properly, the blender requires a constant pressure within the working ranges of the device.

Most current ventilators have oxygen sensors to monitor the FI_{O_2}. The oxygen sensor gives feedback to the operator to adjust the mixture, or alarms if there is a discrepancy between the set and delivered FI_{O_2}. The oxygen sensors detect changes in electrical current, which is proportional to the oxygen concentration. The most common techniques are: (a) paramagnetic, (b) polarographic, and (c) galvanic.[12]

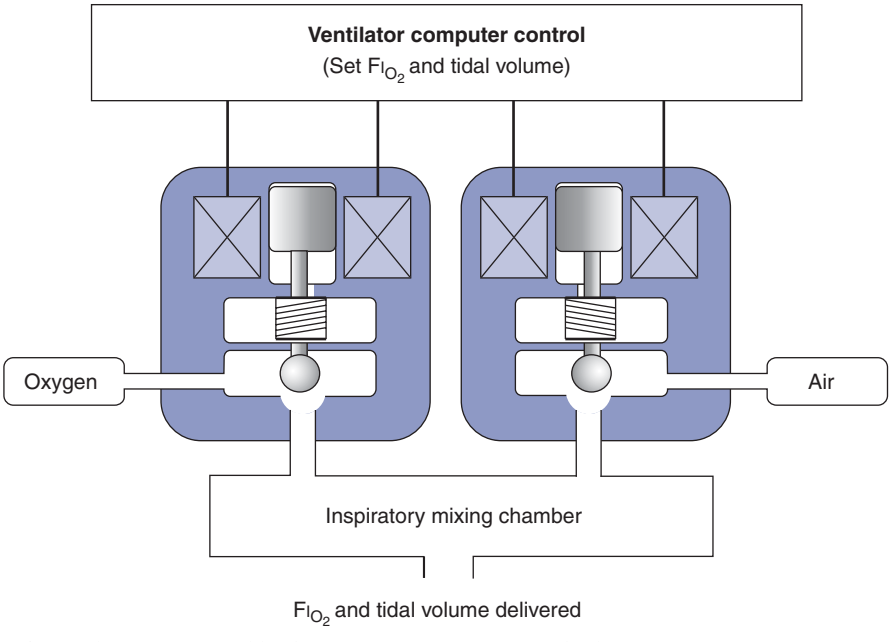


FIGURE 3-10 Schematic of a ventilator air–oxygen blending system using proportional valves.

TABLE 3-1: PROPERTIES OF PURE GASES AND AIR

Gas	Thermal Conductivity (κ) (μcal · cm · s · °k)	viscosity (η) (Micropoises)	Density (ρ) (g/L)
Helium (He)	352.0	188.7	0.1785
Nitrogen (N_2)	58.0	167.4	1.251
Oxygen (O_2)	58.5	192.6	1.429
Air	58.0	170.8	1.293

HELIOX

Mixtures of helium and oxygen (heliox, HeO_2) instead of air and oxygen are occasionally used to help patients on mechanical ventilation with obstructive airway diseases. Helium is less dense than air (Table 3-1).[13] The decrease in density interferes with flow measurements, inspiratory and expiratory valve accuracy, and gas mixing.[14] Several studies have evaluated the performance of mechanical ventilators delivering heliox[14–16] and have shown that heliox does affect the performance of the ventilator. The interference of heliox is more evident in volume-control modes than in pressure-control modes.[14,17] In pressure-control mode, the ventilator targets a set inspiratory pressure and the delivered tidal volume is dependent only on the mechanical properties of the respiratory system. The time constant may decrease but the delivered volume should be the same as for nonheliox gas delivery. In volume-control mode, delivered volume may be larger than, smaller than, or the same as expected depending on the design of the ventilator.[14] Only a few ventilators (Maquet Servo *i* with heliox option, Hamilton G5 with heliox option, and the Viasys Avea with comprehensive model) are designed and calibrated for heliox delivery. Otherwise, the operator needs to be aware of the specific ventilator performance and correction formulas and factors[14] such that potentially hazardous conditions do not develop.

NITRIC OXIDE

Inhaled nitric oxide (NO) is used as selective pulmonary vasodilator for patients with pulmonary hypertension, life-threatening hypoxia, or right-heart failure. Different devices to deliver NO have been described in the literature. Most of them were custom made and required the use of mixing chambers, stand-alone NO/nitric dioxide monitors, and manual titration of the gas flow. The large amount of custom-made devices led to inconsistent administration of NO.[18] In 1998, the American Society for Testing Materials (ASTM) committee on anesthetic and respiratory equipment developed a standard to provide a minimum degree of safety of the devices used to deliver NO. The recommendation was to use a NO administration apparatus, and a NO/nitrogen dioxide analyzer. The Food and Drug Administration (FDA) enforces this recommendation, and so far, only one device is approved in the United States. The INOvent (Ikaria Inc, Clinton, NJ) delivery system uses a closed-loop scheme to measure and deliver NO in proportion to the inspiratory flow from the ventilator. NO is injected in the proximal limb of the inspiratory circuit, and measured close to the connection between the patient circuit and the endotracheal tube. Two portable systems are available—INO Max DS (Ikaria) and AeroNOx (PulmoNOx, Alberta, CA). As these devices are not universally available, the following formula[19] can be used to calculate the NO flow rate required to achieve a desired concentration of NO when injected in the inspiratory limb at a constant gas flow,

$$Q_{NO} = \left(\frac{C_{NOset}}{C_{NOcyl} - C_{NOset}}\right) \times Q_V \qquad (7)$$

where Q_{NO} is the flow rate of nitric oxide in L/min, C_{NOset} is the desired NO concentration in parts per million (ppm), C_{NOcyl} is the NO concentration in the cylinder in ppm (usually 800 ppm) and the Q_V is the ventilator gas flow.

The formula is accurate for constant flow systems. This presents a major problem when used with intermittent breaths (as most modes of ventilation) the patient will receive variable amounts of NO (a "bolus" with each mechanical breath).[20] Furthermore, whenever the ventilator settings or the patient breathing pattern changes, the NO delivery will change. Finally, the use of NO will alter the gas delivery of the ventilator. For example, the INOvent system will add gas to and extract gas from the delivered breath. At 80 ppm it adds 10% more gas, although it also withdraws 230 mL/min through the gas-sampling port. Thus, the oxygen delivered will decrease, and the tidal volume may increase. The changes seem to be small (unless you see it in pediatric proportions), but it may affect the ventilator's performance. Furthermore, as a flow of gas is introduced, the flow-triggering performance may be affected.

Trigger Variables

A ventilator-assisted breath can be started (triggered) by the machine or the patient. A machine-triggered breath is defined by the start of the inspiratory phase *independent*

of any signal from the patient. The operator typically sets a breath frequency for machine-triggered breaths. A patient-triggered breath is one for which inspiration is started solely by a signal from the patient. The key operator set variable for patient triggering is sensitivity, or the magnitude of the patient signal required to initiate inspiratory flow. The patient signal can be obtained from measuring the airway pressure, flow, volume, electromyogram (EMG),[21] abdominal motion (Graseby capsule[22]), thoracic impedance,[23] or any other measurable signal of respiratory activity.[24] Most intensive care ventilators measure pressure and flow (volume is integrated from flow) at the circuit. There are only a few ventilators that use other sources of signaling, diaphragmatic EMG (Servo *i* NAVA), thoracic impedance (Sechrist SAVI), and abdominal motion (Infant Star STAR SYNC, which is no longer commercially available).[24,25]

Ventilator triggering characteristics can be evaluated using different metrics.[23,26–28] The most sophisticated device for evaluating ventilator performance is the ASL lung simulator (IngMar Medical Ltd., Pittsburgh, PA). This device can simulate both passive lung mechanics (e.g., resistance and compliance) as well as patient inspiratory and expiratory effort. It can display and record pressure, volume, and flow signals, and calculate a wide variety of performance metrics. Figure 3-11 shows an example of these waveforms with specific reference points for calculating performance metrics (from operator's manual for software version 3.2). Using these reference points we can define the following key trigger metrics: P_{min} (maximum pressure drop relative to PEEP during the trigger phase), pressure-time product ($\int Paw–PEEP\,dt$ from start of effort to return of airway pressure [Paw] to PEEP), patient trigger work ($\int Paw–PEEP\,dv$ from start of effort to return of Paw, to PEEP), and time to trigger (period from the start of effort to the return of Paw to PEEP).

TIME

Time is measured by the internal ventilator processor. The next breath is time triggered (in the absence of a patient trigger event) when the expiratory time has reached the threshold to maintain a set respiratory rate (e.g., if the set rate is 10 breaths per minute and the inspiratory time is set at 1 second, then the expiratory time is 5 seconds). Some modes allow the user to set the inspiratory and expiratory time [e.g., airway pressure release ventilation (APRV) and biphasic], thus fixing the inspiratory-to-expiratory timing (*I:E*) ratio and respiratory rate. In an effort to improve patient–ventilator interactions, the ventilator may synchronize the mandatory breath with the patient's triggering signal if it falls within a threshold. The classic example is synchronized intermittent mandatory ventilation (SIMV). More recently APRV, as programmed in the Evita XL, delivers a machine breath if the patient trigger signal falls within 25% of the triggering time.[29] Time triggering is also found as a safety mechanism. The operator or manufacturer enters a time after which the apnea alarm will trigger the delivery of a preset breath after a preset time is reached.

PRESSURE

The patient inspiratory effort causes a drop in pressure in the airway and the circuit. Inspiration starts when pressure falls below the preset "sensitivity" threshold. The site of measurement will have an impact on the performance of the device. Pressure signals travel at the speed of sound, approximately 1 ft/ms.[30] The farther the sensor is from the signal source, the longer the potential time delay. The closest measurements can be done in the trachea. Tracheal pressure measurements reflect actual airway pressure as the endotracheal tube resistance is bypassed. When used for ventilator

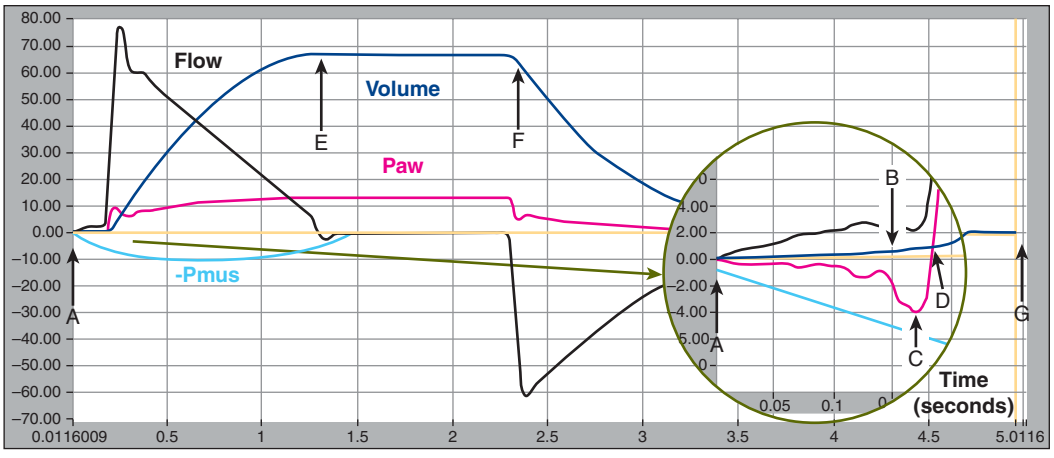


FIGURE 3-11 Reference points on pressure, volume, and flow waveforms recorded by the ASL 5000 (IngMar Medical Ltd, Pittsburgh, PA). **A.** Start of inspiratory effort, **B.** beginning of inhalation as determined by the "breath start volume threshold," **C.** lowest pressure during the trigger phase, Pmin, **D.** return of airway pressure to baseline during the trigger phase, **E.** end of inspiratory time, i.e., negative-going zero flow crossing, **F.** beginning of exhalation as determined by the "expiratory start volume threshold," and **G.** end of expiratory time, i.e., positive-going zero flow crossing. (Reproduced, with permission, from Ingmar Medical. *ASL 5000 v3.2 Operator's Manual.* Pittsburgh, PA: Author.)

TABLE 3-2: ADVANTAGES AND DISADVANTAGES OF THE DIFFERENT CIRCUIT PRESSURE-SENSING SITES

Advantages	Disadvantages
A. Exhalation port: Well protected from mechanical abuse. During mechanical inhalation, accurately reads pressure at the Y. During inhalation, increases in inspiratory or expiratory circuit resistance do not compromise inspiratory flow output, except for manyfold increases.	Requires protection from moisture of exhaled gas. During spontaneous inspiration, underestimates pressure generated at the Y to trigger the ventilator. During exhalation, underestimates pressure at the Y. During exhalation, increases in expiratory circuit resistance compromise expiratory flow. Hence, system requires well-maintained expiratory filter to ensure that expiratory circuit resistance remains low.
B. Inhalation port: Well protected from mechanical abuse. Does not require protection from moisture or additional filters. During exhalation, accurately reads pressure at the Y as long as the inspiratory circuit remains patient. During inhalation, increases in expiratory circuit resistance do not compromise inspiratory-flow output.	During mechanical inhalation, overestimates pressure at the Y. During spontaneous inspiration, underestimates pressure generated at the Y to trigger the ventilator. During inhalation, increases in inspiratory circuit resistance compromise inspiratory flow output. For example, factors such as selection of humidifier and type of patient circuit yield varying patient inspiratory efforts for fixed ventilator settings.
C. Patient Y: During inhalation and exhalation, accurately reads both inspiratory and expiratory pressures. Pressure readings reflect relative condition of inspiratory and expiratory circuits.	Susceptible to mechanical abuse. Requires a separate pressure-sensing tube, which is prone to occlusion, blockage, and disconnection, all of which prevent sensing of patient effort.

Source: Modified, with permission, from Sassoon CSH. Mechanical ventilator design and function: the trigger variable. *Respir Care*. 1992;37:1056–1069.

triggering, tracheal pressure sensing results in decreased work of breathing.[31–33] However, tracheal pressure measurements are not routinely done and require special equipment (endotracheal tube with monitoring port) and no current ventilator uses it to routinely trigger the ventilator.

The other sites of pressure measurement are the patient circuit Y or at the inspiratory or expiratory ports, each with its advantages and disadvantages (Table 3-2). Trigger performance will also be affected by the presence of humidifiers, filters, water condensation, patient circuit and exhalation valves. These will most often dampen, or rarely amplify, the pressure signal. Clinically, the presence of a dampened signal will require a larger pressure change (higher work of breathing) to reach the trigger threshold. On the contrary, presence of water in the pressure tubing may cause oscillation, which can falsely trigger mechanical breaths.

The trigger pressure sensitivity is usually set at 0.5 to 1.5 cm H_2O below the baseline pressure. Common practice is to increase the sensitivity (i.e., decrease the pressure drop) until autotriggering occurs and then reduce sensitivity until the autotriggering just stops.[30] Note that each ventilator comes with predetermined manufacturer set values and can be adjusted.

FLOW

Flow triggering is based on the detection of a change in a constant, small, baseline (bias) flow through the patient circuit. The operator sets a flow sensitivity threshold. When the change in flow reaches the threshold, a breath is delivered. The changes in flow are detected at the expiratory valves or by a flow sensor in the patient circuit. The ventilator measures the flow from the ventilator and from the patient. In a closed circuit, the two flow values should remain equal in the absence of patient effort. When the patient makes an inspiratory effort, the expiratory flow drops, creating a difference between the inspiratory and expiratory flow values. When the difference in values reaches the preset sensitivity threshold, a breath is delivered. Some systems (Puritan Bennett, 7200) allow the operator to set both the bias flow and the trigger sensitivity. Newer devices set the bias flow according to the operator selected value for the triggering sensitivity. For example, the Puritan Bennett 840 sets the flow 1.5 L/min above the selected sensitivity, and the Hamilton G5 automatically sets the bias flow equal to two times the set sensitivity threshold. As a backup, if flow sensor is kinked or taken out of line, an internal pressure trigger of −2 cm H_2O is used until the flow sensor is "online" again.

Flow change may be detected by placing a sensor just before the endotracheal tube. The close proximity to the patient may enhance triggering. It, however, exposes the sensor to secretions and moisture, which may affect its performance. Flow triggering seems more efficient than pressure triggering in terms of work of breathing.[34] This, however, seems of no particular clinical relevance in the presence of appropriately set pressure triggering.[35] Flow sensing may cause autotriggering secondary to noninspiratory flow changes. The flow change can happen in either the ventilator circuit (leak in the circuit or endotracheal tube) or the patient (cardiogenic oscillations or bronchopleural fistula).[36,37]

A novel approach to flow triggering is offered on the Dräger Infinity V500 ventilator in the APRV mode. Rather than setting a T-low time to determine the time triggering of each mandatory breath, the operator may set a percent of peak *expiratory* flow as the trigger threshold.

VOLUME

A breath may be triggered when a preset volume is detected as the result of a patient inspiratory effort. This is similar to

flow triggering but using volume has the theoretical advantage of being less susceptible to signal noise (i.e., integrating flow to get volume cancels out some noise because of flow oscillations). Volume triggering is rare in ventilators but can be found on the Dräger Babylog VN500 infant ventilator.

DIAPHRAGMATIC SIGNAL

The ideal approach to coordinate a mechanical ventilator with the patient inspiratory effort would be to use the neural output of the respiratory center. Direct measurement of the respiratory center output is currently not possible. The phrenic nerve has been used as a trigger signal in animal models,[38,39] but not in humans. The only available clinical approach is measurement of the diaphragmatic electrical activity (Edi). Because the Edi is an electric signal, it easily becomes contaminated by the electrical activity of the heart, the esophagus, and other muscles.[21] More importantly, the Edi requires an intact respiratory center, phrenic nerve, neuromuscular junction, and assumes that the diaphragm is the primary inspiratory muscle (e.g., rather than accessory muscles of ventilation).

The only clinically available system that uses diaphragmatic signal trigging is the neurally adjusted ventilatory assistance (NAVA) system. An esophageal catheter is used to measure the Edi. The sensitivity is set by entering a value above the background electrical noise. The trigger value is set in microvolts and represents the change in the electrical signal rather than an absolute value.[40] The default setting is 0.5 microvolts, but it can be adjusted from 0 to 2 microvolts. As a backup trigger signal in the absence of a measurable Edi, NAVA uses flow or pressure triggering, whichever happens first.

OTHER SIGNALS

The BiPAP Vision (Respironics Inc., Murrysville, PA) uses a triggering mechanism called *shape-signal*. The ventilator microprocessor generates a new flow signal, which is offset from the actual flow by 0.25 L/s and delays it for 300 milli seconds. The delay causes the flow shape signal to be slightly behind the patient's flow rate. The mechanical breath is triggered when a sudden decrease in expiratory flow from an inspiratory effort crosses the shape signal.[41]

The Sechrist SAVI system (Sechrist Industries, Anaheim, CA) is the only mode available that uses transthoracic electrical impedance to trigger the ventilator.[25] The thoracic impedance is obtained by placing two chest leads, one in the anterior axillary line on the right and the other in the posterior axillary line on the left. The sensors are placed high enough to avoid costal and subcostal retractions. The chest sensors measure the electrical impedance across the human body. As a breath occurs, the transthoracic impedance changes as a result of a different ratio of air-to-fluid in the thorax. The triggering threshold can be adjusted. The cardiac cycle may also cause interference with the signal.[22,25]

Target Variables

During inspiration, the variable limiting the magnitude of any parameter is called the target variable (previously known as the limit of the control variable, but the term *limit* is now reserved for alarm and safety conditions rather than control settings).[42]A target is a predetermined goal of ventilator output. Targets can be viewed as the parameters of the targeting scheme (see Chapter 2). *Within-breath targets* are the parameters of the pressure, volume, or flow waveform. Examples of within-breath targets include inspiratory flow or pressure rise time (set-point targeting), inspiratory pressure and tidal volume (dual targeting), and constant of proportionality between inspiratory pressure and patient effort (servo targeting). *Between-breath targets* serve to modify the within-breath targets and/or the overall ventilatory pattern. Between-breath targets are used with more advanced targeting schemes, where targets act over multiple breaths. A simple example of a between-breath target is to compare actual exhaled volume to a preset between-breath tidal volume so as to automatically adjust the within-breath constant pressure or flow target for the next breath. Examples of between-breath targets and targeting schemes include average tidal volume (for adaptive targeting), percent minute ventilation (for optimal targeting), and combined partial pressure of carbon dioxide, volume, and frequency values describing a "zone of comfort" (for intelligent targeting).

PRESSURE

The ventilator uses microprocessors to control the delivery of pressure. The pressure can be delivered with any pressure profile and in response to many signals. Currently, most modes of ventilation in which inspiratory pressure is targeted deliver the pressure rapidly and attempt to maintain the pressure constant throughout the inspiratory phase (square waveform). This means that the performance of the ventilator depends on the delivery of the pressure waveform and any departure from the ideal waveform leads to differences in performance between ventilators.[43,44]

Inspiratory Pressure. The pressure rise during inspiration associated with volume and flow delivery is set by the operator (pressure control–continuous mandatory ventilation) or closed-loop algorithms (e.g., pressure-regulated volume control). Care should be exercised while setting the ventilator or reading the literature as there is significant variability between ventilator manufacturers and peer-reviewed literature in the definitions and nomenclature related to inspiratory pressures.[43] The main problem stems from what historically has been used to define the inspiratory pressure. For example, in the same ventilator, for

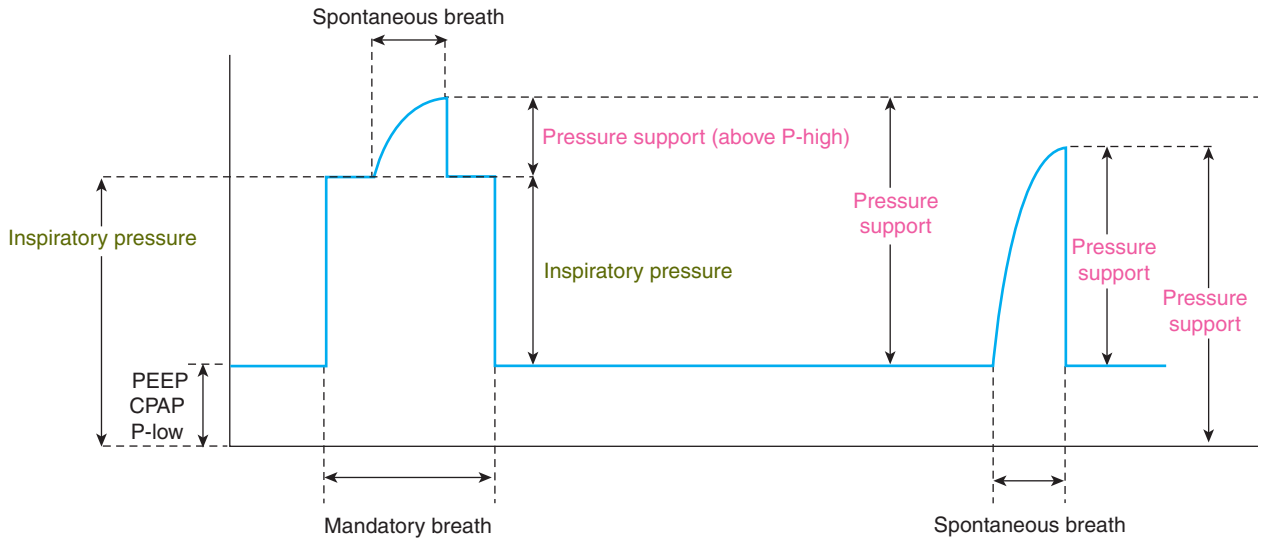


FIGURE 3-12 Idealized airway pressure waveform showing various conventions used for pressure parameters. Note that there are two ways to define inspiratory pressure for mandatory breaths (*green*) and four ways to define inspiratory pressure (i.e., pressure support) for spontaneous breaths (*red*). *CPAP*, continuous positive airway pressure; *PEEP*, positive end-expiratory pressure; *P-high*, high pressure; *P-low*, low pressure. (Reproduced, with permission, from Chatburn RL, Volsko TA. Documentation issues for mechanical ventilation in pressure-control modes. *Respir Care.* 2010;55(12):1705–1716.)

pressure control–continuous mandatory ventilation breaths the peak inspiratory pressure is stated in reference to the set end-expiratory pressure (PEEP), but for APRV the peak inspiratory pressure is stated in reference to the atmospheric pressure. To compound the confusion, on some ventilators the value of pressure support is set relative to PEEP (e.g., Drager Evita XL, Puritan Bennett 840), on others (LTV 950) pressure support is set relative to the atmospheric pressure (i.e., atmospheric pressure = zero airway pressure), and on at least one ventilator (BiVent in Servo *i*) pressure support may be set relative to inspiratory pressure (P-high). Figure 3-12 illustrates the two different ways used to define inspiratory pressure and the four different ways to define pressure support. Figure 3-13 illustrates the proposed solution to this problem.[43] In this proposal, the term *inspiratory pressure* is defined as the set change in airway pressure during inspiration relative to set end-expiratory airway pressure during pressure-control modes.

On some ventilators, inspiratory pressure rise is set relative to atmospheric pressure rather than set end-expiratory pressure. To distinguish this from inspiratory pressure as defined relative to PEEP, the term *peak inspiratory pressure* has been proposed.[43] In contrast "peak *airway* pressure" is the *measured* peak airway pressure relative to atmospheric pressure. Often, for a good pressure-control system, there is seemingly no difference between set peak inspiratory pressure and measured peak airway pressure on the airway-pressure waveform during pressure-control modes. And even if the operator sees a transient small difference, this is not considered clinically important in most nonalarm cases. This leads clinicians to conceptually oversimplify what they see and make the mistake of assuming inspiratory pressure and peak airway pressure are synonymous. For example, measured peak airway pressure is often higher than set peak inspiratory pressure because of pressure transients from an underdamped pressure-control system or noise from patient movement. The introduction of the so-called active exhalation valve made possible unrestricted spontaneous breaths during the inspiratory phase of a mandatory pressure-control breath. New modes brought new terms. For example, P-high or PEEP high refers to the peak inspiratory pressure above atmospheric pressure in APRV (again, there is no standardization of either terminology or symbology in this mode).

P_{max}. The Drager Evita XL, when set in volume-control modes, allows the operator to set the maximum pressure (P_{max}) that can be achieved during the delivery of a mandatory breath. The goal is to prevent pressure peaks while maintaining the set tidal volume. When the P_{max} is reached during a given inspiration, the ventilator switches from volume control to pressure control (dual targeting) using the P_{max} setting as the inspiratory pressure target. If the set tidal volume cannot be reached in the set inspiratory time, the ventilator will alarm.[45]

Rise Time. The speed with which the airway pressure reaches the set inspiratory pressure is called the *rise time*. (Rise time for flow can be set in the Maquet Servo *i*, but this feature is rare on ventilators.) The rise time may be set by the operator or automatically adjusted based on a computer algorithm (e500, Newport Medical Instruments Inc, Newport Beach, California). The name used to indicate pressure rise time varies by ventilator brand (e.g., inspiratory

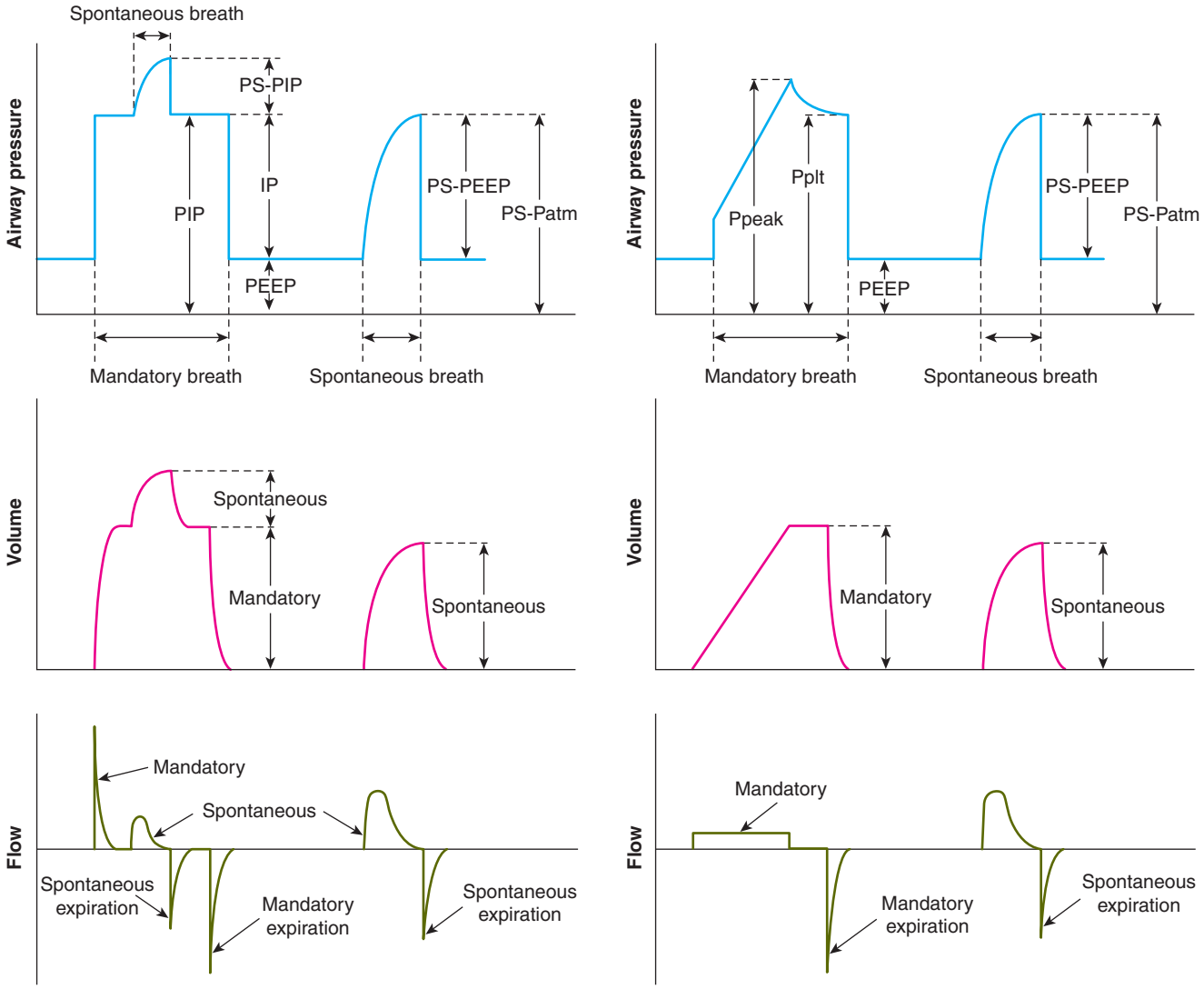


FIGURE 3-13 Idealized pressure, volume, and flow waveforms for pressure control and volume control illustrating the use of proposed conventions for both set and measured airway pressures. *IP*, inspiratory pressure; *PEEP*, positive end-expiratory pressure; *PIP*, peak inspiratory pressure; *Ppeak*, peak pressure; *Pplt*, plateau pressure; *PS-Patm*, pressure support relative to atmospheric pressure; *PS-PEEP*, pressure support relative to positive end expiratory pressure; *PS-PIP*, pressure support relative to peak inspiratory pressure. (Reproduced, with permission, from Chatburn RL, Volsko TA. Documentation issues for mechanical ventilation in pressure-control modes. *Respir Care*. 2010;55(12):1705–1716.)

slope, P-ramp, plateau%, and slope rise time). Adjusting the rise time influences the synchronization between the patient and the ventilator secondary to changes in the initial inspiratory flow rate. The lower the rise time, the faster the pressurization rate[46] and the higher the peak inspiratory flow.[47] A higher initial inspiratory flow rate may decrease the work of breathing but can lead to patient discomfort and worse patient–ventilator synchrony. Conversely, too slow a rise time may result in increased work of breathing and longer mechanical inspiratory time, leading to a dissociation between patient breathing effort and the mechanical breath. That is, the relation between work of breathing, respiratory drive, and comfort with the duration of the rise time is not proportional.[46,48] Because rules for setting an optimal rise time are lacking, based on these studies, both very rapid and slow rise time should be avoided. A more gradual rise may be needed in awake patients (for comfort) or patients with low compliance to prevent pressure overshoot and premature cycling of inspiration (Fig. 3-14).

TIDAL VOLUME

The operator is required to enter a tidal volume in any volume-control mode. This may be a direct setting or an indirect one by setting frequency or minute ventilation. The ventilator will control the tidal volume and the pressure will be the dependent variable. A tidal volume target, however, may also be set when the mode uses adaptive targeting in pressure control (e.g., pressure-regulated volume control [PRVC] on the Maquet ventilators).[49] In such a case, inspiratory pressure

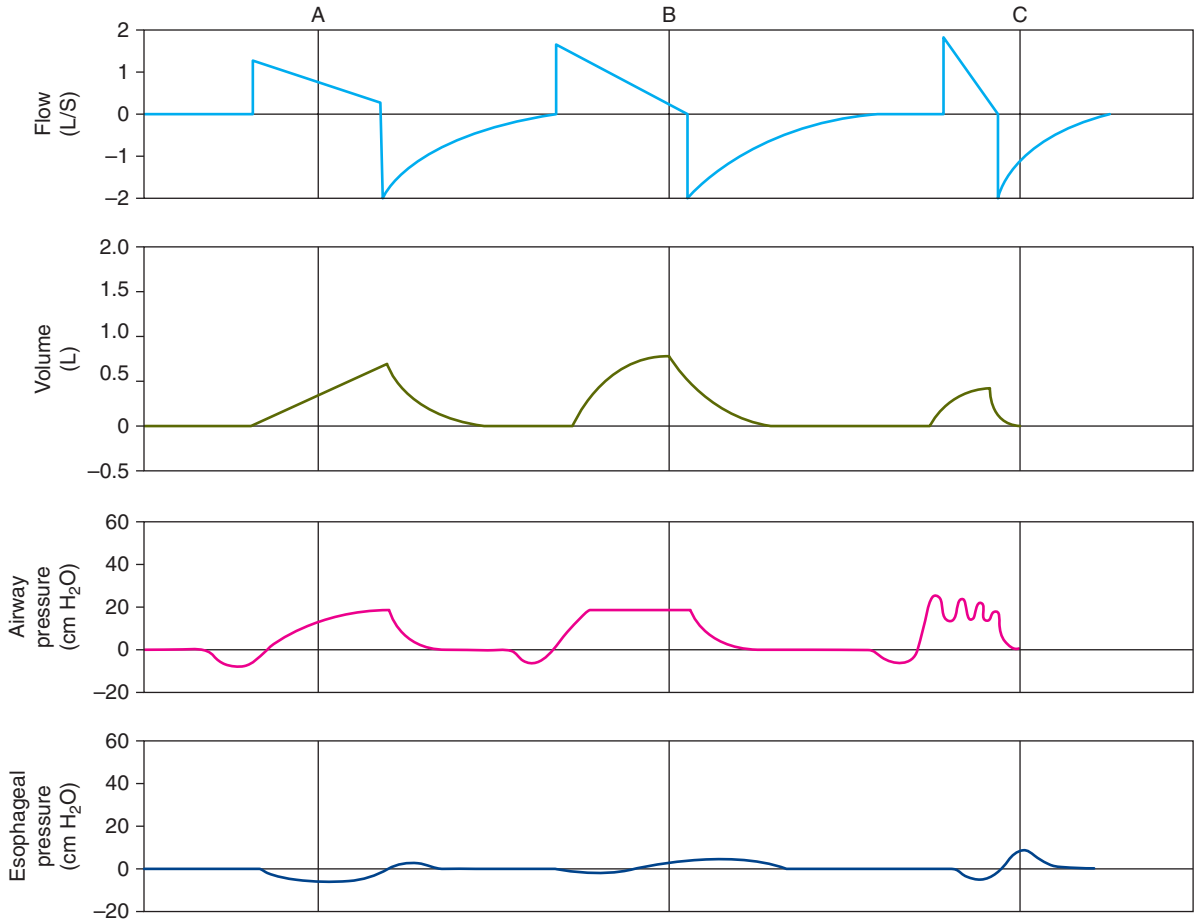


FIGURE 3-14 Examples of different pressure rise times in three breaths in pressure-support mode. **A.** Rise time is set very low, resulting in a lower peak inspiratory flow. **B.** Rise time is set higher, resulting in a higher peak flow and shorter inspiratory time. **C.** Rise time is set very high, resulting in "ringing" of airway pressure signal and peak flow that is uncomfortable to the patient, who exerts an expiratory effort and prematurely terminates inspiration (indicated by the positive deflection of esophageal pressure). (Reproduced, with permission, from Macintyre NR. Patient-ventilator interactions: optimizing conventional modes. *Respir Care*. 2011;56(1):73–81.)

is automatically adjusted between breaths by the ventilator to achieve an average measured tidal volume equal to the operator set target. There are four basic ways ventilators deliver a preset tidal volume (from least used to most commonly used):

1. By measuring the volume delivered and using the signal in a feedback control loop to manipulate the volume waveform.
2. By the displacement of a piston or bellows. An example of this is the Puritan Bennett LP10 home-care ventilator (piston) or some anesthesia ventilators (bellows).
3. By controlling the inspiratory pressure within a breath and automatically adjusting it between breaths to deliver a minimum set tidal volume. The volume delivered is targeted by a closed-loop algorithm, known as adaptive pressure control (see Chapter 2). This targeting scheme is available in most modern critical care ventilators under multiple names (e.g., PRVC, autoFlow, VC+, APV). A common confusion is that this is a volume-control mode, when, by the equation of motion, what is being controlled is pressure during a breath. A caveat with this targeting scheme is that in the presence of the patient's inspiratory efforts, the tidal volume may be higher than set, and the support provided by the ventilator may be inappropriately low.[50,51]
4. By controlling flow, the volume delivered is indirectly controlled. Because flow and volume are inverse functions of time (i.e., volume is the integral of flow and flow is the derivative of volume), controlling one controls the other. In simple ventilators, there is no feedback signal for flow, just a known flow for an adjustable amount of inspiratory time. On more sophisticated ventilators, the operator can regulate the shape of the inspiratory flow waveform. A square waveform will create higher peak airway pressures and will require less time to deliver the set volume (which may result in lower mean airway pressures) than a descending ramp pattern.[52–54] Some ventilators offer one waveform (e.g., the Dräger Evita XL offers only the

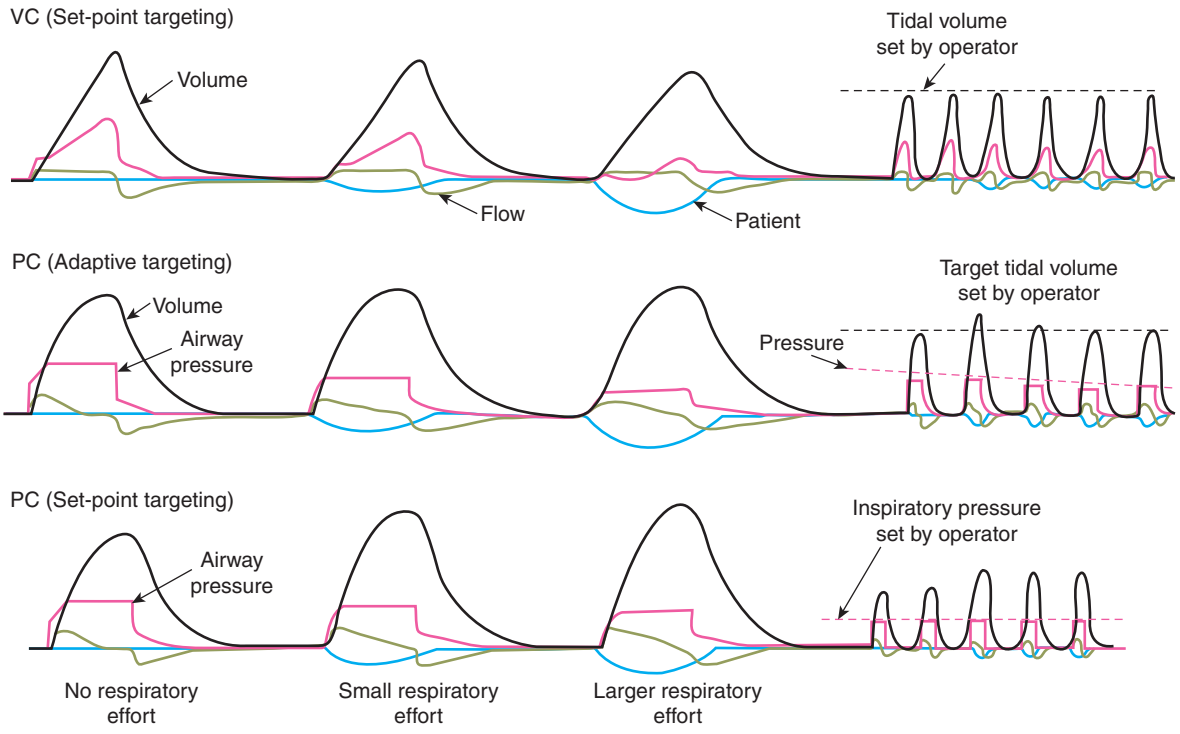


FIGURE 3-15 Volume delivery in volume control (VC) and pressure control (PC) modes using set-point targeting versus pressure control using adaptive targeting. Notice how tidal volume (flow) remains constant in volume control with set-point targeting in the setting of increased patient effort. In adaptive pressure targeting, the inspiratory pressure is adjusted by an algorithm to keep the tidal volume at a target. The tidal volume, however, may be larger if the patient effort is large enough. In set-point pressure targeting, the pressure remains constant, and the tidal volume increases in response to patient effort.

square waveform) others have more (e.g., the Hamilton Veolar offers 50% or 100% descending ramps, sinusoidal, and square).[55] Most current ventilators only provide the square waveform or a descending ramp profile.

Figure 3-15 compares volume delivery between standard volume and pressure control modes versus modes using adaptive pressure control.

MINUTE VENTILATION

In volume-control modes, the minimum minute ventilation is set by entering the tidal volume and respiratory rate. This assures that the patient will receive a minimum amount of ventilatory support. Some modes provide the option to enter a target minute ventilation (as a percent of the calculated minute ventilation for a given ideal body weight, adaptive-support ventilation [ASV]; e.g., Hamilton G5), while others will calculate it from the entered tidal volume and respiratory rate (mandatory minute volume [MMV]; e.g., Dräger Evita XL). The concept of automatically adjusting the ventilator settings to maintain a constant minute volume was first described by Hewlett and Plat in 1977.[56] As implemented, for example, on the Dräger Evita XL ventilator, MMV is a form of volume control–intermittent mandatory ventilation. The operator presets the target minute ventilation by setting tidal volume and frequency. The ventilator then monitors the total minute ventilation as the sum of the minute ventilations generated by mandatory and spontaneous breaths. If the total minute ventilation is below the target value, the mandatory breath frequency will increase. As long, however, as the spontaneous minute ventilation is at least equal to the target value, mandatory breaths will be suppressed. In this way, the proportion of the total minute ventilation generated by spontaneous breaths can range from 0% to 100%. As a result, MMV may be considered a mode of automatic weaning.

Another version of MMV was used on the Hamilton Veolar ventilator (now obsolete); the target minute ventilation was maintained by automatic adjustment of inspiratory pressure (adaptive pressure support). That mode was replaced by ASV on newer Hamilton ventilators.[49] ASV is the only commercially available mode to date that uses optimal targeting. It was first described by Tehrani in 1991.[57] The operator inputs the patient's height and percent of minute ventilation to be supported (25% to 350%). The ventilator then calculates the ideal body weight and estimates the required minute alveolar ventilation assuming a normal dead space fraction. Next, an optimum frequency is calculated based on work by Otis et al[9] that predicts a frequency resulting in the least mechanical work rate. The target tidal volume is calculated as minute ventilation divided by

TABLE 3-3: DETERMINANTS OF MINIMUM AND MAXIMUM MINUTE VENTILATION FOR SOME COMMON MODES

Mode Name	A/C	SIMV	MMV	ASV	Smart Care
Operation	Operator enters a set rate and tidal volume. Patient may trigger breaths above set rate.	Operator enters a set rate and tidal volume. Patient may breath in between mandatory breaths with or without assistance.	Operator enters a set rate and tidal volume. Patient may breath with or without assistance. If his minute ventilation falls below minimum, then mandatory breaths initiate at a set rate.	Adaptive pressure control breaths target tidal volume and rate according to mathematical model.	Pressure support is titrated based on expert rules to achieve the range $etPCO_2$.
Control variable	Volume	Volume	Volume	Pressure	Pressure
Breath sequence	CMV	IMV	IMV	IMV	CSV
Minimum minute ventilation	set $V_T \times$ set f	set $V_T \times$ set f	set $V_T \times$ set f	Targeted by ventilator based on operator-entered body weight.	Targeted by ventilator to maintain "comfort zone" based on V_T, f, and $etPCO_2$.
Maximum minute ventilation	Variable: $V_T \times$ total f	Variable: $V_T \times$ total f	Variable: $V_T \times$ total f	Variable but ventilator will reduce support if patient attempts to increase above estimated minute ventilation requirement.	Variable but ventilator will reduce support if patient attempts to increase above estimated minute ventilation requirement.

Abbreviations: *A/C*, assist/control; *ASV*, adaptive support ventilation; *$etPCO_2$*, end-tidal pressure of carbon dioxide; *f*, ventilatory frequency—total f reflects the sum of machine- and patient-triggered breaths; *MMV*, mandatory minute volume; *SIMV*, synchronized intermittent mandatory ventilation; *V_T*, tidal volume.

respiratory frequency (MV/f). In ASV, there are two breath patterns based on the patient's respiratory effort. If there is no patient effort, the ventilator delivers adaptive pressure-control ventilation; if there is patient effort, the patient receives adaptive pressure support. In both instances, the inspiratory pressure within a breath is controlled to achieve a target tidal volume.[49]

Table 3-3 summarizes the determinants of minimum and maximum minute ventilation for some common modes.

INSPIRATORY FLOW

The inspiratory flow can be adjusted by the operator on most ventilators that provide volume-control modes (see "Tidal Volume" above). In general, the ventilator operator will choose a peak flow and may have some waveform pattern options (e.g., square waveform or descending ramp). Although these settings appear simple, there are several points that may cause differences in performance and interpretation of data. First, the ventilator uses a microprocessor to control the delivery according to the preset tidal volume, inspiratory time, flow pattern, pressure limits, and ventilator-specific algorithms. During the breath, the flow delivery is adjusted according to a closed-loop feedback mechanism and proprietary software.[2] The consequence is a difference in performance among ventilator brands, even in the same mode.[27] Second, the interface may add confusion. For example, in the Dräger Evita XL, while on volume control, the operator will need to set the inspiratory flow, the inspiratory time, and tidal volume, whereas on the Hamilton G5, the options are customizable in three different ways! (Hopefully, all conducive to the same output.) The operator can enter (a) the *I:E* and the percent pause in inspiration, (b) the peak inspiratory flow and inspiratory time, or (c) the percent inspiratory time and plateau pause time. Underscoring that knowledge of the device used is essential. Finally, to add to the confusion, there are incorrect conclusions that sometimes permeate practice:

1. *In pressure-control mode, the flow is controlled as a descending ramp*. In a pressure-controlled breath, the volume and the flow are the manifestation of the respiratory system characteristics (resistance and compliance) and the patient's respiratory effort. If the patient is passive (no respiratory effort), the flow will decay exponentially (see Fig. 3-7, *A*). If the patient has a respiratory effort, the flow pattern will be variable, according to the characteristics of the patient effort, the ventilator settings (inspiratory pressure, pressurization algorithm, triggering, etc.), and the respiratory system characteristic. The only way to have a standard descending ramp is to select that waveform and have the computer control the flow delivery in volume control.

2. *The "autoflow" function adjusts the flow in a volume-controlled breath to the patient's demand.* Autoflow is available in Dräger Evita ventilators. It appears as an add-on for three modes of volume-control ventilation (controlled mechanical ventilation [CMV] or intermittent positive-pressure ventilation [IPPV], SIMV, and MMV). This "add on" is defined in the manual as automatic regulation of the inspiratory flow adjusted to the changes in lung conditions and to the spontaneous breathing demands.[58,59] What this "add on" does is turn the mode from a volume-control mode to an adaptive pressure-control mode. This is the same as being on PRVC on the Maquet ventilators. They all automatically adjust the inspiratory pressure to achieve a target tidal volume and because this is a pressure-controlled breath, the flow will be variable (see "Tidal Volume" above).

The inspiratory flow setting has importance at different levels. The work of breathing is related to the peak flow and the pressurization rate. The balance between patient and ventilator work of breathing will be affected by the inspiratory flow setting. In regards to cycling, high flows can lead to high peak inspiratory pressures (peak inspiratory pressure [PIP] is directly proportional to resistance, the higher the flow, the higher the PIP), which may lead to reaching the pressure or flow-cycling threshold and ending the breath prematurely.[59] But a more practical issue is this: does the flow-wave shape itself have any effect on patient outcome? Like most other questions about ventilator settings affecting patient outcome, after more than 30 years of research on this particular subject we still do not know the answer.

Studies from the early 1960s to early 1980s produced conflicting results, prompting Al-Saady and Bennett to design a better-controlled study, keeping tidal volume, minute ventilation, and *I:E* ratio constant.[60] They discovered that compared to a constant inspiratory flow, a descending ramp flow (what they and many subsequent authors have called "decelerating flow") resulted in a lower peak airway pressure, total respiratory resistance, work of inspiration, dead space-to-tidal volume ratio, and alveolar–arterial oxygen tension gradient. They also noted an increase in compliance and partial pressure of arterial oxygen (Pa_{O_2}) with no changes in partial pressure of arterial carbon dioxide (Pa_{CO_2}) or any hemodynamic variables. In 1991, Rau et al compared peak and mean airway pressure for seven different inspiratory flow waveforms (including square, ascending and descending ramps, and sinusoidal) under three different lung model conditions.[54] For all models, the descending ramp flow waveform produced the lowest peak and the highest mean airway pressures, whereas the ascending ramp produced the opposite: the highest peak and lowest mean values. When compliance was low, mean airway pressure increased as peak airway pressure increased. When resistance was high, peak airway pressure was more affected by the peak flow setting than the waveform setting.

In 1996, Davis et al[52] tested the hypothesis that a descending ramp flow waveform is responsible for improvements in gas exchange during pressure-control ventilation for acute lung injury. They compared volume control with a square or descending ramp waveform to pressure control with a square pressure waveform. Both pressure control and volume control with a ramp waveform provided better oxygenation at lower peak airway pressure and higher mean airway pressure compared to volume control with the square-flow waveform.

Polese et al[61] compared square, sinusoidal, and descending ramp flow waveforms in patients after open heart surgery. They found that Pa_{O_2} and Pa_{CO_2} were not affected by changes in waveform. Peak airway pressure was highest with the sinusoidal waveform while mean airway pressure and total work of breathing were least with the square waveform. Yang et al[53] applied square, sine, and descending ramp flow waveforms to patients with chronic obstructive pulmonary disease (COPD) and found that the descending ramp reduced inspiratory pressure, dead space-to-tidal volume ratio, and Pa_{CO_2}, but increased alveolar–arterial oxygen tension difference with no change in arterial oxygenation or hemodynamic variables.

Our own experience is that many clinicians prefer the descending ramp flow waveform when using volume control modes, with the observation that patients tend to be more comfortable, perhaps because of the higher flow earlier in the inspiratory phase.

Figure 3-16 illustrates an algorithm that can be used to adjust inspiratory flow to improve patient–ventilator synchrony.[62]

PERCENT SUPPORT

Proportional-assist ventilation (PAV)[63] delivers pressure-control breaths with a servo targeting scheme (see Chapter 2).[49] The pressure applied is a function of patient effort: the greater the inspiratory effort, the greater is the increase in applied pressure (Fig. 3-17). The form of PAV implemented on the Dräger Evita XL ventilator (called proportional pressure support) requires the operator to input desired assistance values for elastance and resistance. PAV implemented on the Puritan Bennett 840 ventilator (called PAV +) uses a different algorithm. It automatically calculates the resistance of the artificial airway, and combines resistance and elastance such that the operator enters only a single value representing the percentage work of breathing to be supported.[64] The design differences between proportional pressure support and PAV + lead to significant performance differences.[65]

NEURALLY ADJUSTED VENTILATORY SUPPORT LEVEL

NAVA is a mode that applies airway pressure proportionately to patient effort based on the voltage recorded from diaphragmatic activity. The "NAVA level" is the constant

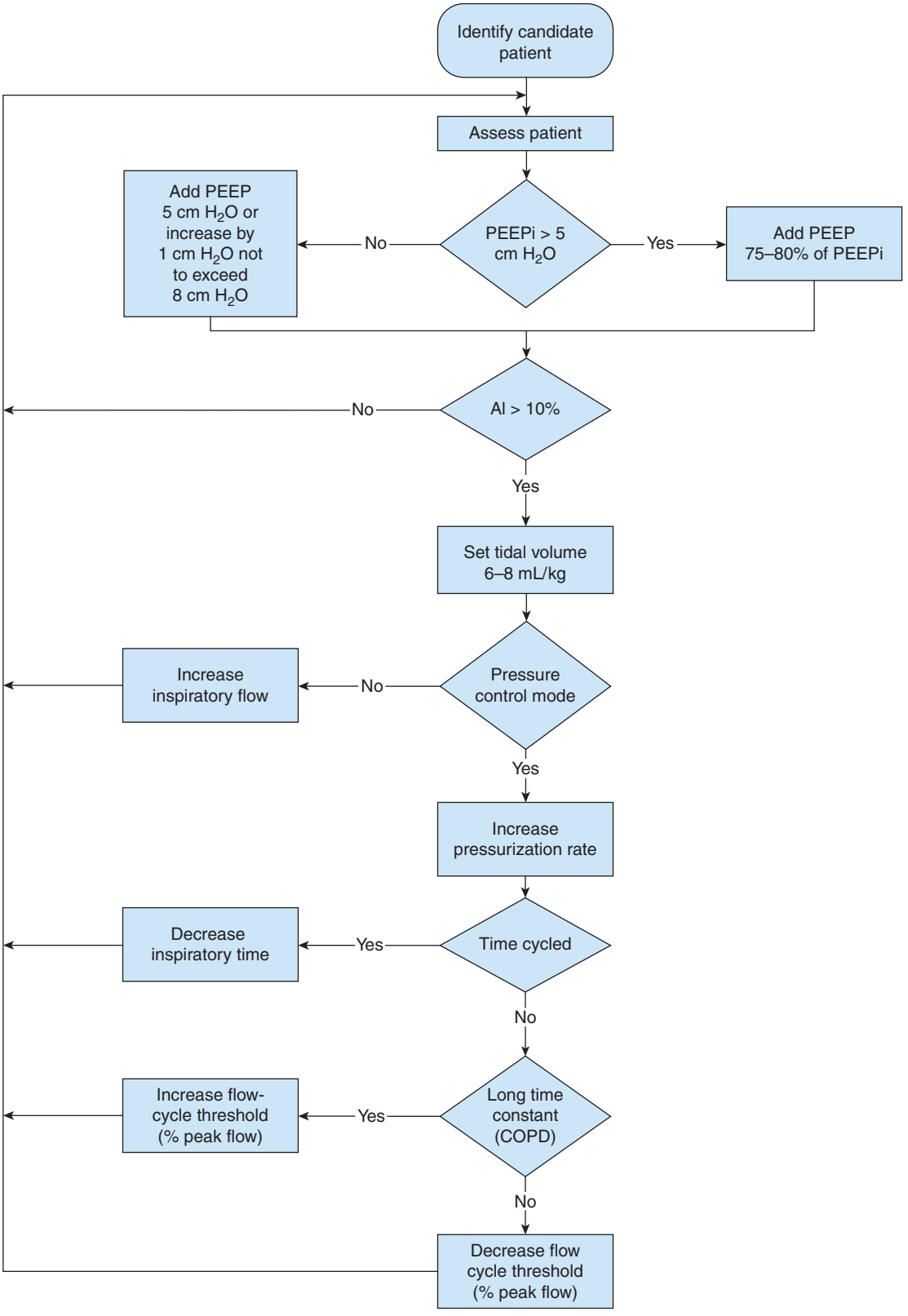


FIGURE 3-16 Algorithm for improving patient–ventilator synchrony. *AI*, asynchrony index, percent of inspiratory efforts that failed to trigger a breath; *COPD*, chronic obstructive pulmonary disease; *PEEPi*, intrinsic PEEP (aka auto-PEEP). (Modified from, with permission, Sassoon CSH. Triggering of the ventilator in patient-ventilator interactions. *Respir Care.* 2011;56(1):39–48.)

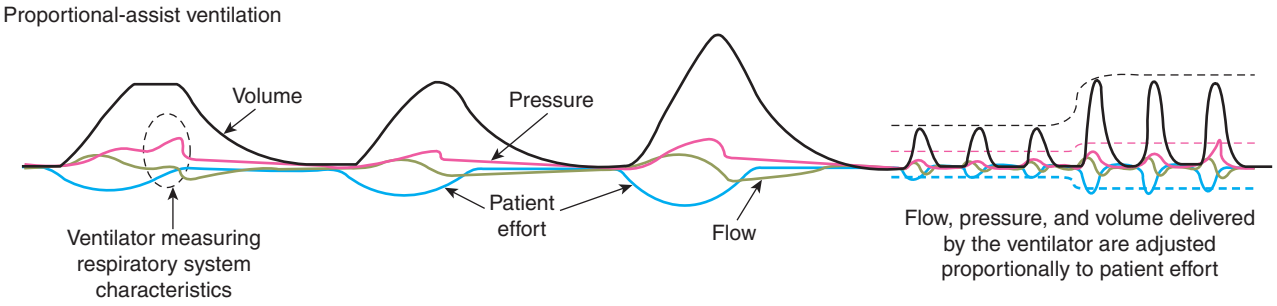


FIGURE 3-17 Pressure, volume, and flow waveforms for proportional assist ventilation.

of proportionality (gain) between voltage and airway pressure. The operator enters the NAVA level, then the ventilator delivers pressure equal to the product of gain and the Edi. In simple terms, it states how much pressure the patient will receive for each microvolt of diaphragmatic activity:

$$Paw(t) = Edi(t) \times \text{NAVA level} \quad (8)$$

where $Paw(t)$ is the airway pressure (cm H_2O) as a function of time (t), $Edi(t)$ is the electrical activity of the diaphragm as a function of time (t), in microvolts (μV), and the NAVA level is the operator-set level of support in cm H_2O/μV. The range is 0 to 30 cm H_2O/μV.

The NAVA level is set according to the operator ventilation goals, level of inspiratory pressure support, tidal volume, apparent patient work of breathing, or respiratory rate. Recently, Roze et al[66] proposed using the maximum Edi during a spontaneous breathing trial to help set the NAVA level (Fig. 3-18). By titrating the NAVA level to the a target Edi, the goal is to avoid excessive diaphragmatic unloading as well as respiratory muscle fatigue.

AUTOMATIC TUBE COMPENSATION

Automatic tube compensation (ATC) is a mode that compensates for the flow-dependent pressure drop across an endotracheal tube during inspiration and expiration. It is thus intended to reduce or eliminate the resistive work of breathing imposed by the artificial airway. ATC is an add-on feature on several ventilators. When ATC is activated, the ventilator supplies airway pressure in proportion to the square of flow times, a gain factor that is determined by the size of the endotracheal tube. Because flow is positive during inspiration and negative during expiration, ATC pressure either adds to inspiratory pressure or subtracts from expiratory pressure (Fig. 3-19). Some ventilators calculate and display tracheal pressure as airway pressure minus ATC pressure. ATC can be used alone or added to the ventilating pressure in pressure-control modes. Interestingly, the way ATC was implemented in the intensive care unit ventilators is different from the original concept, where negative pressure could be applied during exhalation.[67,68]

Cycle Variables

The inspiratory phase of a mechanical breath ends (cycles off) when a threshold value for a measured variable is reached. This variable is called the *cycle variable*, and it ends the inspiratory time. Cycling is characterized by the initiation of expiratory flow. The cycle variable may be preset (by the operator or the ventilator manufacturer), or automatically defined by the ventilator. Many different signals are used, for example, time, volume, pressure, flow, diaphragmatic signal, and thoracic impedance.

INSPIRATORY TIME

Inspiratory time is defined as the period from the start of inspiratory flow to the start of expiratory flow. Inspiratory time has two components; inspiratory flow time (period when inspiratory flow is above zero) and inspiratory pause time (period when flow is zero). In pressure-controlled or volume-controlled breaths, the inspiration is cycled (terminated) when the set inspiratory time elapses. In spontaneous modes of ventilation (NAVA, PAV, pressure support), the inspiratory time is dependent on the patient's own neurally determined inspiratory time, level of support, cycling rule (flow, pressure, time, diaphragm activity), and safety rules (maximum set inspiratory time).

Inspiratory time is usually an operator-entered input but some modes of ventilation can automatically set it and change it based on expert rules and closed-loop feedback algorithms. Two notable algorithms are ASV and Adaptive I-Time. In ASV (Hamilton G5), the inspiratory time is automatically set at one expiratory time constant (of the measured respiratory system characteristics and it is never shorter than 0.5 second or longer than 2 seconds). In the Adaptive Flow and Adaptive I-Time in the Versamed iVent (GE Healthcare, Madison, WI), the ventilator automatically adjusts the inspiratory time and inspiratory flow to maintain a target *I:E* ratio of 1:2 and deliver the operator-set tidal volume.[49]

In volume-control modes, there are four possibilities for setting inspiratory time:

1. Operator sets tidal volume and inspiratory flow: inspiratory time is equal to the tidal volume divided by mean inspiratory flow.

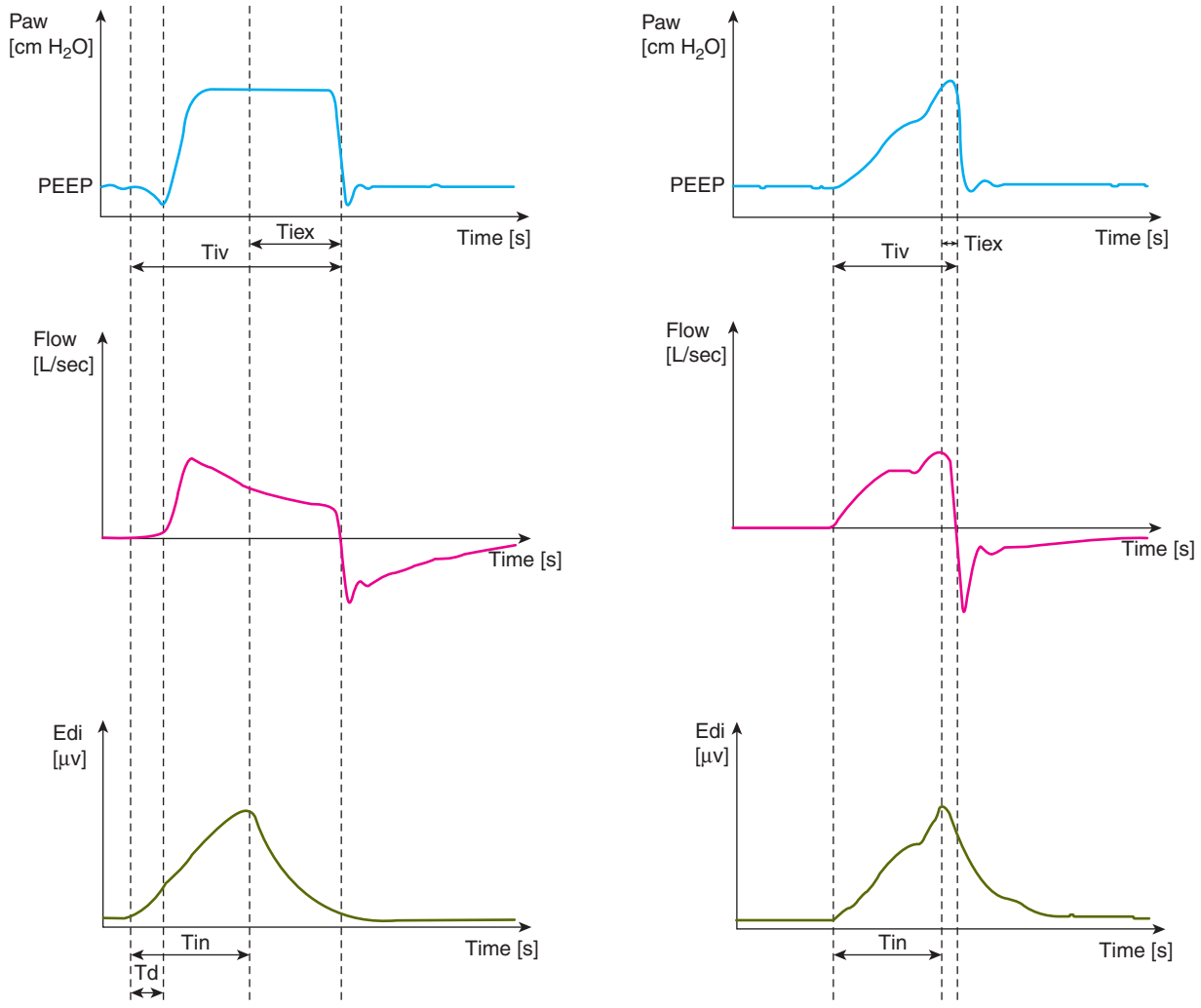


FIGURE 3-18 Airway pressure, flow, and electrical diaphragmatic activity curves in pressure support (left) and in neurally adjusted ventilatory assist (right). *Edi*, electrical activity of the diaphragm; *PEEP*, positive end-expiratory pressure, *Td*, trigger delay; *Tiex*, inspiratory time in excess; *Tin*, neural inspiratory time; *Tiv*, ventilator pressurization time. (Reproduced, with permission, from Piquilloud L, Vignaux L, Bialais E, et al. Neurally adjusted ventilatory assist improves patient–ventilator interaction. *Intensive Care Med.* 2011;37(2):263–271.)

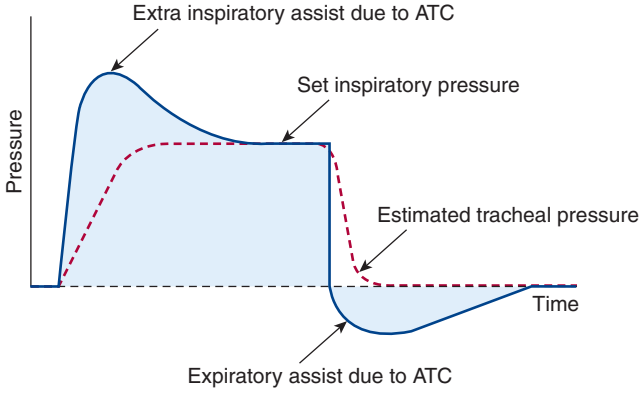


FIGURE 3-19 Pressure waveforms illustrating automatic tube compensation (ATC). (Modified, with permission, from Dräger Medical AG & Co. KG. *Infinity V500 Operator's Manual.* Luebeck, Germany.)

2. Operator sets tidal volume and inspiratory time: mean inspiratory flow is equal to the tidal volume divided by the inspiratory time.
3. Operator sets tidal volume, inspiratory flow, and inspiratory time: if the inspiratory time is longer than the inspiratory flow time (set tidal volume divided by set flow), then an inspiratory hold is created and the pause time is equal to the inspiratory time minus the inspiratory flow time. For example, if the tidal volume is 600 mL (0.6 L) and the set inspiratory flow is 60 L/min (1L/s) then the inspiratory flow time is (0.6/1 = 0.6 s). Now, if the operator also sets the inspiratory time to 1 s, an inspiratory pause is created and it lasts 1.0 – 0.6 = 0.4 s.
4. On some ventilators, the operator sets pause time directly.

In pressure-control modes, the operator presets the inspiratory time directly for mandatory breaths. Thus, prolonging the inspiratory time causes the ventilator to decrease the expiratory time, possibly resulting in air trapping, larger tidal volumes, or cycle asynchrony. One must remember that the effect on tidal volume of the inspiratory time in a pressure-control breath will depend on the respiratory system characteristics (i.e., the time constant). Thus, a patient with a long time constant (high compliance and/or high resistance) will require a longer inspiratory time to achieve full pressure equilibration, cessation of flow, and complete tidal volume delivery.

Figure 3-16 illustrates an algorithm that can be used to adjust inspiratory time to improve patient–ventilator synchrony.[62]

Inspiratory Pause. The inspiratory pause is the period during which flow ceases but expiration has not begun (see inspiratory time). The expiratory valves are closed during this period. The inspiratory pause time is part of the inspiratory time. It is also named plateau time (PB 840, Covidien, Mansfield MA), Pause time (Servo i, Maquet,) or Pause (G5, Hamilton Medical). When set directly, pause time may be entered in seconds or as a percentage of the inspiratory time. When it is activated, most ventilators will display a plateau pressure (i.e., static inspiratory hold pressure). Increasing the inspiratory pause time will increase the mean airway pressure and thus the time the lung is exposed to volume and pressure. This may have a positive effect on oxygenation and ventilation by increasing mixing time and decreasing dead space.[69,70]

I:E Ratio and Duty Cycle. *I:E* is the ratio of inspiratory time to expiratory time (Fig. 3-20).

$$I{:}E = T_I : T_E = \frac{T_I}{T_E} \tag{9}$$

The *I:E* can also be described as the duty cycle or percent inspiration. In engineering, the duty cycle is defined as the time spent in active state as a fraction of the total time. In mechanical ventilation, the active state is the inspiratory time, and the total time is the sum of the inspiratory and expiratory times. It is expressed as a percentage. The larger the percentage, the longer the inspiratory time in relation to the total cycle time.

$$Duty\ Cycle = \frac{T_I}{T_I + T_E} \times 100 \tag{10}$$

One can convert one to the other by the following formula:

$$I : E = \frac{Duty\ Cycle}{100 - Duty\ Cycle} \tag{11}$$

Example: A duty cycle of 50% is an *I:E* of 1:1, a duty cycle of 33% is an *I:E* 1:2.

The relevance of *I:E* is highlighted in the context of the time constant. The time constant is a measure of how quickly the respiratory system can passively fill or empty in

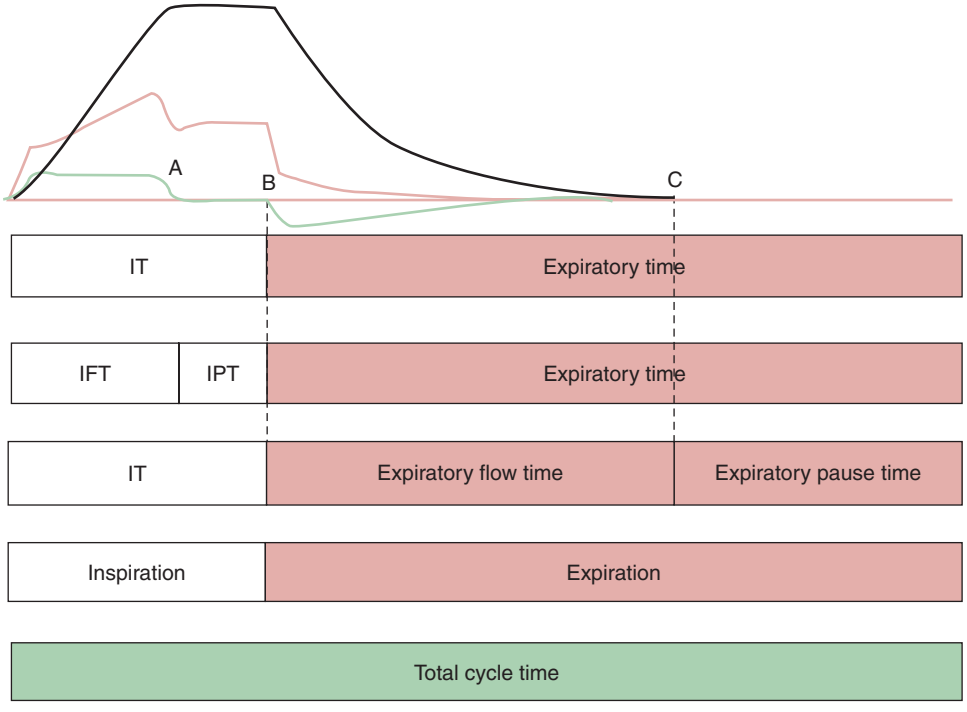


FIGURE 3-20 Divisions of the inspiratory and expiratory periods. A volume-controlled breath is depicted. **A.** End of inspiratory flow. **B.** Start of expiratory flow. **C.** End of expiratory flow. *IFT*, Inspiratory flow time; *IPT*, inspiratory pause time; *IT*, inspiratory time.

TABLE 3-4: EFFECT OF LUNG CONDITION ON TIME CONSTANT AND EXPIRED VOLUME

	Expiratory Time (s)			Expiration		
Time Constant	Normal Lung	ARDS	COPD	Tidal Volume Remaining (mL)	Tidal Volume Exhaled	Tidal Volume Remaining
0	0	0	0	500	0	100
1	0.780	0.510	1.000	184	63%[a]	37%
2	1.560	1.020	2.000	68	86%	14%
3	2.340	1.530	3.000	25	95%	5%
4	3.120	2.040	4.000	9	98%	2%
5	3.900	2.550	5.000	3	99%	1%

Abbreviations: *ARDS*, acute respiratory distress syndrome; *COPD*, chronic obstructive pulmonary disease.
[a]The exact value is $(1 - e^{-1}) \times 100\%$.

response to a step change in transrespiratory pressure.[23] It is calculated as the product of resistance and compliance. The value obtained is the time that takes to achieve 63% of steady state. This percent change remains a constant, regardless of the combination of resistance and compliance. It follows that *each* time constant will lead to a 63% decrease or increase in volume. In Table 3-4, one can see the difference among time constants for different lung conditions. In COPD, the time constant is longer so the time required for exhalation is longer than for patients with acute respiratory distress syndrome. This table demonstrates the effect of the time constant during passive exhalation using previously published[71] expiratory time constants for three conditions (normal lung was 0.78 seconds, for acute respiratory distress syndrome 0.51 seconds, and for COPD 1 second). In this example, expiration starts from a lung volume of 500 mL above functional resting capacity. When expiratory time equals one time constant, 63% of the tidal volume will be exhaled, leaving 37% of the tidal volume yet to be exhaled.

The *I:E* ratio can be an operator-entered value, or just displayed as a calculated value based on common scenarios for mandatory breaths:

- Preset *I:E* ratio and frequency.
- Preset inspiration time (T_I in seconds) and frequency (breaths/min). The frequency sets the ventilatory period ($1/f$) and the expiratory time is the period minus T_I:

$$I{:}E = T_I{:}\,[(60 \div rate) - T_I] \tag{12}$$

- Expiratory time and inspiratory time are fixed:

$$I{:}E = T_I{:}\,T_E \tag{13}$$

Note: some ventilators will synchronize inspiration and/or expiration of a mandatory breath if the patient effort is detected in a trigger/cycle window (e.g., SIMV or APRV), which may alter the *I:E* from the expected value based on settings.

PRESSURE

Pressure cycling occurs when the ventilator reaches a preset peak airway pressure. Pressure cycling is most often a safety feature (i.e., an alarm setting) with current modes of ventilation. When a preset high-pressure alarm threshold is crossed, the ventilator will cycle the ventilator. The goal is to prevent the patient from exposure to hazardous pressures. Pressure cycling without an alarm is the normal operational state for some devices (e.g., VORTRAN automatic resuscitator).

VOLUME

Volume cycling occurs when a preset volume is reached. This occurs when the operator sets a tidal volume in volume-control modes. Volume cycling implies that inspired volume is monitored by the ventilator's control system during inspiration and compared to a threshold value (the set tidal volume). But on some ventilators, despite the setting of a tidal volume, the actual cycle variable is time, that is, the time it takes to deliver the set tidal volume with the set inspiratory flow. Manufacturers seldom make this distinction clear in the operator's manual.

Volume cycling can also be found as a default safety feature. In PAV + (Covidien PB 840 ventilator), one of the cycling criteria is volume. Once the operator-preset high inspired tidal volume limit is reached, the ventilator cycles the breath and alarms.

FLOW

Flow cycling occurs when a preset flow or percentage of the peak flow is reached for pressure-control breaths. Flow cycling is most commonly found with the pressure-support mode but can be added as an "advanced setting" in other pressure-control modes on at least one ventilator (Avea, CareFusion). The flow-cycling threshold preset by the operator has been given many names: expiratory trigger sensitivity (Hamilton ventilators); trigger window (Engstrom Ohmeda); inspiratory termination peak inspiratory flow (Dräger Evita XL); expiratory threshold (Newport); flow termination (Pulmonetics LTV ventilators); PSV cycle (Avea, CareFusion); inspiratory cycle off (Servo *i*, Maquet); Ecycle (V200 respironics); and E sens (PB 840, Puritan Bennett).

During a breath in the pressure-support mode, the ventilator provides enough initial flow to achieve the set inspiratory pressure. The initial flow is high and then decays exponentially. Some ventilators have a preset default value for flow cycling (range: 5% to 30% of peak inspiratory flow); others allow the operator to adjust it (range: 1% to 80% of peak inspiratory flow). Only one device (e500, Newport Medical, Costa Mesa, CA) has automatic adjustment of the flow-cycling criteria. This device has a proprietary algorithm called FlexCycle. It will change the cycle criterion from 10% to 50% of peak flow based on measurements of airway pressure, the expiratory time constant, and expert-based rules applied through a closed-loop system.[72]

A default cycle criterion of 25% to 30% of the peak flow seems inappropriate as a "fit all" measure. The goal of adjusting the flow-cycling criterion is to avoid expiratory asynchrony.[59] In expiratory asynchrony, the ventilator ends inspiration before or after the patient inspiratory effort. We must remember that flow is a manifestation of the respiratory system characteristics, respiratory muscle effort (inspiratory and expiratory) and the integrity of the lung-ventilator circuit. If the respiratory system has a prolonged time constant, a standard flow-termination criterion may be inappropriate as it will prolong inspiration. That may be the case for patients with COPD, where the standard criterion of 25% may be too low, and lead to expiratory asynchrony and increased work of breathing.[73,74] Finally, a leak in the ventilator circuit (mask) or in the patient (endotracheal cuff or a bronchopleural fistula) may lead to lack of decay in the flow curve and thus asynchrony.[72]

Figure 3-16 illustrates an algorithm that can be used to adjust the flow-cycle threshold to improve patient–ventilator synchrony.[62]

DIAPHRAGMATIC SIGNAL

One goal of mechanical ventilation is to improve the patient–ventilator synchrony. In a perfect setting, the beginning and end of an assisted breath would be correlated with the neural signal driving the inspiratory muscles. In conventional ventilation that is rarely the case.[75] NAVA attempts to achieve this goal with the use of an electromyogram signal obtained from the diaphragm (Edi). As diaphragmatic activity decreases, so does the amplitude of the Edi curve. When it decreases below 70% of the peak signal (or 40% when the peak value is low), inspiration is cycled off. As a safety feature there is also a time-cycling mechanism. Piquilloud et al compared NAVA versus pressure support with the usual cycling criteria and found a significant improvement in expiratory synchrony (see Fig. 3-18).[76]

Baseline Variables

The baseline variables are the variables controlled during the expiratory time. Expiratory time is the period from the beginning of expiratory flow to the initiation of inspiratory flow. Flow and volume are not directly controlled during this period on any current ventilator. The most common value controlled is pressure relative to atmospheric pressure (zero-gauge pressure).

Positive End-Expiratory Pressure

The PEEP is established by the ventilator exhalation valve. A common source of confusion is the term continuous positive airway pressure versus PEEP. Continuous positive airway pressure is generally considered to be a mode on mechanical ventilators (or a mode of treatment for sleep apnea), whereas PEEP is the elevation of the baseline pressure during any mode of ventilation and is generally a setting for a mode. Until recently, the selection of PEEP has been a relatively arbitrary process and the meaning of "optimum PEEP" is debatable.[77] Now, Hamilton Medical has developed the INTELLiVENT system for the G5 ventilator that uses an algorithm for automatic targeting of PEEP and FIo_2. A closed-loop algorithm based on expert rules defines the response of the ventilator to measured ventilation variables, end-tidal carbon dioxide and pulse oximetry.

P-Low. P-low is one of the settings entered for so-called "bilevel" modes like APRV (Fig. 3-21). P-low is just another name for PEEP. Similar to PEEP, the settings are dependent on the user. There is, however, a large discrepancy with the objective of PEEP. In APRV, P-low is set to zero.[78] The goal is to maintain lung recruitment with the use of auto-PEEP induced by short T-low settings. P-low can also be set based on the biphasic model,[79] where complete exhalation is allowed and P-low is then set with the same goals as PEEP.

Expiratory Time. Expiratory time is defined as the period from the start of expiratory flow to the start of inspiratory flow. As stated above, the expiratory time is commonly dependent on the set inspiratory time, and set respiratory rate. It is rarely a fixed value. This occurs because making it a fixed value would produce, in most modes, changes in the inspiratory phase (inspiratory time, flow, and pressure). The most common exception to this is on ventilators that offer some form of APRV/biphasic pressure-control mode where expiratory time is set as "T-low."

T-Low. With exception of APRV/biphasic, in all the modern modes of ventilation the expiratory time is dependent on the inspiratory time and frequency; it is not an operator-set value. In APRV/biphasic, the operator sets the time spent at lower pressure, that is, exhalation (see Fig. 3-21). T-low can be set by the operator based on the peak expiratory flow,[78] targeting exhaled tidal volume or allowing complete exhalation.[80] Setting T-low sets the time trigger threshold for mandatory breaths. Among the methods described in setting T-low in APRV, targeting percent of peak expiratory flow (%PEF) is perhaps the most promoted method. The goal is to set the T-low short enough to avoid full exhalation,

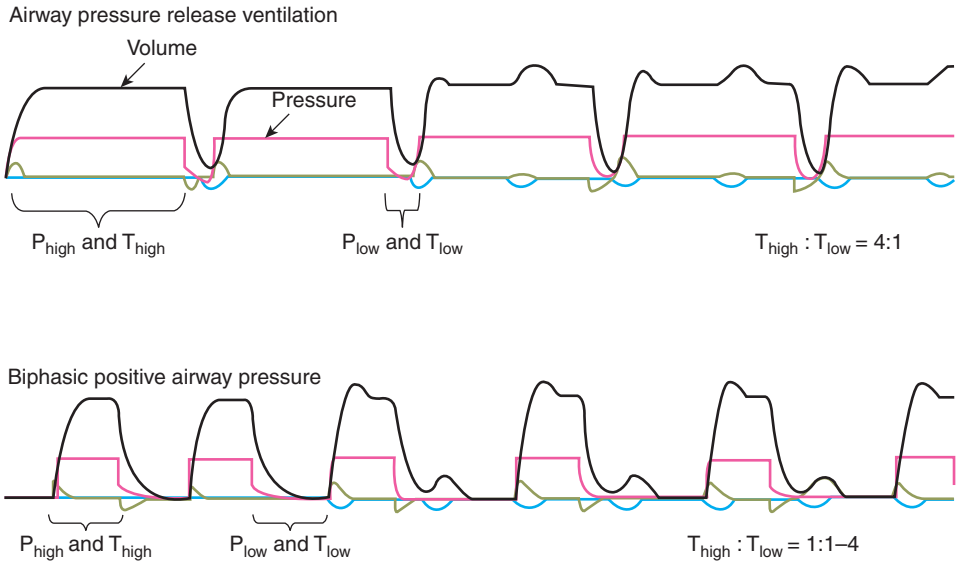


FIGURE 3-21 Differences in P-low and T-low settings for airway pressure release ventilation and biphasic positive airway pressure. Notice the difference in I:E ratio. The operator enters P-high, P-low, T-high, and T-low. The patient may breath spontaneously. Green curves show flow and blue curves show inspiratory effort.

thereby generating air trapping.[29] Adjusting T-low on the ventilator to manually maintain %PEF at 50% to 75% may be a tedious process, which may seem simple on paper, but in a spontaneously breathing patient can become a true challenge. Newer ventilators, like the Dräger Evita Infinity V500, have attempted to make the process easier by allowing the operator to set a trigger threshold based on a percentage of peak *expiratory* flow.

Alarms

Ventilator alarms bring unsafe events to the attention of the clinician. Events are conditions that require clinician awareness or intervention. Events can be classified according to their level of priority.[81]

Immediately life-threatening events are classified as Level 1. They include conditions like insufficient or excessive gas delivery to the patient, exhalation valve failure, control circuit failure, or loss of power. Level 1 alarm indicators should be mandatory (cannot be turned off by the operator), redundant, and noncanceling.

Level 2 events range from mild irregularities in machine function to dangerous situations that could threaten patient safety if left unattended. Some examples are failure of the air–oxygen blending system, inadequate or excessive PEEP, autotriggering, circuit leak, circuit occlusion, inappropriate *I:E* ratio, and failure of the humidification system. Alarms in this category may be self-canceling (i.e., automatically turned off if the event ceases) and are not necessarily redundant.

Level 3 events indicate changes in the amount of ventilator support provided to the patient consequent to changes in the patient's ventilatory drive or respiratory system mechanics and the presence of auto-PEEP. These events often trigger the same alarms as Levels 1 and 2.

Level 4 events are based entirely on patient condition. They may include events such as changes in gas exchange, dead space, oxygenation, and cardiovascular functions. Ventilators generally monitor these events and external monitors are required for alarms (the exception being exhaled carbon dioxide-level alarms built into the ventilator display).

Currently, ventilators do not display alarm settings as levels of priority. Instead, they tend to lump them all together on one screen that shows alarm limits and controls for changing them (Fig. 3-22). How to set alarm thresholds is a complicated topic that has been studied but for which little information is available regarding mechanical ventilation. The goal is to minimize false alarms and maximize true alarms. A high false alarm rate leads to clinician habituation and can also lead to inappropriate responses. In a recent study of an intensive care unit, 1214 alarms occurred and 2344 tasks were performed. On average, alarms occurred six times per hour; 23% were effective, 36% were ineffective, and 41% were ignored.[82] In another intensive care unit study, alarms occurred at a rate of six per hour. Approximately 40% of the alarms did not correctly describe the patient condition and were classified as technically false; 68% of those were caused by manipulation. Shockingly, only 885 (15%) of all alarms were considered clinically relevant.[83] Although these studies did not address mechanical ventilator alarms specifically, it is not hard to imagine similar results for such a study.

Ventilator alarms are usually set by the operator as either an arbitrary absolute value or a percentage of the current value. Examples would be airway-pressure alarms (high and low) set at the current value plus or minus 5 cm H_2O or low and tidal volume/minute ventilation set at plus or minus 25% of the current value.[81] The problem is that the parameters for which alarms are important, and these three

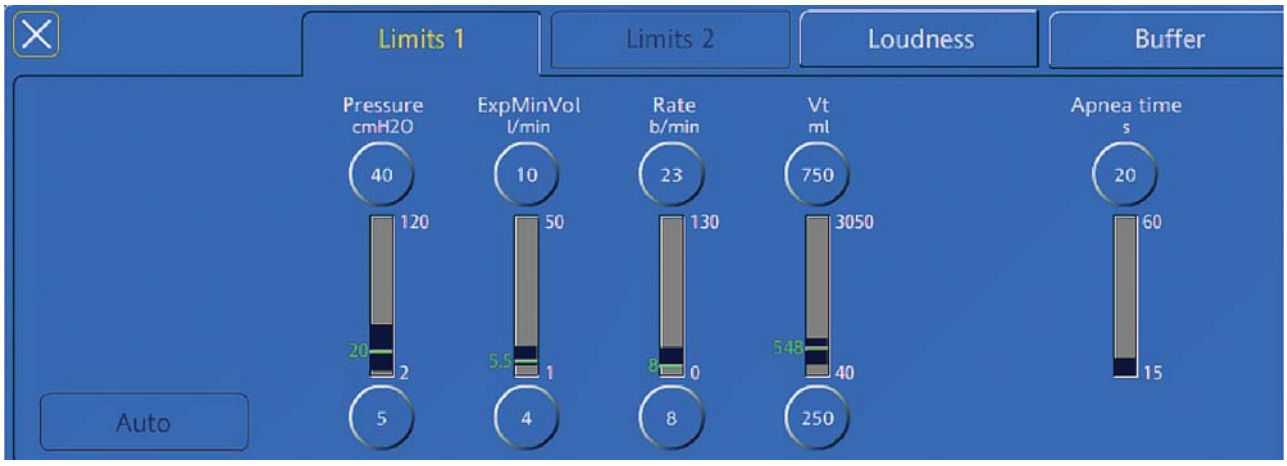


FIGURE 3-22 Alarm screen from the G5 ventilator. (Reproduced, with permission, from Hamilton Medical.)

in particular, are highly variable, with significant portions at extreme values.[84] Thus, limits set as absolute values or percentages may reduce safety for some extreme values while increasing nuisance events for other values. An alternative approach might be a type of "smart alarm," whereby the alarm limits are automatically referenced to the current value of the parameter such that extreme values have tighter limits. Further research is needed to identify optimization algorithms (i.e., minimize both harmful and nuisance events).

VENTILATOR OUTPUTS (DISPLAYS)

Display Types

Ventilator output displays represent the values of monitored parameters that result from the operator settings. There are four basic ways to present the monitored data: as numbers, as waveforms, as trend lines, and in the form of abstract graphic symbols.

NUMERIC VALUES

Data are most commonly represented as numeric values such as FIo_2, peak, plateau, mean and baseline airway pressures, inhaled/exhaled tidal volume, minute ventilation, and frequency. Depending on the ventilator, a wide range of calculated parameters may also be displayed including resistance, compliance, time constant, airway occlusion pressure at 0.1 second (P0.1), percent leak, *I:E* ratio, and peak inspiratory/expiratory flow (Fig. 3-23).

TRENDS

Many ventilators provide trend graphs of just about any parameter they measure or calculate. These graphs show how the monitored parameters change over long periods of time, so that, for example, significant events or gradual changes in patient condition can be identified (Fig. 3-24). In addition, ventilators often provide an alarm log, documenting such things as the date, time, alarm type, urgency level, and events associated with alarms, for example, when activated and when canceled. Such a log could be invaluable in the event of a ventilator failure leading to a legal investigation.

WAVEFORMS AND LOOPS

Many ventilators display waveforms (sometimes called "scalars") of airway pressure, volume, and flow as functions of time. Such displays are useful for identifying the effects of changes in settings or mechanics on the level of ventilation.[85] They are also very useful for identifying sources of patient–ventilator asynchrony, such as missed triggers, flow asynchrony, and delayed or premature cycling.[86] They can also display one variable against another as an *x-y* or "loop" display. The most common loop displays show pressure on the horizontal axis and volume on the vertical axis, or volume on the horizontal axis and flow on the vertical axis. Pressure-volume loop displays are useful for identifying optimum PEEP levels (quasistatic loops only) and over distension. Flow-volume loops are useful for identifying the response to bronchodilators. Figure 3-25 is an example of a composite display showing numeric values, waveforms, and loops.

ADVANCED GRAPHICS

As ventilators have become more complex, their displays have become more confusing and difficult to use. A recent trend is to move away from the traditional display screens in favor of a more integrative approach using creative graphic elements. For example, one study showed that observers detected and treated obstructed endotracheal tubes and auto-PEEP problems faster with graphical rather than conventional displays. They also reported significantly lower subjective workloads using the graphical display.[87]

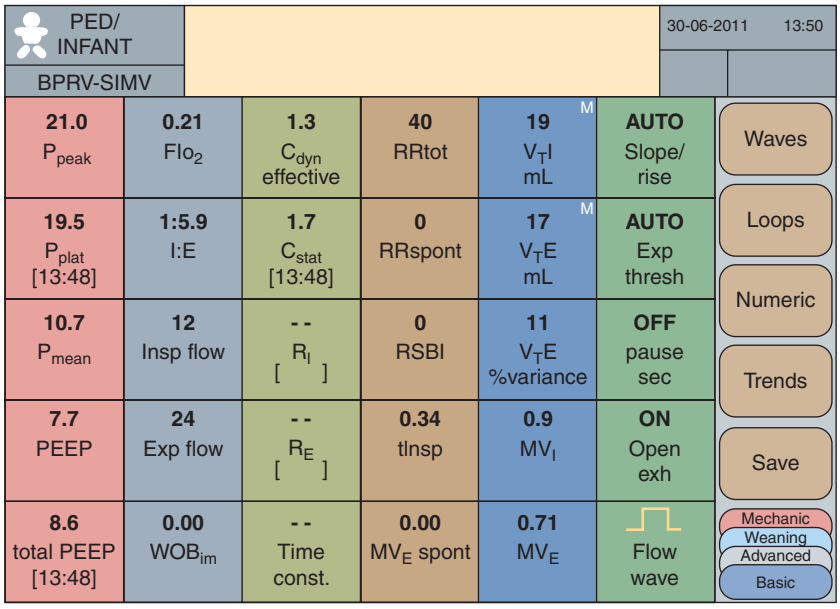


FIGURE 3-23 Digital display of monitored and calculated parameters from the Newport e360 ventilator. (Reproduced, with permission, from Newport Medical.)

Hamilton Medical was the first to make use of innovative picture graphics on their G5 ventilator. They created a graphic representation of the lungs, called a "dynamic lung panel," that visually displays information about resistance and compliance by the shape and color of the lungs and airways (Fig. 3-26). This panel is supplemented by a unique graphic, called the "vent status panel," which displays key parameters (e.g., oxygenation, ventilation, and spontaneous breathing activity). Furthermore, the display shows when each item is in or out of an acceptable zone and for how long. This makes weaning status easy to identify. Preliminary data[88] suggest that this display reduces the time required for clinicians to identify common problems, for example, normal, restrictive, and obstructive lungs; occluded endotracheal tube, right main-stem intubation, pre-spontaneous breathing trial (SBT), SBT in progress, and post-SBT phase.

Dräger Medical recently introduced a similar graphic display called "Smart Pulmonary View." The shapes of the graphic elements quickly indicate relative values of respiratory system resistance and compliance as well as the balance between mandatory and spontaneous breaths (Fig. 3-27). Digital values are also displayed.

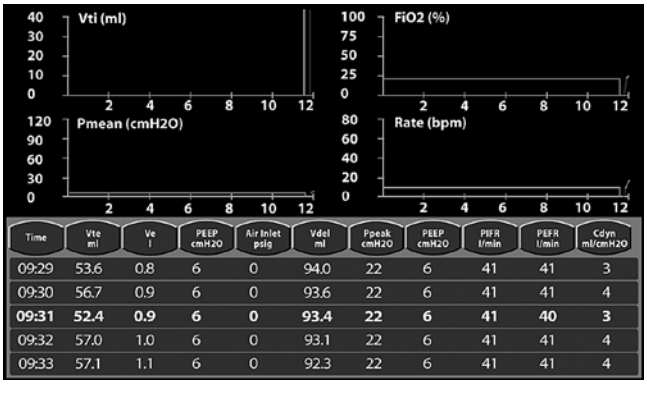


FIGURE 3-24 Trend display from the Avea ventilator. (Reproduced, with permission, from CareFusion.)

THE FUTURE

Better Operator Interfaces

As modes have become more complex, the operator interfaces on ventilators with computerlike displays has become cumbersome. Multiple options for control settings tend to get lost in layers of different screen views. Worse, screen views are often customizable such that if strict control is not exerted by an individual hospital department, each ventilator will be "stylized" by individual operators and chaos will ensue. Clearly, flexibility is a double-edged sword.

Very few studies have been published on ease of use or the problems with current displays. We need to identify optimal ways for ventilator displays to provide three basic functions: to allow input of control and alarm parameters, to monitor the ventilator's status, and to monitor the ventilator–patient interaction status. There is a long way to go before the user interface provides an ideal experience with these functions. This may be a fruitful area of future research.[6,8]

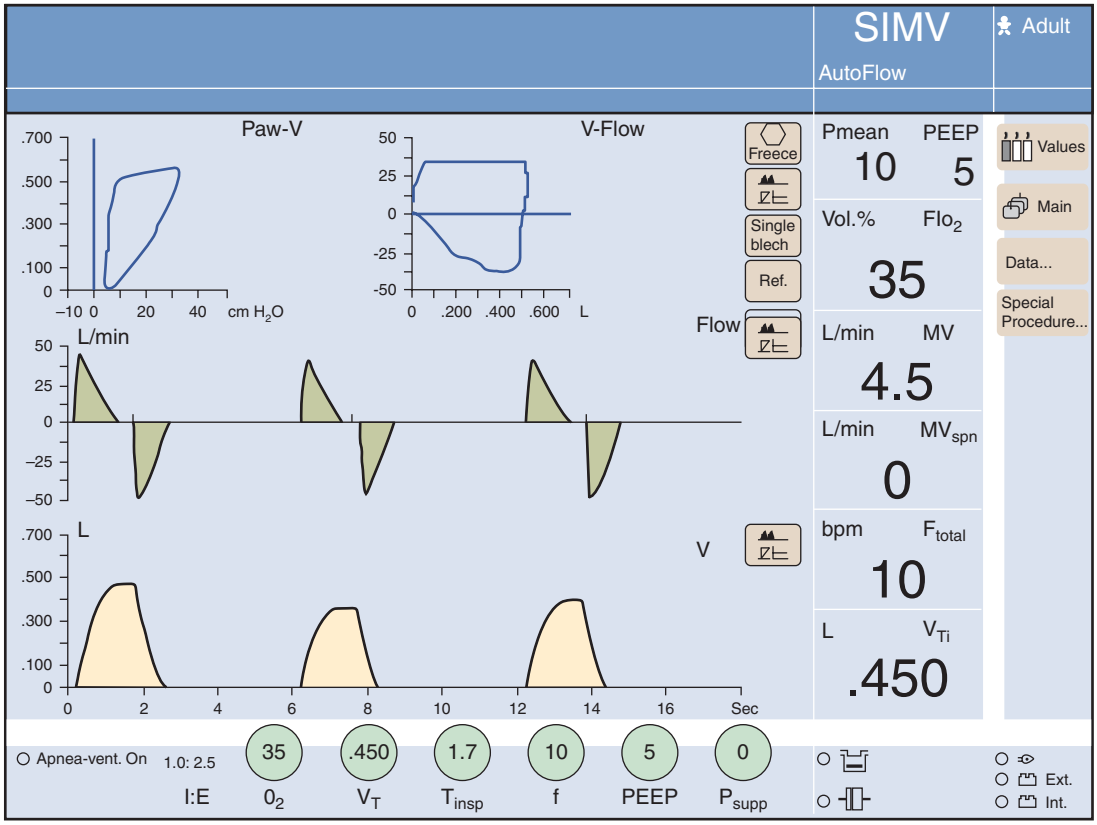


FIGURE 3-25 An example of both scalar and loop displays. (Reproduced with permission from Draeger Medical GmbH, Luebeck, Germany.)

Better Patient Interfaces

The interface between a modern ventilator and the patient is a piece of plastic tubing, that is, the "patient circuit," whose design has not changed much in several decades.

FIGURE 3-26 Example of picture graphic display from the Hamilton G5 ventilator showing the dynamic lung panel and the vent status panel. (Reproduced, with permission, from Hamilton Medical.)

Certainly, humidification systems using heated wires and automatic-temperature control have evolved, but we still are not capable of measuring and directly controlling a primary variable of gas conditioning: humidity. Indeed, after all this effort at evolving humidification systems, there are data to show that simple, unheated circuits provide better humidification of inspired gas.[89] In addition, the compliance of the patient circuit degrades the accuracy of flow delivery and must be "compensated" for by complex mathematical algorithms. It seems to us that a major revolution in patient-interface design would be to simply make the patient circuit a permanent part of the ventilator and treat water molecules the way we treat molecules of oxygen, nitrogen, helium, and nitric oxide. But to do this, ventilator manufacturers would have to merge with humidifier manufacturers and collaborate in systems design rather than seeing the patient circuit and humidifier as devices separate from the ventilator (see Chapter 2).

Better Targeting Systems

Chapter 2 provides a conceptual framework and suggestions for better targeting systems of the future. In essence, evolution in this area involves more and better sensors and the software algorithms required to manage the data they provide. The clear trend here, both in basic research and

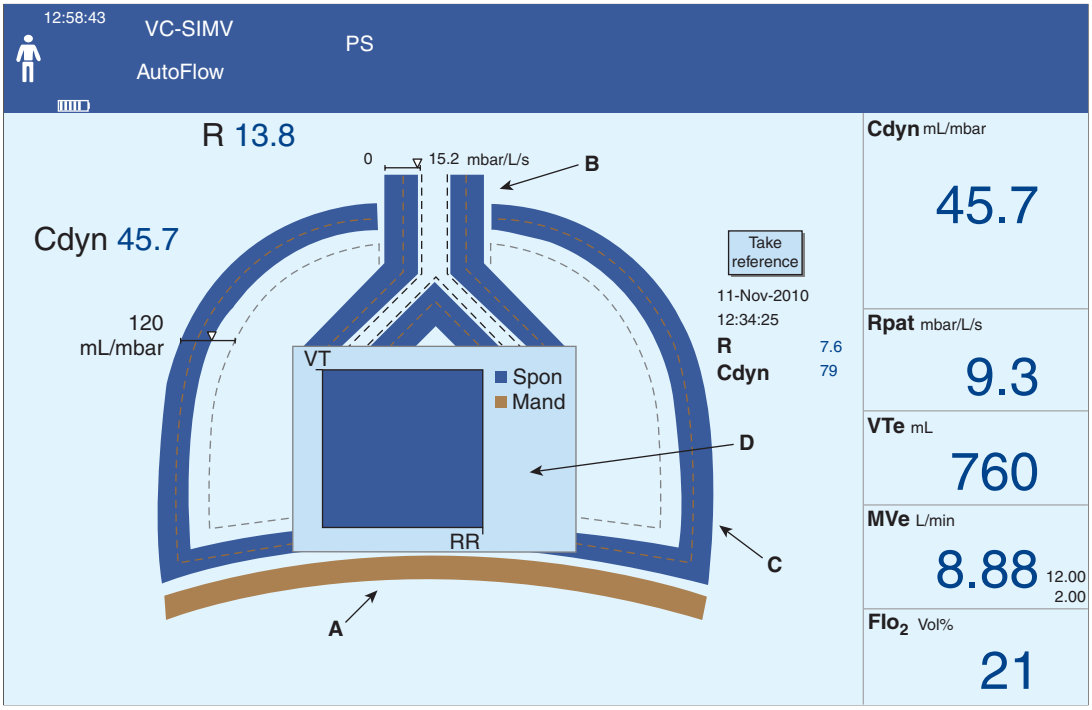


FIGURE 3-27 Example of picture graphic display from the Dräger Evita Infinity V500 ventilator showing the Smart Pulmonary View. **A.** The movement of the diaphragm indicates synchronized mandatory breaths or supported (triggered) breaths. **B.** The blue line around the trachea indicates the resistance R. The higher the resistance, the thicker the line. The numeric value is also displayed. **C.** The blue line around the lungs indicates the compliance Cdyn. The higher the compliance, the thinner the line. The numeric value is also displayed. **D.** Diagram displaying the relationship between spontaneous breathing and mandatory ventilation. The following parameters are displayed in different colors: spontaneous tidal volume (*VT spon*), spontaneous respiratory rate (*RR spon*), mandatory tidal volume (*VT mand*), and mandatory respiratory rate (*RR mand*). (Reproduced, with permission, from Draeger Medical GmbH, Luebeck, Germany.)

commercial applications, is to develop "closed-loop" targeting systems based on mathematical models of physiologic processes, or artificial intelligence, or combinations thereof, with the goal of automating the moment-to-moment adjustment of ventilator output to patient needs. The best example so far is a mode called INTELLiVENT-ASV (G5 ventilator, Hamilton Medical) and is currently available only in Europe.

This mode is an improvement on the optimal targeting scheme that is the basis of the mode called ASV (see Chapter 2). Like ASV, INTELLiVENT-ASV is a form of pressure control intermittent mandatory ventilation using adaptive-pressure targeting to automatically adjust inspiratory pressure to maintain a target tidal volume, which, in turn, is selected by an optimization model. An "optimal" targeting scheme attempts to either maximize or minimize some performance metric.[49] In the case of ASV, the ventilator attempts to select a tidal volume and frequency (for passive ventilation) that minimizes the work rate of ventilation for the patient's particular state of lung mechanics. As the lung mechanics change, the ventilatory pattern changes. ASV requires that the operator input the patient's weight, however, so that the ventilator can calculate an estimated minute ventilation requirement. The operator must also manage PEEP and FIo_2. INTELLiVENT-ASV takes ASV a step further by adding input data from end-tidal CO_2 monitoring and pulse oximetry. These extra data, along with advanced targeting software algorithms, allow the ventilator to automatically select and adjust minute ventilation, PEEP, and FIo_2. This makes INTELLiVENT "… the world's first complete closed-loop ventilation solution that offers automated adjustment of oxygenation and ventilation."[90]

Along with the new targeting systems, this mode also provides a unique operator interface that Hamilton refers to as the "Ventilation Cockpit," an apparent reference to the "autopilot" feature in airplanes. The interface is designed to facilitate understanding complex information in a visually intuitive way. In addition to displaying the usual digital parameters and waveforms, the new mode offers several other screens. The "Dynamic Lung" screen integrates data on lung mechanics, end-tidal carbon dioxide ($P_{ET}CO_2$), and pulse oximetry (SpO_2), and offers a metric called the "heart–lung interaction" index (Fig. 3-28). A graphic element called the "Ventilation Map" plots $P_{ET}CO_2$ against peak airway pressure as shown in Figure 3-29. Another display, the "Oxygenation Map," is very similar to the Ventilation Map: it provides detailed information about the oxygenation status based on the major physiologic input, as measured by pulse oximetry (SpO_2), and the resulting treatment ($PEEP/FIo_2$).

FIGURE 3-28 The operator interface of the Hamilton G5 ventilator with INTELLiVENT-ASV option, called the "Ventilation Cockpit." This screenshot shows the "Dynamic Lung" display including the "Heart–Lung Interaction" index. (Reproduced, with permission, from Chatburn RL. Computer control of mechanical ventilation. *Respir Care.* 2004; 49:507–515.)

Early studies of INTELLiVENT show that compared to ASV, patients ventilated with INTELLiVENT spent more time with optimal ventilation and less time with nonsecure ventilation. In addition, INTELLiVENT delivered lower volumes and pressures for equivalent gas exchange.[91] In another preliminary study, patients managed with INTELLiVENT spent less time with nonsecure and nonoptimal ventilation (3%) compared to conventional ventilation (47%, $P = 0.03$) after cardiac surgery.[92]

We speculate that modes of the future will continue this trend toward automation and include protocols for automatic weaning for various populations of patients. They will provide means for communication with electronic medical records and move us closer to integration of vast amounts of data into useful information for measurable improvements in patient outcomes. This process, however, will present significant challenges to vendors and end users to develop standardized vocabularies, taxonomies, and data transfer protocols in order to assure higher levels of accuracy, security, and usability.

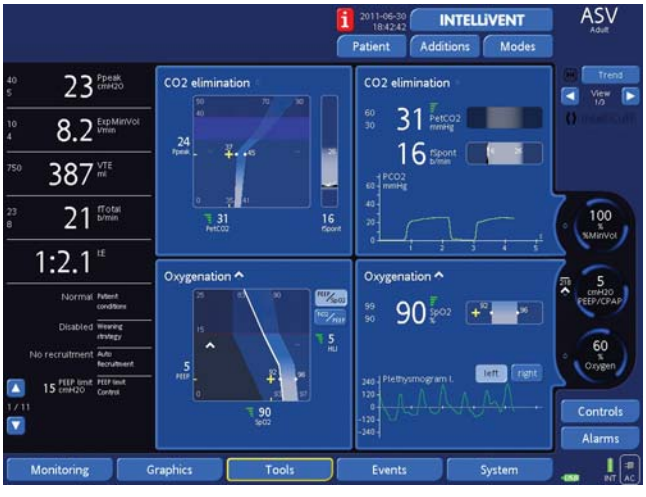


FIGURE 3-29 The operator interface of the Hamilton G5 ventilator with INTELLiVENT-ASV showing details of ventilation and oxygenation management.

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III

INDICATIONS

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4

INDICATIONS FOR MECHANICAL VENTILATION

Franco Laghi
Martin J. Tobin

This chapter discusses the indications for mechanical ventilation in adult patients. We focus on patients who are already in the intensive care unit (ICU) or who are considered for transfer to the ICU, that is, patients with new onset of signs and symptoms over minutes or hours. We do not deal with the indications for mechanical ventilation for chronic respiratory failure or in pediatric patients; these subjects are covered in Chapters 23, 18, 33, and 34.

There is a paucity of research—and no clinical trials—on the indications for mechanical ventilation. This situation contrasts with the growing amount of research on the discontinuation of mechanical ventilation. Although it is tempting to apply indices used for predicting the outcome of weaning trials as indices to identify patients who require mechanical ventilation, such an approach has not been tested. It is also probably unwise.

Two factors account for the limited research on indications for mechanical ventilation. First, such patients are extremely ill. Any intervention—such as careful collection of physiologic measurements—that delays institution of ventilation might be viewed as unethical. Second, the nosology of respiratory failure is unsatisfactory (see "Nosology" below). In everyday practice, clinicians do not decide to institute mechanical ventilation because a patient meets certain diagnostic criteria. Instead, clinicians typically decide to institute ventilation based on their assessment of a patient's signs and symptoms. This decision is also grounded on a foundation of solid biomedical theory, specifically principles of pulmonary pathophysiology. Accordingly, we develop our discussion of ventilator indications along these two lines: physical examination and pathophysiologic principles.

OVERALL ASSESSMENT

Clinical presentations that cause a physician to institute mechanical ventilation are protean. They range from patients presenting with frank apnea to patients with clinical signs of increased work of breathing with or without laboratory evidence of impaired gas exchange.[1]

Apnea

Apneic patients, such as those who have suffered catastrophic central nervous system (CNS) damage, need immediate institution of mechanical ventilation. To advocate controlled trials to determine the need for mechanical ventilations in apneic patients is unethical.

Clinical Signs of Increased Work of Breathing

Asthma, chronic obstructive pulmonary disease (COPD), pneumonia, cardiogenic pulmonary edema, and acute respiratory distress syndrome (ARDS) are just a few of the many conditions that cause an increase in work of breathing and, with it, increased energy expenditure by the respiratory muscles.

The energy expenditure of the respiratory muscles can be quantified in terms of pressure-time product[2]—the time integral of the difference between the esophageal pressure tracing and the estimated recoil pressure of the chest wall[3,4] (Fig. 4-1). The pressure-time product of patients in acute respiratory failure is about four times[5–7] the normal value (100 cm H_2O·s/min), and it can be increased sixfold in individual patients.[5,6] The inspiratory pressure-time product can be partitioned into resistive, elastic, and intrinsic positive end-expiratory pressure (PEEP) components (Fig. 4-1).[6] Patients in respiratory distress typically have a 30% to 50% greater inspiratory resistance,[6] 100% greater dynamic elastance,[6] and 100% to 200% greater intrinsic PEEP[5,6] than do similar patients who are not in acute respiratory failure. Inspiratory effort is almost equally divided in offsetting intrinsic PEEP, elastic recoil, and inspiratory resistance.[6] The increase in respiratory effort means that the respiratory muscles account for a much larger fraction of the body's oxygen consumption. In healthy subjects, this fraction is only 1% to 3% of total oxygen consumption. In patients with acute hypoxemic respiratory failure and shock who are undergoing cardiopulmonary resuscitation, the respiratory muscles account for approximately 20% of total oxygen consumption.[8]

Increased work by the respiratory muscles causes respiratory distress. Clinical manifestations of respiratory distress include nasal flaring, retraction of the eyelids, accessory

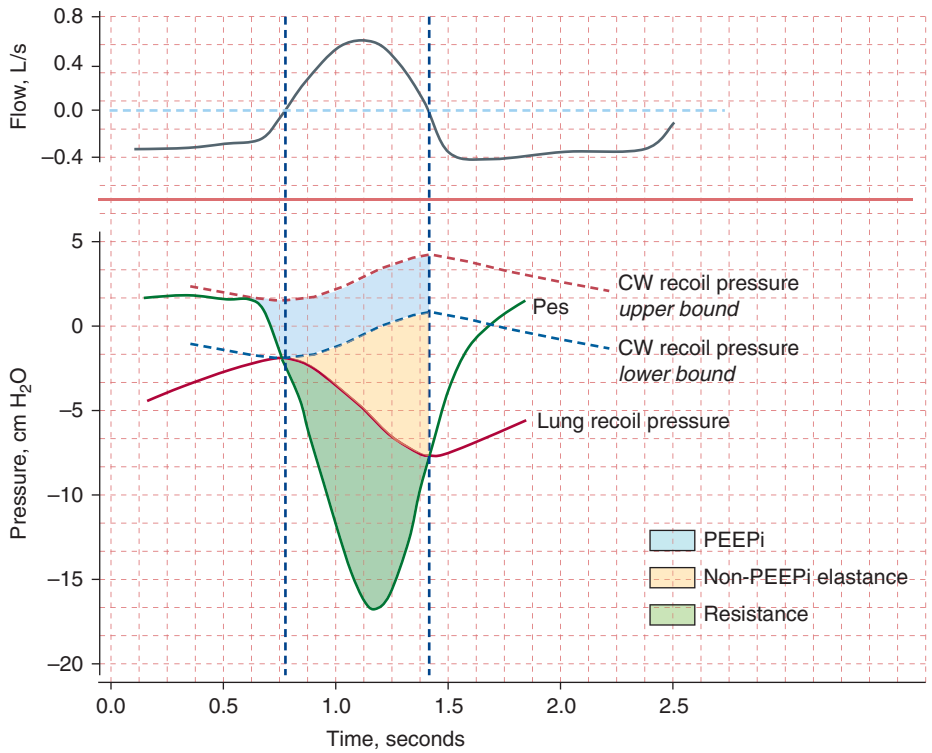

FIGURE 4-1 Flow (*inspiration upward*) and pressure tracings during spontaneous breathing. Recoil pressures of the chest wall (*CW*) and lung are calculated from dynamic elastances of the chest wall and lung, respectively, and lung volume. Inspiratory pressure-time product (PTP) is calculated using the integral of the difference between esophageal pressure (Pes) and CW recoil pressure from the onset of the rapid decrease in Pes to the transition from inspiratory to expiratory flow (upper-bound PTP). The component of PTP caused by intrinsic positive end-expiratory pressure (*PEEPi*) is computed using the integral of the difference between the upper-bound PTP and CW recoil pressure from the onset of rapid decrease in Pes to the transition from inspiratory to expiratory flow (lower-bound PTP). The component of PTP caused by non-PEEPi elastance is computed using the integral of the difference between lung recoil pressure and lower-bound CW recoil pressure from the onset of inspiratory flow to the moment of transition from inspiratory to expiratory flow. The resistive fraction of PTP is computed using the integral of the difference between Pes and lung recoil pressure. The *vertical interrupted lines* represent points for zero flow. (Modified, with permission, from Jubran and Tobin.[6])

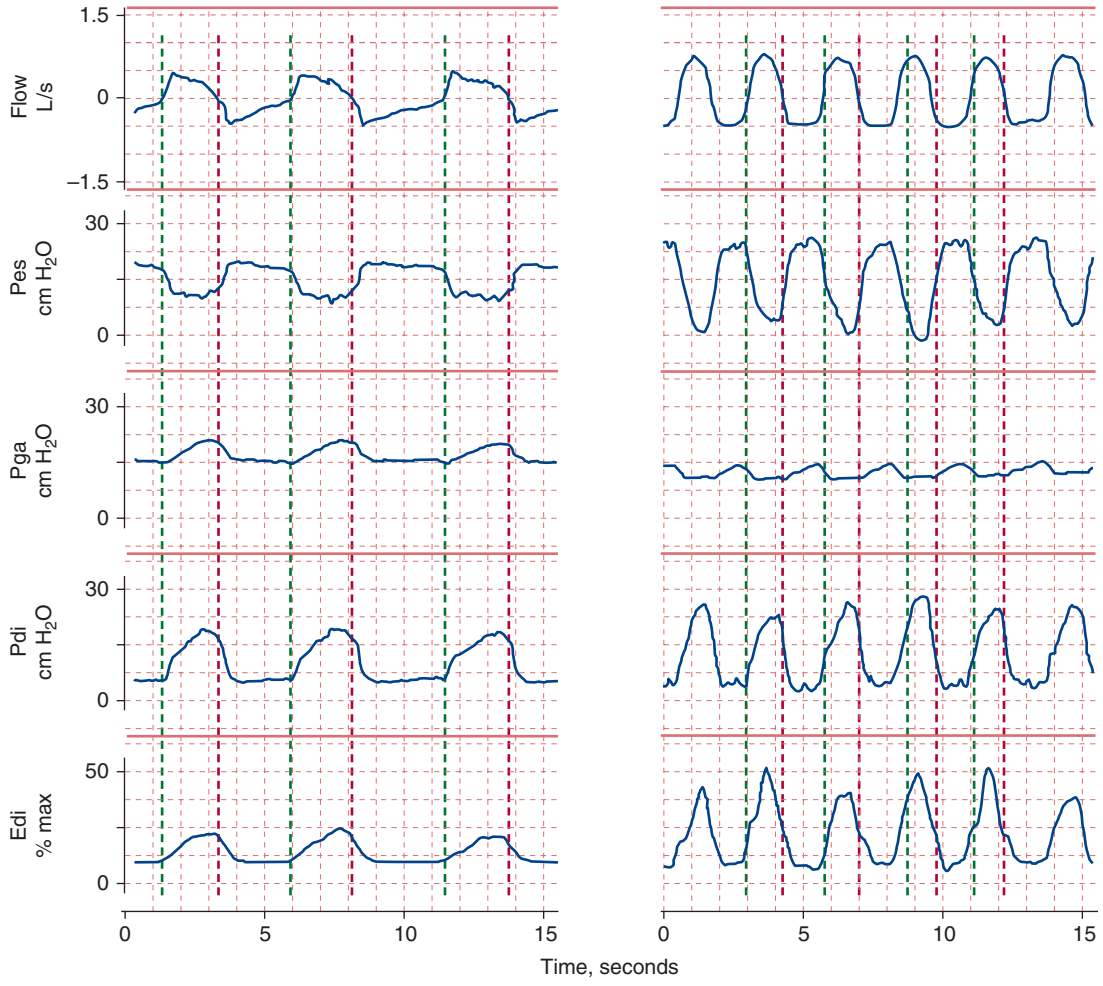

FIGURE 4-2 Respiratory effort during unassisted respiration. Recordings of flow (*inspiration upward*), esophageal (*Pes*), gastric (*Pga*), and transdiaphragmatic (*Pdi*) pressures and electrical activity of the diaphragm (*Edi*) in a stable patient with COPD (*left*) and in a patient with respiratory failure (*right*). The *green vertical lines* indicate the onset of inspiratory flow and the *red vertical lines* indicate the onset of expiratory flow. The excursions in Pes and Edi in the patient in respiratory failure are three times greater than in the stable patient, signifying heightened respiratory motor output. The increase in Pga during exhalation in the patient with respiratory failure signifies expiratory muscle recruitment.

muscle recruitment, expiratory muscle recruitment (Fig. 4-2), tracheal tug, intercostal recession, tachypnea, tachycardia, hypertension or hypotension, diaphoresis, and changes in mental status.

FACIAL SIGNS OF RESPIRATORY DISTRESS

Many intensivists decide to institute mechanical ventilation based on a patient's facial appearance.[9] Gilston has provided an insightful description of many signs that go unstated in reviews on mechanical ventilation.[9] Consider, for example, the mouth. At an early stage of respiratory distress, the mouth opens slightly and to a variable extent during inhalation (Fig. 4-3). At a later stage, the mouth opens throughout the respiratory cycle. Patients may switch to mouth breathing perhaps to decrease respiratory work[9,10] and physiologic dead space ventilation.[9] An open mouth is sometimes seen in patients with a tracheostomy (Fig. 4-4) and in patients receiving ventilator support.[9] The tongue may be seen to jerk in unison with inspiratory efforts.[9]

Some distressed patients also exhibit pursed-lip breathing during exhalation (see Fig. 4-3).[9] In stable, ambulatory patients with COPD, pursed-lip breathing is associated with an increase in tidal volume,[11] a decrease in respiratory rate,[11] and, in patients with severe obstruction, with a decrease end-expiratory lung volume.[12] Pursed-lip breathing can improve the arterial tensions of both carbon dioxide (Pa_{CO_2}) and oxygen (Pa_{O_2}), whereas oxygen uptake ($\dot{V}_{O_2}$) remains unchanged.[11] The latter finding suggests that pursed-lip breathing may allow a decrease in cardiac output without changing tissue oxygenation.[11] Alternatively, if cardiac output does not decrease, pursed-lip breathing may increase mixed venous oxygen saturation, resulting in better tissue oxygenation.[11] Pursed-lip breathing is thought to improve gas exchange by preventing airway collapse. As a result, gas trapping is decreased, resulting in an increase in tidal volume.[11]

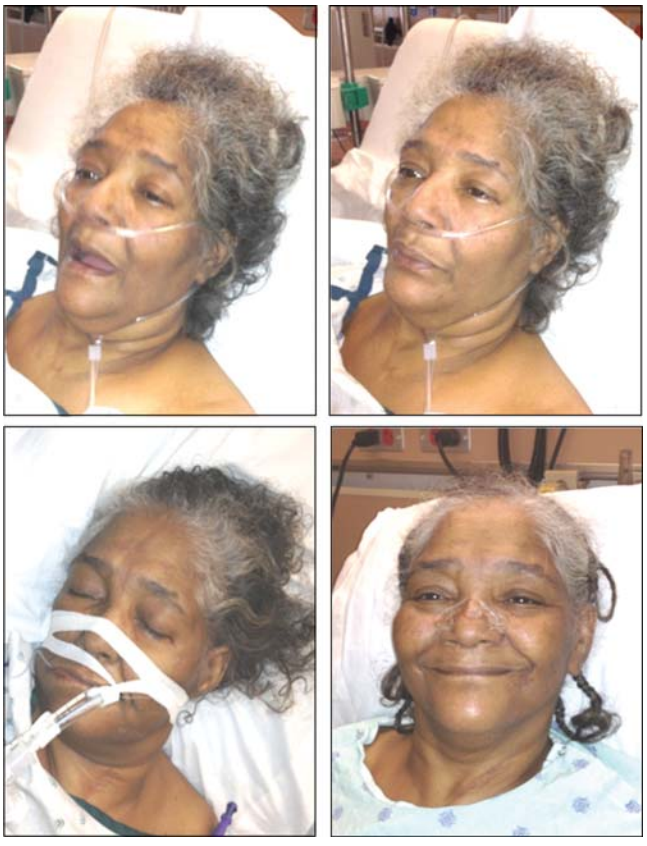

FIGURE 4-3 Change in facial appearance during the development and resolution of acute respiratory failure resulting from congestive heart failure and exacerbation of chronic obstructive pulmonary disease. *Left upper panel:* The patient is dyspneic and her mouth is open on inhalation. *Right upper panel:* The patient exhibits pursed-lip breathing on exhalation. Over the ensuing 24 hours, the patient developed hypercapnic respiratory failure and failed a trial of noninvasive ventilation (not shown). *Left lower panel:* The patient is intubated and receiving mechanical ventilation. *Right lower panel:* The patient is successfully extubated 4 days after institution of mechanical ventilation.

A few patients in respiratory distress moan during exhalation. Such moans have been compared with the grunting that is typical of neonates with the respiratory distress syndrome.[9] Grunting results from glottic closure and expiratory muscle recruitment during early exhalation.[13] It is associated with a rise in transpulmonary pressure and oxygenation.[13] If grunting is prevented by tracheal intubation, oxygenation deteriorates.[13] Use of continuous positive airway pressure (CPAP) improves oxygenation and eliminates grunting.[14] The improvement in oxygenation may result from grunting acting as a natural form of PEEP that recruits collapsed alveoli and partially overcomes inequalities in gas distribution caused by differing time constants. Of course, grunting also can arise with disease outside the thorax, such as with an acute abdomen.[15]

Nasal flaring, another facial sign of respiratory distress, is caused by contraction of the alae nasi, the dilator muscle of the external nares.[10] In adults, nasal flaring reduces nasal resistance by approximately 40% to 50% and total airway resistance by approximately 10% to 30%.[10] Factors regulating alae nasi activity include chemical stimuli that cause hyperpnea (hypoxia and hypercapnia),[10,16,17] inspiratory resistive loading,[17] and local stimuli (negative intraluminal nasal pressure).[16] The proportion of patients in respiratory distress who present with nasal flaring is unknown, as is the level of interobserver agreement in detecting flaring. Ventilator support reduces or eliminates alae nasi activity.[18,19]

Diaphoresis, often best detected on the forehead,[9] accompanies respiratory distress in some patients. Among forty-nine patients admitted to the emergency ward for acute bronchial asthma, Brenner et al[20] found that nine patients had profuse sweating. This subgroup displayed greater abnormalities in peak expiratory flow rate and Pa_{CO_2}. In patients with respiratory distress, diaphoresis may result from increased work of breathing,[21] sympathetic stimulation,[21,22] and hypercapnia-associated cutaneous vasodilation.[21,23] In contrast, diaphoresis in patients with heart failure often is associated with hypoperfusion of the skin, vasoconstriction, and cold extremities.[21]

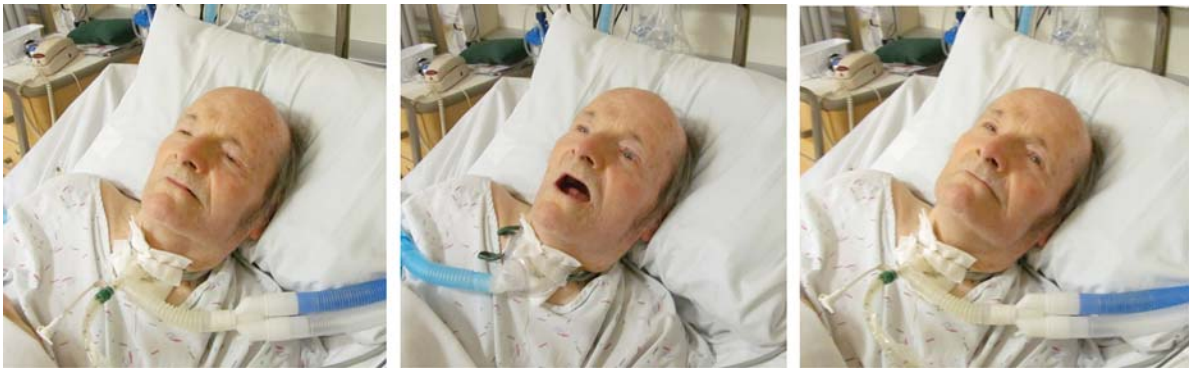

FIGURE 4-4 Change in the configuration of the mouth in a patient with a tracheostomy who becomes dyspneic. *Left:* The patient is resting during full ventilator support and his mouth is closed. *Middle:* Twelve minutes after disconnection from the ventilator, the patient has developed dyspnea and anxiety and his mouth is open. *Right:* Thirty minutes after reconnection to the ventilator, the patient's respiratory distress has resolved and his mouth is closed.

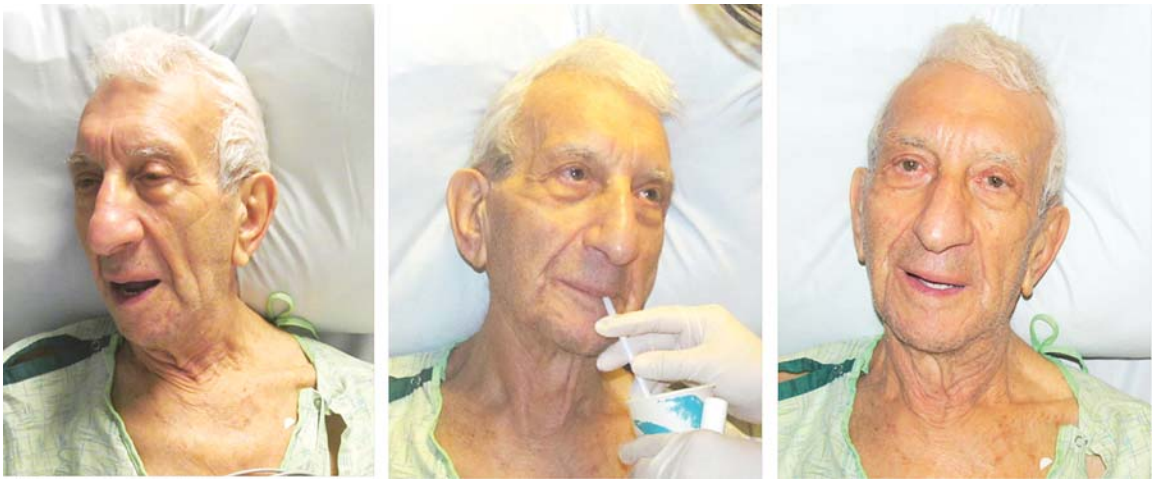

FIGURE 4-5 Drooping of the eyelids accompanying deterioration of mental status during an episode of respiratory failure. *Left:* A patient developed respiratory compromise secondary to atrial fibrillation and heart failure 2 days after prostate surgery. The patient is drowsy with drooping eyelids, and is moderately dyspneic with an open mouth and groans during exhalation. *Middle:* Despite respiratory compromise, the patient is able to drink. *Right:* After 2 days of medical therapy, the patient's dyspnea has resolved and he is alert, cheerful, and talkative.

Mentation can be evaluated by inspection of the face and by simple questioning. With early respiratory distress, nearly all patients are anxious, and their eyelids are retracted. As distress increases, the level of consciousness often decreases, and the lids tend to fall (Fig. 4-5). Instead of remaining alert to their surroundings, patients gaze vacantly ahead.[9] If respiratory failure is left untreated, apathy leads to drowsiness and then coma. These changes in mentation arise because of the underlying cause of respiratory failure (decreased cardiac output in cases of shock, impaired neurologic function in sepsis), acute hypercapnia,[24] or to a lesser extent, hypoxemia.[24,25] In a classic description, Campbell noted that most (nonhypotensive) patients with an exacerbation of COPD have preserved consciousness on arrival to the emergency room despite Pa_{O_2} being as low as 20 to 40 mm Hg.[25] Although extremely useful in overall patient assessment, facial signs of respiratory distress do not necessarily translate into an automatic decision to intubate a patient (Fig. 4-5).

ACCESSORY AND EXPIRATORY MUSCLE RECRUITMENT

Increased respiratory loads in healthy subjects[26,27] and in ambulatory patients with COPD[28] are met with a proportionately greater use of the rib-cage muscles than of the diaphragm.[26–28] As the load increases, the expiratory muscles are recruited.[26,27,29] In addition to increased activity of rib cage and abdominal muscles, the respiratory centers may increase activity of the accessory muscles, especially the sternomastoids.[30–32] The sternomastoids are activated in patients with respiratory compromise[30] and in healthy subjects breathing with a high level of inspiratory effort. The threshold for sternomastoid activation, however, is lower in patients.[31] In patients with respiratory distress,[5,33] sternomastoid recruitment can be phasic (during inhalation) (Fig. 4-6) or tonic.[29,32] Some patients hold their head off the pillow to enhance sternomastoid action.[9]

TACHYPNEA, PARADOX, TRACHEAL TUG, INTERCOSTAL RECESSIONS

Changes in respiratory rate are one of the most useful signs in evaluating the need for mechanical ventilation. Tachypnea is a near-universal sign accompanying respiratory distress.

Obtaining reliable measurements of respiratory rate and interpreting the values are not straightforward. First, bedside assessment often is inaccurate. In one study, 40% of nurses' estimations of respiratory frequencies deviated by more than 20% from the true value.[34] Agreement as to the presence of tachypnea among physicians, expressed as a κ value (κ of 0 indicates that agreement is no better than chance; κ of 1 indicates complete agreement), was only 0.25.[35] Second, the

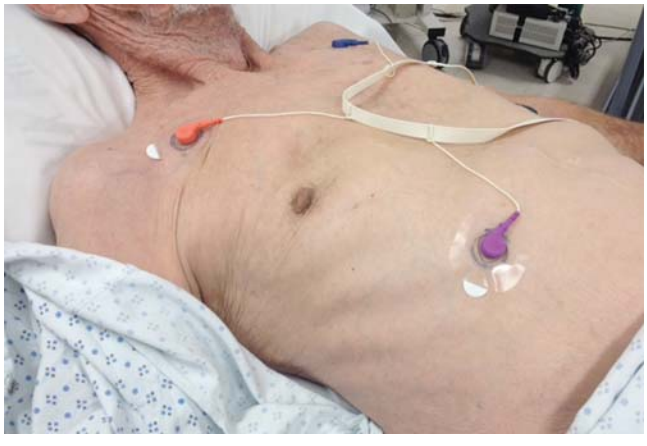

FIGURE 4-6 Sternomastoid muscle recruitment and intercostal recession during an episode of respiratory distress.

TABLE 4-1: RESPIRATORY RATES IN HEALTH AND DISEASE

Condition	Number of Subjects	Mean (breaths/min)	SD	Mean + 2 SD
Healthy nonsmoker	65	16.6	2.8	22.2
Healthy smoker	22	18.3	3.0	24.3
Asthma	17	16.6	3.4	23.4
COPD, eucapnia	16	20.4	4.1	28.6
COPD, hypercapnia	12	23.3	3.3	29.9
Restrictive lung disease	14	27.9	7.9	43.7
Pulmonary hypertension	7	25.1	6.4	37.9
Chronic anxiety	13	18.3	2.8	23.9

Abbreviations: COPD, chronic obstructive pulmonary disease; SD, standard deviation.

Source: Data from Tobin et al.[37]

within-day (within an individual) coefficient of variation in respiratory rate among young, healthy adults is 21 ± 12%; in old, healthy adults, it is 29 ± 11%.[36] Thus, accurate quantification of respiratory rate requires counting more breaths than contained in the usual 15-second sample.[36,37] Third, the day-to-day coefficient of variation of respiratory rate is 7 ± 2% in healthy individuals[36]; the value in patients with pulmonary diseases is unknown. Fourth, the typical respiratory rate in patients with different disease states varies from one state to the next[37] (Table 4-1); a rate that is judged high in a previously healthy subject may arouse no concern in a patient with restrictive disease. The upper limit of normal (mean + 2 standard deviations [SD]) in health is 22 breaths/min.[37] The equivalent value for stable patients with COPD is 30 breaths/min, and for patients with restrictive lung disease, 44 breaths/min.[37]

Despite limitations in its measurement, tachypnea is an important clinical sign. In a retrospective case-controlled study of patients discharged from an ICU, the only continuous variables that predicted readmission to the ICU were higher respiratory rate (24 vs. 21 breaths/min) and lower hematocrit.[38] Readmitted patients had a much higher mortality than the control patients, 42% and 7%, respectively, and respiratory problems accounted for more than half the readmissions. Of eighteen patients who were discharged from the ICU with a respiratory rate of more than 30 breaths/min, twelve required readmission. In a study of patients who had experienced a cardiopulmonary arrest, 53% had documented deterioration in respiratory function in the 8 hours preceding the arrest.[39] Of interest, respiratory rate was elevated in most patients (mean: 29 ± 1 [SE (standard error)] breaths/min), whereas other routine laboratory tests showed no consistent abnormalities. That detection of tachypnea did not lead to a change in patient management (in an effort to prevent the arrest) led the authors to surmise that physicians do not fully appreciate its clinical importance.

Shallow respiration (when measured with instrumentation) is common in patients with acute respiratory distress.[40] Judging tidal volume as shallow based on physical examination is very unreliable.[41,42] Clinical skill in this task is not improved by years of experience.[42]

Patients in distress commonly display abnormal chest wall movements.[43,44] Abnormal movements can be separated into three categories. One, asynchrony, consists of a difference in the rate of motion of the rib cage and abdomen (Fig. 4-7). Two, paradox, consists of one compartment moving in the opposite direction to tidal volume (Fig. 4-7). The third abnormality is greater-than-normal breath-to-breath variation in the relative contribution of the rib cage and abdomen to tidal volume; this pattern, termed *respiratory alternans*, represents recruitment and derecruitment of the accessory intercostal muscles and the diaphragm. In the past, it was thought that these three abnormalities of motion represented respiratory muscle fatigue.[45] It is now known that they represent signs of increased load and occur in the absence of fatigue.[46] These abnormalities are seen not only in patients with respiratory distress,[47] but also in some ambulatory patients[37,47] and during sleep (sleep apnea syndrome).[48]

Increased tidal swings in intrathoracic pressure are axiomatic to increases in the work of breathing. The greater downward movement of the diaphragm tends to pull down the trachea (just as a sexton ringing a bell) with each inspiration,[49] producing a sign termed *tracheal tug.* Tracheal tug correlates closely with severity of airway obstruction (Fig. 4-8).[50]

The intercostal spaces normally bulge inward during inhalation and outward during exhalation.[15] Inspiratory retraction of the intercostal space—serving as a window into the pleural space—is increased in patients with respiratory disease (see Fig. 4-6). The suprasternal fossa also moves inward in direct proportion to swings in pleural pressure.[51,52] Focal exaggerated retraction of the intercostal space can occur with a flail chest. Focal expiratory bulging may be seen on the side of a tension pneumothorax or over the area of a flail chest.[15] As with other physical signs, studies often reveal poor agreement among physicians.[35,53] For example, Godfrey et al[53] found agreement among eleven relatively experienced chest physicians in identifying tracheal tug to be midway between chance and maximum possible agreement. Spiteri et al[35] found poor agreement among experienced physicians for detecting reduced chest movements ($\kappa = 0.38$) and cricosternal distance ($\kappa = 0.28$)[35]; they did not address tracheal tug or inspiratory retractions.

The interpretation of data generated by studies that quantify physical signs is hazardous. The entity that researchers are quantifying can be very different from the skill involved in the physician's actions. Physical examination is an art—learned through apprenticeship, not out of a book. Thus, we should bear in mind Braque's caution about art appreciation: "The only thing that matters in art can't be explained." Likewise, the essence of physical examination is its tacit

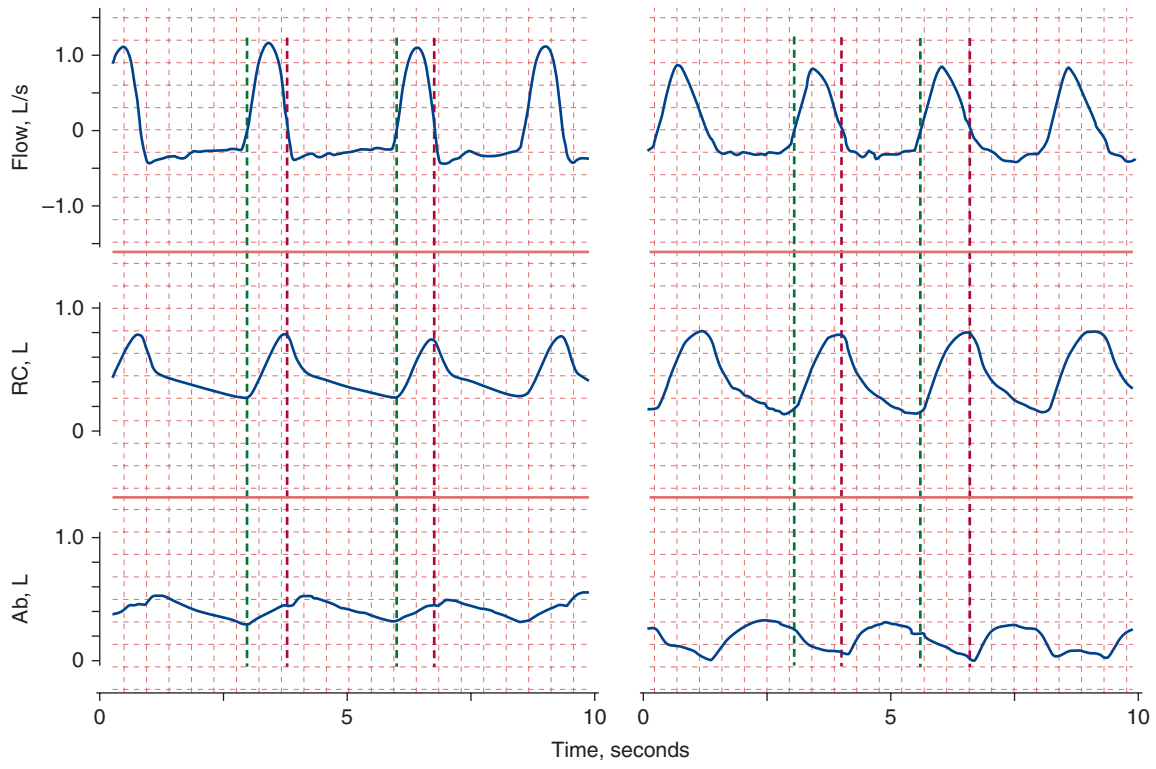

FIGURE 4-7 Recordings of flow (*inspiration upward*), rib cage (*RC*), and abdominal (*Ab*) cross-sectional areas in two patients in respiratory distress. The *green vertical lines* indicate the onset of inspiratory flow and the *red vertical lines* indicate the onset of expiratory flow. On the *left*, expansion of the rib cage is occurring faster than expansion of the abdomen (asynchrony). On the *right*, while the rib cage expands during inspiration, the abdominal cross-sectional area is getting smaller (paradox).

coefficient; the explicit, measurable components may be the least relevant. Another problem with research on physical signs is test-referral bias. For example, the studies of Godfrey et al[53] and Spiteri et al[35] were confined to patients with respiratory diseases; a more appropriate design also would have included healthy subjects and patients with diseases not affecting the lungs. These flaws in the methodology of such studies markedly underestimate the diagnostic power of physical examination.

CARDIOVASCULAR SIGNS OF RESPIRATORY DISTRESS

Respiratory distress frequently is associated with tachycardia and hypertension. Tachycardia and hypertension likely are caused by increased sympathetic discharge.[54] In some patients, such as those with sepsis, cardiac impairment, or severe hypoxemia, respiratory distress is associated with hypotension and not hypertension.

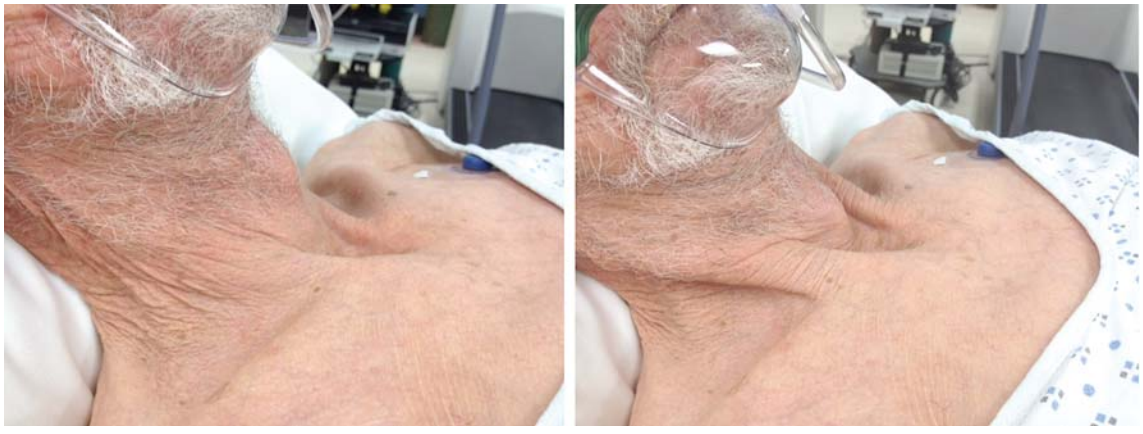

FIGURE 4-8 Tracheal tug in acute respiratory failure. *Left:* During exhalation, the cricoid cartilage is located 2 fingerbreaths above the suprasternal notch (normally, at least 4 fingers). *Right:* During inhalation, the cricoid cartilage is pulled below the suprasternal notch and the thyroid cartilage is 1 fingerbreath above the suprasternal notch, whereas it was 5 fingerbreaths above the notch on exhalation (*left*).

Pulsus paradoxus is defined as an inspiratory fall in systolic pressure of greater than 10 mm Hg.[15] Pulsus paradoxus is very common in patients with an exacerbation of asthma but also in patients with COPD, shock, and pericardial tamponade (see Chapter 36).[15,20]

NONUNIFORM PRESENTATION

Patients with impending respiratory failure do not have a uniform presentation. The spectrum ranges from a patient complaining of dyspnea to a patient with impending respiratory arrest. Several factors are responsible. Patients differ in the balance between work of breathing and the capacity of the respiratory muscles to generate pressure. They also differ in the central processing of neural afferents. For instance, patients with a history of near-fatal asthma have a blunted perception of dyspnea,[55] reduced sensitivity to added inspiratory resistive loads,[56] and a reduced chemosensitivity to hypoxia.[55] Alexithymia, the difficulty in perceiving and expressing emotions and body sensations, occurs more often in patients who experience near-fatal asthma than in less-severely affected patients.[57] In addition, hypoxia, and possibly hypercapnia, can impair sensations of respiratory load.[58]

IMPENDING RESPIRATORY FAILURE

Development of impending respiratory failure is a commonly listed indication for mechanical ventilation.[59] But *impending respiratory failure* has no clear definition. Some clinicians use the term to mean development of severe tachypnea, diaphoresis, and use of accessory muscles of respiration; others use it to mean agonal breathing.

In some circumstances, physicians do not institute mechanical ventilation until they obtain results of diagnostic testing, such as chest radiographs, electrocardiograms, or arterial blood-gas analyses. Even in this situation, clinicians commonly do not change their mind when the test results are different from those expected. In most circumstances, a patient's clinical presentation is so dramatic that mechanical ventilation is instituted without performing arterial blood-gas analysis. If arterial blood-gas results are not available before connecting a patient to a ventilator, they are almost invariably available shortly after. Arterial blood-gas analysis is helpful in choosing the type of support best suited to a patient's needs. Analysis also serves to classify patients into two broad groups: hypoxemic respiratory failure (Table 4-2) and hypercapnic respiratory failure; some patients display features of both.[60]

Hypoxemic Respiratory Failure

PATHOPHYSIOLOGY

The pathophysiologic mechanisms responsible for hypoxemia can be grouped into two broad categories depending on whether there is (or is not) an increased alveolar-arterial oxygen gradient ($A\text{-}aD_{O_2}$).* An increased $A\text{-}aD_{O_2}$ results from either ventilation–perfusion ($\dot{V}_A/\dot{Q}$) abnormalities or excessive right-to-left shunt. (Diffusion impairment, a third cause of increased $A\text{-}aD_{O_2}$, plays only a marginal role in the development of hypoxemia.) Patients with hypoxemic respiratory failure and a normal $A\text{-}aD_{O_2}$ typically have alveolar hypoventilation or inadequate inspiratory partial pressure of oxygen. Hypoxemia results from a low inspired P_{O_2} or when the fractional concentration of inspired oxygen (FI_{O_2}) is less than 0.21, such as at high altitude or when O_2 is consumed from ambient gas secondary to a fire. A low FI_{O_2} also can arise during anesthesia if a low-oxygen gas mixture is administered inadvertently. Hypoxemic respiratory failure also can be caused by the combination of a decreased mixed venous oxygen content and impaired gas exchange, such as in patients with heart failure and concurrent $\dot{V}_A/\dot{Q}$ derangements or increased shunt.

A right-to-left shunt is present when venous blood returning from the tissues passes to the systemic arterial circulation without coming into contact with gas-containing alveoli. The shunt is the major mechanism of abnormal gas exchange in patients with pulmonary edema, ARDS, pneumonia, and atelectasis. In all these instances, the shunt results from the perfusion of alveoli that are unventilated because they are filled with fluid or collapsed.

TABLE 4-2: COMMON CAUSES OF HYPOXEMIC RESPIRATORY FAILURE

Pneumonia
Cardiogenic pulmonary edema
Acute respiratory distress syndrome
Aspiration of gastric contents
Multiple trauma
Immunocompromised host with pulmonary infiltrates
Pulmonary embolism

*$A\text{-}aD_{O_2}$ is calculated as $PA_{O_2} - Pa_{O_2}$, where PA_{O_2} (alveolar O_2 tension) can be estimated according to the simplified alveolar gas equation:

$$PA_{O_2} = FI_{O_2} \times (P_B - PH_2O) - Pa_{CO_2}/R$$

where FI_{O_2} is fractional concentration of inspired O_2 (approximately 0.21 when breathing room air), P_B is barometric pressure (approximately 760 mm Hg at sea level), PH_2O is water vapor pressure (usually taken as 47 mm Hg at 37°C [98.6°F]), and R is respiratory exchange ratio of the whole lung. The respiratory exchange ratio (R) = CO_2 production/O_2 consumption ($\dot{V}_{CO_2}/\dot{V}_{O_2}$) is normally approximately 0.8. In steady state, R is determined by the relative proportions of free fatty acids, protein, and carbohydrate consumed by the tissues. In this equation, it is assumed that alveolar P_{CO_2} and Pa_{CO_2} are the same (usually they nearly are). In healthy young subjects (≤30 years old) breathing air at sea level, $A\text{-}aD_{O_2}$ is usually less than 10 mm Hg, but it increases to as much as 28 mm Hg in some healthy 60-year-old subjects.

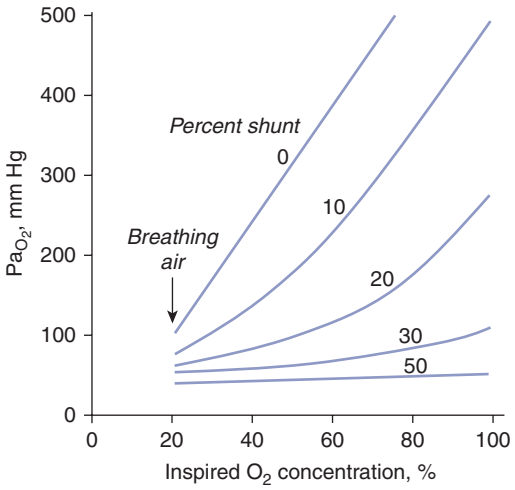

FIGURE 4-9 Relationship between arterial P_{O_2} (Pa_{O_2}) and increases in inhaled oxygen concentrations for different levels of shunt. When the shunt fraction is 30% or more of cardiac output, Pa_{O_2} increases little despite marked increases in inhaled oxygen concentration. The plot is a simplification that ignores factors such as cardiac output and oxygen uptake, which influence the location of the lines. (Modified, with permission, from West.[61])

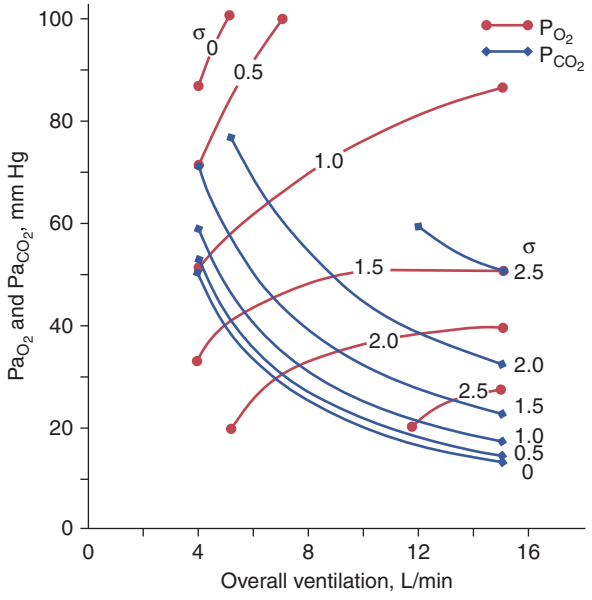

FIGURE 4-10 Effect of increasing overall ventilation on Pa_{O_2} and Pa_{CO_2} (lung model) as a function of different degrees of $\dot{V}_A/\dot{Q}$ mismatching, represented in terms of dispersion or standard deviations (σ) of the log-normal distribution of ventilation and perfusion. (Dispersion of 0.30 to 0.05 = normal $\dot{V}_A/\dot{Q}$ mismatch; 1.0 = moderate $\dot{V}_A/\dot{Q}$ mismatch; 2.0 = severe $\dot{V}_A/\dot{Q}$ mismatch.) Increases in overall ventilation have a powerful effect on Pa_{O_2} and Pa_{CO_2} when $\dot{V}_A/\dot{Q}$ dispersion is small. Abnormal $\dot{V}_A/\dot{Q}$ dispersion does not cause an increase in Pa_{CO_2} as long as patients are able to increase minute ventilation sufficiently. Pa_{O_2} also increases with increases in overall ventilation, although when $\dot{V}_A/\dot{Q}$ dispersions are (very) altered, normal Pa_{O_2} cannot be reached very easily, and further effects on ventilation have little effect on Pa_{O_2}. In the patients who cannot maintain a high rate of ventilation owing to the increased work of breathing and in those whose respiratory motor output increases only slightly when Pa_{CO_2} is high, hypercapnia can ensue. (Modified, with permission, from West.[64])

A characteristics feature of a shunt is the failure of Pa_{O_2} to increase to the expected level when a patient breathes 100% oxygen (Fig. 4-9).[61]

In patients with a large shunt, Pa_{CO_2} may be low because the low Pa_{O_2} stimulates respiratory motor output and minute ventilation ($\dot{V}_E$).[62] A shunt typically produces more severe hypoxemia than does $\dot{V}_A/\dot{Q}$ inequality.

Optimal uptake of oxygen depends on proper matching of ventilation and perfusion within the lung. In semirecumbent young healthy subjects breathing room air, the range (or dispersion) of $\dot{V}_A/\dot{Q}$ ratios is quite small: More than 95% of both ventilation and perfusion is limited between $\dot{V}_A/\dot{Q}$ ratios of 0.3 and 2.1.[63] The dispersion increases with age.[63] With pulmonary disease, the range of $\dot{V}_A/\dot{Q}$ ratios widens,[64] varying from 0 (perfused but unventilated, i.e., shunt) to infinity (ventilated by unperfused, i.e., alveolar dead space). In other words, $\dot{V}_A/\dot{Q}$ inequality does not refer to alterations in the ratio of total ventilation to total perfusion, which constitute global hyperventilation or hypoventilation. (One lung could receive all ventilation and the other all perfusion for an overall $\dot{V}_A/\dot{Q}$ ratio of 1.0).[65] $\dot{V}_A/\dot{Q}$ inequality refers to regional mismatching of ventilation to perfusion. $\dot{V}_A/\dot{Q}$ inequality, no matter what its mechanism, interferes with overall efficiency of the lung for exchanging all gases, including oxygen, CO_2, CO, and anesthetic gases.[62]

$\dot{V}_A/\dot{Q}$ mismatch is the most common cause of hypoxemia. Several compensatory mechanisms tend to minimize the effects of abnormal $\dot{V}_A/\dot{Q}$ ratios. The low PA_{O_2} associated with a low $\dot{V}_A/\dot{Q}$ ratio causes pulmonary vasoconstriction. The low PA_{CO_2} associated with a high $\dot{V}_A/\dot{Q}$ ratio causes hypocapnic bronchoconstriction (e.g., pulmonary embolism).[66] These responses, however, only achieve partial compensation. As $\dot{V}_A/\dot{Q}$ inequality increases in the presence of a constant $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$, there is an immediate and marked fall in Pa_{O_2} and a slower increase in Pa_{CO_2}. The increase in Pa_{CO_2} and, to a lesser extent, the fall in Pa_{O_2} stimulates the chemoreceptors and leads to an increase in $\dot{V}_E$. In patients without a significant reduction in ventilatory capacity, the increase in ventilation is sufficient to bring Pa_{CO_2} back to normal, although it has only a small effect on the fall in Pa_{O_2} (Fig. 4-10). Thus, most patients with $\dot{V}_A/\dot{Q}$ inequalities have a low Pa_{O_2} but normal Pa_{CO_2}.[67] Ventilation in excess of normal alveolar requirement is termed *wasted ventilation*.[62] All normocapnic patients with COPD have increased ventilation of their alveoli, as do most hypercapnic patients.[62]

The different responses of Pa_{O_2} and Pa_{CO_2} to an increase in the level of ventilation is caused by the different shapes of the oxyhemoglobin and CO_2 dissociation curves (Fig. 4-11). The oxyhemoglobin dissociation curve is flat in the normal range. Thus, only units with moderately low $\dot{V}_A/\dot{Q}$ ratios benefit appreciably from the increased ventilation. Lung units that are positioned on the upper portion of the dissociation

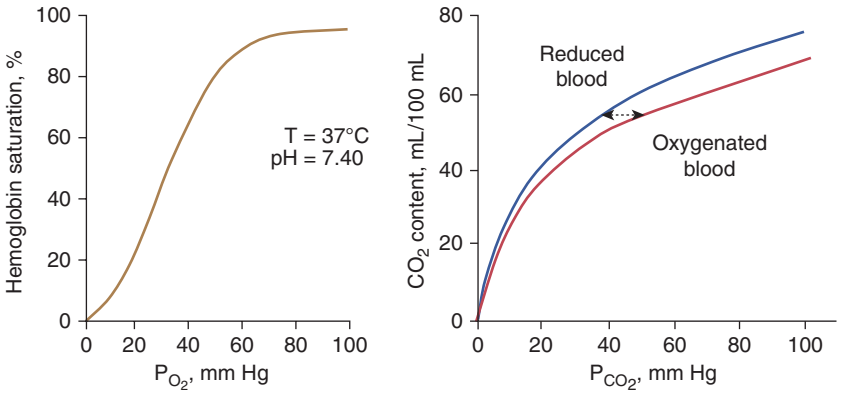

FIGURE 4-11 *Left:* Normal oxyhemoglobin dissociation curve. The curve has a sigmoid shape because when one subunit of the normal tetrameric form of the adult hemoglobin becomes oxygenated, it induces a structural change in the whole complex. Consequently, the three other subunits gain a greater affinity for oxygen until four molecules of oxygen are combined with hemoglobin. *Right:* The CO_2 dissociation curve for oxygenated and reduced blood. The relationship is steeper and more linear than the oxyhemoglobin dissociation curve. Oxygenation of blood causes the curve to shift to the right (Haldane effect), and, for a given CO_2 content, oxygenated blood has a higher P_{CO2} than reduced blood.

curve (high $\dot{V}_A/\dot{Q}$ ratio) develop little increase in the oxygen concentration of their effluent blood. The net result is that with increasing $\dot{V}_E$, the mixed Pa_{O_2} rises only modestly, and some hypoxemia always remains.[62] By contrast, the CO_2 dissociation curve is almost linear in the physiologic range (Fig. 4-11). Thus, an increase in $\dot{V}_E$ raises CO_2 output of lung units with both high and low $\dot{V}_A/\dot{Q}$ ratios.[62] The different shapes of the two dissociation curves are the main reason that patients with parenchymal lung disease have greater hypoxemia relative to hypercapnia. One final compensatory adjustment is possible: increase in cardiac output.[68] Adrenergic stimulation by arterial hypoxemia can raise cardiac output by 50% or more; this improves arterial blood gases by raising mixed venous oxygen and by lowering mixed venous CO_2.[68]

Administration of supplemental oxygen in patients with $\dot{V}_A/\dot{Q}$ inequality will cause arterial hypoxemia to reverse impressively because PA_{O_2} of even poorly ventilated units increases sufficiently to achieve saturation (Fig. 4-12). Unless FI_{O_2} is 1.0, it is impossible to determine the relative contribution of right-to-left shunt versus $\dot{V}_A/\dot{Q}$ inequality to an increase in $A\text{-}aD_{O_2}$.[69] After breathing 100% oxygen for a sufficient time, only units that are totally or almost totally unventilated (shunt, true shunt, or anatomic shunt) will contribute to hypoxemia.[69]

Systemic hypotension and hypertension modulate the ventilatory responses to hypoxemia (and hypercapnia). This so-called ventilatory baroreflex increases the operating point of the ventilatory response to hypoxemia (and hypercapnia) during hypotension and it decreases the operating point of the ventilatory response to hypoxemia (and hypercapnia) during hypertension.[70]

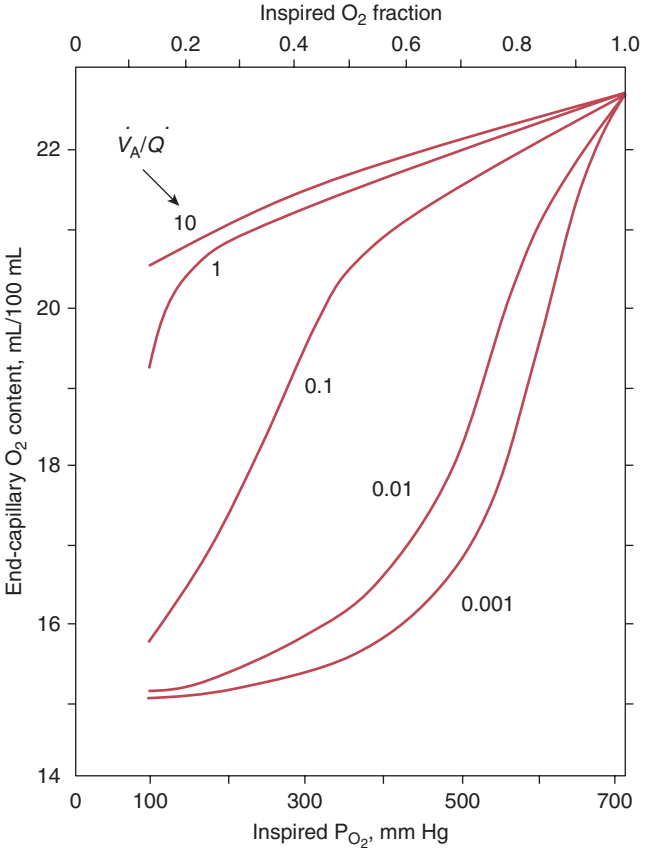

FIGURE 4-12 The effect of alterations in inhaled partial pressure of oxygen (P_{O_2}) on oxygen content of end-capillary blood of a lung unit. Each line depicts a different ventilation–perfusion ratio ($\dot{V}_A/\dot{Q}$). With mild to moderate degrees of $\dot{V}_A/\dot{Q}$ inequality ($\dot{V}_A/\dot{Q}$ down to 0.1), end-capillary oxygen content increases as inhaled oxygen is increased. With severe $\dot{V}_A/\dot{Q}$ inequality ($\dot{V}_A/\dot{Q}$ below 0.1), the increase in end-capillary oxygen content with an increase in inhaled oxygen is much slower; only when inspired P_{O_2} is more than 400 to 500 mm Hg does end-capillary oxygen content of the lung unit reach values equivalent to those seen with mild to moderate degrees of $\dot{V}_A/\dot{Q}$ inequality. (Modified, with permission, from West.[64])

PHYSIOLOGIC EFFECTS OF HYPOXIA

Although the physiologic effects of hypoxia are graded, the damaging effects are sudden.[71] A remarkable degree of

arterial hypoxemia is required to cause tissue hypoxia.[25] In clinical practice, Campbell[25] observed that the lowest Pa_{O_2} compatible with life is 20 mm Hg (equivalent to an arterial oxygen saturation [Sa_{O_2}] of 30% to 40%). Evidence of end-organ damage is difficult to demonstrate in patients with a Pa_{O_2} above 40 mm Hg (equivalent to an Sa_{O_2} of approximately 70%).[25] Obviously, the duration of hypoxemia and the state of circulation (oxygen delivery) play major roles in determining the minimum Pa_{O_2} that does not cause end-organ damage or death.

The threshold Pa_{O_2} commonly used to diagnose hypoxemic respiratory failure is 60 mm Hg, which corresponds to an Sa_{O_2} of 90% (hypoxic hypoxia). Pa_{O_2} values below 60 mm Hg fall on the steep portion of the oxyhemoglobin dissociation curve, and decreases below that value are associated with precipitous falls in Sa_{O_2} (see Fig. 4-11). Although physiologically reasonable, for self-evident ethical reasons, the 60 mm Hg (Pa_{O_2}) threshold cannot be validated experimentally.

The main concern with hypoxemia is impaired tissue oxygenation, especially of the heart and brain. The factors determining oxygen supply to the tissues include hemoglobin concentration, Sa_{O_2}, the affinity of hemoglobin for oxygen (P_{50}), cardiac output, regional oxygen consumption-to-perfusion relationships, and the diffusion of oxygen from the capillary to intracellular sites. The amount of oxygen delivered to the tissues is calculated as

$$O_2 \text{ delivery} = Ca_{O_2} \times \text{cardiac output}$$

where arterial oxygen content (Ca_{O_2}) is calculated as

$$Ca_{O_2} = (Hb \times 1.34 \times Sa_{O_2}/100) + (0.003 \times Pa_{O_2})$$

Even with a satisfactory Pa_{O_2}, tissue hypoxia may arise because of decreased Ca_{O_2} (e.g., decreased hemoglobin concentration or decreased hemoglobin function, such as in carbon monoxide poisoning or anemic hypoxia), decreased oxygen delivery (e.g., cardiogenic shock or stagnant hypoxia), and decreased capacity of the tissues to use oxygen (e.g., sepsis, cyanide intoxication, or histotoxic hypoxia). Otherwise stated, tissue hypoxia can be present despite adequate Pa_{O_2}, or it can be absent despite an abnormally low Pa_{O_2}.[59]

Respiratory Responses. Peripheral chemoreceptors (carotid and aortic bodies) detect changes in arterial oxygen. Within seconds after the onset of hypoxia, they initiate reflexes that are important for maintaining homeostasis.[72–74] The aortic bodies play a minor role in modulating spontaneous respiratory activity, although they have a discernible effect when their gain is increased by hypercapnia.[75]

Hypoxia augments sensory discharge from the peripheral chemoreceptors, which, in turn, send neural impulses to the respiratory centers (inspiratory neurons of the dorsal respiratory group and ventral respiratory group[76]), causing an increase in the $\dot{V}_E$.[72,73,77,78] Hyperpnea, in turn, activates pulmonary afferents, thereby buffering the sympathetic response to hypoxemia.[79]

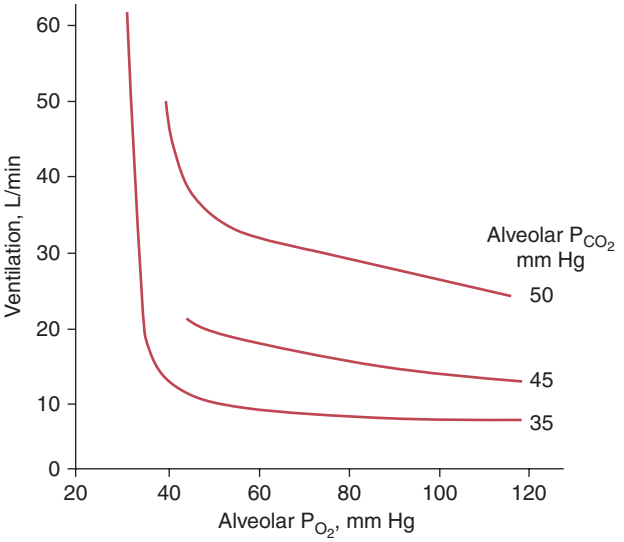

FIGURE 4-13 Relationship between ventilation and alveolar pressure of oxygen (P_{O_2}) at various levels of alveolar carbon dioxide (P_{CO_2}). The ventilatory response increases with the increase in P_{CO_2}. At alveolar P_{CO_2} 35 mm Hg, ventilation exhibits virtually no increase until alveolar P_{O_2} falls below 40 mm Hg and, thereafter, ventilation increases abruptly.

The ventilatory response to progressive hypoxia is hyperbolic[72] and increases in the presence of concurrent hypercapnia[75] (Fig. 4-13). It decreases with age.[80] Chronic hypoxia may induce a reduced ventilatory response to hypoxia in patients with COPD,[75] although the role of airway narrowing in producing this effect cannot be excluded.[75]

The ventilatory response to hypoxemia is attenuated or abolished in patients who have undergone surgical excision of the carotid bodies.[73,74,78,81] The increase in ventilation in response to hypoxemia probably contributes to coronary vasodilation.[82] Stimulation of the carotid bodies with nicotine under normoxic conditions causes an increase in ventilation and coronary vasodilation.[82] Coronary vasodilation does not occur if the increase in ventilation is prevented by general anesthesia.[82]

Cardiovascular Responses. Hypoxic stimulation of chemoreceptors triggers reflex adrenergic vasoconstriction in muscle and coronary vasodilation but does not elicit a reflex response in the cerebral vessels.[74,79,82,83] Hypoxia also causes local vasodilation.[72,79] The net effects are increases in heart rate, cardiac output (resulting from the positive chronotropic effect of hypoxemia, not increased stroke volume[84]), pulmonary artery resistance,[85] and cerebral and coronary blood flow.[74,79,80,82–84] Hypoxemia fails to increase systemic blood pressure[84] or increases it very modestly (<10 mm Hg rise in systolic and diastolic pressures).[77] The increase in blood pressure, but not in heart rate, is absent in patients in whom the carotid bodies are inactivated.[74,77] Persistent tachycardic response to hypoxemia in patients with bilateral carotid body ablation likely is mediated by the effect of hypoxemia on the aortic bodies.[72]

Tachycardia caused by hypoxemia is mediated by multiple factors, including CNS-mediated sympathetic discharge, effect of P_{O_2} on the cardiac pacemaker, and concomitant hyperpnea.[77] These mechanisms presumably override the cardioinhibitory signals (bradycardic effect) from the carotid body.[77] The importance of hyperpnea in overriding the bradycardic effect is supported by the observation that hypoxemia combined with cessation of lung inflation (sleep apnea,[86] breath holding,[87] or neuromuscular blockade during intubation[88]) or diminution of lung inflation (such as when hyperpnea is prevented by controlled ventilation[89,90]) is more apt to produce bradycardia than tachycardia.[72,86] Bradycardia results from the concurrent activation of the carotid bodies by hypoxia and increased cardiac vagal activity induced by apnea.[79,83] The increased vagal activity (induced by apnea) can be so intense as to induce bradycardia in the absence of coexisting hypoxemia; this response has been described in patients with spinal cord injury within seconds of discontinuation from a ventilator.[91] Simultaneously with the increase in cardiac vagal activity, diminution of lung inflation causes marked potentiation of the sympathetic vasoconstrictor response to hypoxemia (secondary to the lack of inhibitory influence of the pulmonary stretch receptors).[83] (This combination of sympathetic vasoconstriction and vagal bradycardia constitutes part of the diving reflex.[83])

Severe hypoxemia is not tolerated by the CNS because it has a high rate of oxygen consumption and lacks alternative energy reserves.[92] Therefore, severe hypoxemia causes cerebral depression.[73] Patients with cerebral hypoxia develop bradycardia, hypotension,[88] and hypoventilation,[93] which further worsens hypoxia and induces a potentially lethal vicious cycle.

CLINICAL PRESENTATION OF HYPOXEMIA

Cyanosis. Physicians commonly view cyanosis as the hallmark of hypoxemia.[72] Cyanosis is recognized as a blueness of the capillary blood visible through the mucous membranes or skin, where capillaries are numerous and close together and the tissues over them are thin and transparent, such as the lips (central cyanosis) and nail beds.[72]

Based on the classic work of Lundsgaard and Van Slyke, it is widely believed that central cyanosis represents the presence of at least 5 g/dL of deoxygenated hemoglobin in the blood of the capillaries.[94] Because the arteries and most of the veins are so far away from the skin, their content cannot influence skin color.[94] Importantly, it is the quantity of reduced hemoglobin per deciliter of capillary blood, not the relative lack oxygenated hemoglobin, that produces the blue coloration of cyanosis.[95] Lundsgaard and Van Slyke demonstrated the crucial effect of hemoglobin on the development of cyanosis.[94] When hemoglobin is 15 g/dL, cyanosis reflects an Sa_{O_2} of 78%. In an anemic patient with a hemoglobin of 9 g/dL, cyanosis will not occur until Sa_{O_2} falls to 65%, whereas in a polycythemic patient, with a hemoglobin of 18 g/dL, cyanosis will occur at a Sa_{O_2} of 83% (Fig. 4-14). In addition to hemoglobin, detection of cyanosis also depends on variables

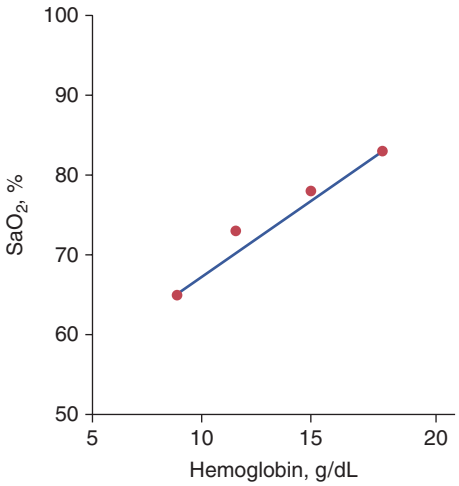

FIGURE 4-14 The dependence of cyanosis—resulting from the presence of 5 g of reduced hemoglobin per deciliter of capillary blood—on prevailing hemoglobin. In anemic patients, cyanosis signifies more severe hypoxemia than in a polycythemic patient. (Based on data from Lundsgaard and Van Slyke.[94])

such as thickness and opacity of the skin and perfusion status, as well as on the visual skills of the observer.[96,97] In seventy-two patients who had Sa_{O_2} values ranging between less than 75% and 100%, agreement among three observers was only 69% when inspecting the tongue, 61% when inspecting the lips, and 53% when inspecting the nail bed.[97] In that study,[97] cyanosis of the tongue and lips was recorded in 40% to 45% of patients with normal Sa_{O_2} values. Rather than a blue or pink color, pallor is seen with both anemia and shock. Thus, severe or fatal tissue hypoxia may occur without cyanosis.[72]

Cardiopulmonary Manifestations. Acute hypoxemia increases respiratory frequency, tidal volume, and $\dot{V}_E$ in almost all subjects.[72] Increases in $\dot{V}_E$, however, are an unreliable guide because the interindividual response is considerable.[96] The standard deviation for the within-subject variability in day-to-day hypoxic ventilatory response is approximately 22%.[98] The respiratory response to mild or moderate hypoxemia may be barely measurable or absent.[72] An increase in heart rate is equally of limited value because many other factors, such as fever, low blood pressure, pain, apprehension, and drugs, can cause it to rise.[72] Moreover, under specific circumstances (see "Cardiovascular Responses" above), hypoxemia causes bradycardia rather than tachycardia. Hypoxemia tends to increase systolic blood pressure in some subjects; the wide variations in response[77] renders arterial pressure of little value in the diagnosis of hypoxemia.[72]

Neurologic Manifestations. The metabolic needs of the brain largely depend on oxidation of glucose to CO_2 and water.[92] The brain cannot store oxygen. It survives only for minutes after the supply is reduced to critical levels.[92] In acute anoxia, consciousness is lost within 15 seconds.

TABLE 4-3: NEUROLOGIC SIGNS AND SYMPTOMS OF HYPOXIA

Pa_{O_2}, mm Hg	Signs and Symptoms of Hypoxia
35 to 50	Loss of critical judgment, confusion, delirium (resembling alcohol intoxication), tremors, asterixis
25 to 35	Somnolence, obtundation, myoclonic jerks, seizures
20 to 25	Loss of consciousness
<20	Death

The electroencephalogram slows with a Pa_{O_2} of less than 35 mm Hg or with blood flow of less than 40% of normal.[92] Loss of the electroencephalogram tracing occurs when cerebral P_{O_2} reaches 20 mm Hg or following 20 seconds of complete anoxia.[92]

In the absence of defects of cerebral blood flow, Pa_{O_2} below 40 mm Hg is required to produce prominent symptoms (Table 4-3).[24,99,100] Confusion and delirium (resembling alcohol intoxication) appear at Pa_{O_2} values of 35 to 50 mm Hg.[65] Tremors and asterixis (flapping tremor elicited by dorsiflexing the wrists with the arms outstretched and caused by a momentary interruption of normal continuous action potentials to both flexor and extensor muscles) are infrequent even when the Pa_{O_2} is less than 40 mm Hg.[24,25] Somnolence and obtundation occur at Pa_{O_2} values of 25 to 35 mm Hg. Some patients develop myoclonic jerks (bursts of excitation to resting muscles) and seizures.[24] At approximately 25 mm Hg, consciousness is lost,[65] and death often ensues.

When considering the neurologic manifestations of hypoxemia, Pa_{O_2} is only a small part of a complex situation. A decrease in Pa_{O_2} may be well tolerated if oxygen delivery is maintained by the combination of increased cardiac output and systemic vasoconstriction.[101] These compensatory mechanisms, however, can be overwhelmed by anemia or carbon monoxide poisoning, which decrease oxygen-carrying capacity (anemic hypoxia), or by atherosclerosis or other causes of vascular occlusion (ischemic hypoxia) in which the increased cardiac output does not suffice to prevent tissue damage.

Hypercapnic Respiratory Failure

PATHOPHYSIOLOGY

Hypercapnic respiratory failure is a state in which ventilation is insufficient to maintain a normal Pa_{CO_2} for the level of metabolic activity (measured by CO_2 production, $\dot{V}_{CO_2}$).[1] Common causes include COPD, severe asthma, conditions where respiratory motor output is decreased (e.g., neoplasm and infections of the CNS, medications, and drugs), neuromuscular-skeletal diseases (e.g., myasthenia gravis, Guillain-Barré syndrome, and trauma), and upper airway obstruction.

Under steady-state conditions, the relationship between Pa_{CO_2}, alveolar ventilation ($\dot{V}_A$), and $\dot{V}_{CO_2}$ is given by the equation

$$Pa_{CO_2} = (\dot{V}_{CO_2}/\dot{V}_A) \cdot K$$

The constant K is usually stated as 0.863; it converts measurements of $\dot{V}_{CO_2}$ from standard conditions to body-temperature conditions. The term $\dot{V}_A$ represents the portion of $\dot{V}_E$ that reaches the terminal gas-exchange units and is calculated as

$$\dot{V}_A = \dot{V}_E - V_D$$

where V_D equals dead space ventilation. A reduction in $\dot{V}_A$ may result from an inadequate $\dot{V}_E$ or an increase in V_D (resulting from an increase in true V_D or a functional increase in V_D secondary to lung regions with high $\dot{V}_A/\dot{Q}$ relationships).

The mechanisms responsible for hypercapnia can be grouped into two categories, depending on whether there is (or is not) an increased A-aD_{O_2}. In pure alveolar hypoventilation (e.g., neuromuscular diseases, drug overdoses, and CNS pathologies), A-aD_{O_2} is usually normal (unless lung abnormalities are present). In disorders associated with $\dot{V}_A/\dot{Q}$ inequality (e.g., COPD and ARDS), A-aD_{O_2} is increased.

Pa_{CO_2} in excess of 90 mm Hg is unlikely in patients breathing room air because the concomitant degree of hypoxia is incompatible with survival.[25] Such Pa_{CO_2} values can occur if a patient is breathing oxygen-enriched air.[102]

PHYSIOLOGIC EFFECTS OF HYPERCAPNIA

Hypercapnia elicits autonomic and ventilatory responses primarily through central chemoreceptors located in the rostral ventrolateral medulla.[74] These respond to changes in hydrogen ion concentration.[74] Hypercapnia, probably via a reduction in intracellular pH, also stimulates peripheral arterial chemoreceptors located in the carotid bodies, aortic bodies, and abdomen.[103,104] Only 15% to 30% of the ventilatory response to hypercapnia results from peripheral chemoreceptor stimulation.[105,106] Not surprisingly, the Pa_{CO_2} of patients with bilateral resection of the carotid bodies is higher (by 4.6 ± 1.3 [SD] mm Hg) than in healthy subjects.[81]

Respiratory Responses. Hypercapnia causes an increase in $\dot{V}_E$; stimulation peaks with an inhaled CO_2 of 10%.[107] In contrast to the hyperbolic response to progressive hypoxemia (see Fig. 4-13), the hypercapnic ventilatory response is linear (Fig. 4-15).[72] The ventilatory response to CO_2 is enhanced in the presence of hypoxia or metabolic acidosis[108] and decreases with age.[80]

Hypercapnia and hypoxia induce different patterns of neuromuscular activation as $\dot{V}_E$ rises—even when the respiratory components of tidal breathing (tidal volume and inspiratory and expiratory times) are similar.[76] First, hypercapnia is a more potent stimulus for expiratory muscle recruitment than is hypoxemia—one-third of subjects do not recruit their expiratory muscles during hypoxemia.[76] Second, activation of the diaphragm is greater during

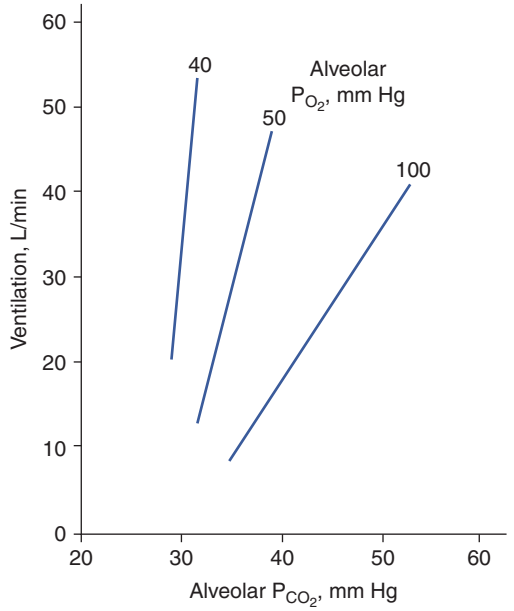

FIGURE 4-15 Ventilatory response to progressive hypercapnia. Ventilation increases linearly with increase in alveolar carbon dioxide (P_{CO_2}). Decreases in alveolar oxygen (P_{O_2}) produce a steeper ventilatory response to progressive hypercapnia.

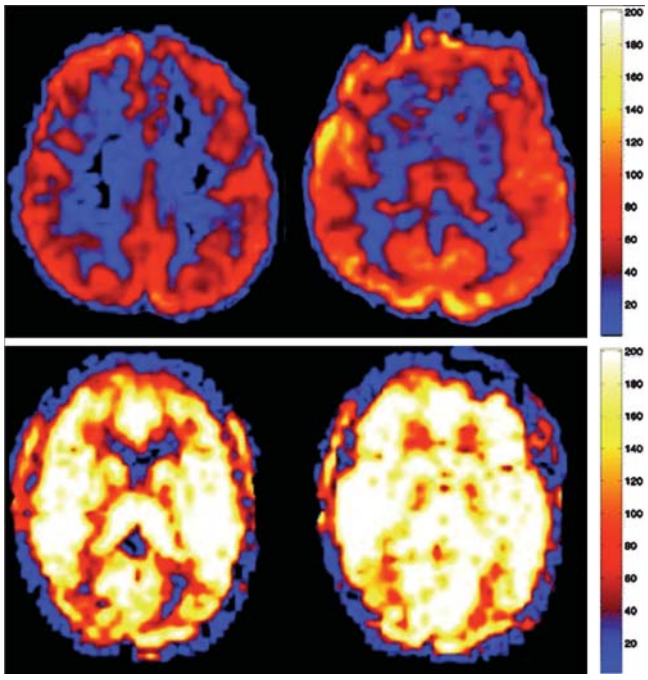

FIGURE 4-16 Arterial spin-labeled magnetic resonance perfusion imaging. *Upper panel:* A patient with normocapnia (Pa_{CO_2} 39 mm Hg), in whom the left image passes through the corona radiata and the right through the thalamus. Cerebral blood flow throughout the gray matter (red discoloration) is normal (mean: 63 mL/100 g tissue/min). *Lower panel:* A patient with emphysema and hypercapnia (Pa_{CO_2} 56 mm Hg), in whom the left image passes through the thalamus and the right through the basal ganglia. Cerebral blood flow is markedly increased (white-yellow discoloration; mean: 175 mL/100 g tissue/min), signifying global hyperperfusion. (Modified, with permission, from Pollock et al.[112])

hypoxemia than during hypercapnia.[76] (The lack of expiratory recruitment during hypoxemia may increase end-expiratory lung volume, which increases oxygen reserves.[76]) The ventilatory response to CO_2 in healthy subjects exhibits a very wide range, 0.47 to 8.16 L/min/mm Hg, although approximately 80% of subjects have a response between 1.5 and 5 L/min/mm Hg.[1]

Cardiovascular Responses. Hypercapnia causes greater increases in sympathetic activity[104,109] and (usually) greater increases in systemic blood pressure (approximately 30 mm Hg rise in systolic pressure and approximately 25 mm Hg rise in diastolic pressure[110]) than does hypoxemia.[104] Acting via baroreflexes, this greater hypertensive response may be partly responsible for the more limited rise in heart rate during hypercapnia than during hypoxemia.[104] The tachycardic response to hypercapnia is blunted in the elderly.[80] Apnea increases the sympathetic nerve activity elicited by hypercapnia.[104] This increase, however, is less than the increase during hypoxemia.[104]

Combined hypoxia and hypercapnia have a synergistic effect on sympathetic nerve activity[104] and hyperpnea. This potentiation may arise because hypercapnia sensitizes the response of peripheral chemoreceptor afferents to hypoxia.[104] Another possibility is that both peripheral and central chemoreceptors synapse on common nuclei in the brainstem.[104]

Hypercapnia not only has a sympathetic vasoconstrictor effect (secondary to chemoreceptor activation) but also has a direct vasodilator effect on systemic arterioles[23,72]; dilation of conjunctival and superficial facial vessels may be noted. The first action, however, is predominant in conscious persons, and blood pressure and heart rate increase. If the vasomotor center cannot respond (e.g., secondary to brain damage, severe ischemia or hypoxia, or deep anesthesia) or is disconnected from peripheral parts of the sympathetic nervous system (e.g., secondary to spinal cord damage or blocking drug or spinal anesthesia), direct vasodilation becomes the sole or dominant effect, and blood pressure falls.[23,72,111]

Hypercapnia causes cerebral hyperperfusion (Fig. 4-16).[112] The increase in blood flow is proportional to the severity of hypercapnia.[112] Cerebrovascular reactivity to CO_2 depends on age (i.e., there is reduced cerebral perfusion reserve in the elderly)[113] and state (i.e., there is a 70% reduction in cerebrovascular reactivity to CO_2 during non–rapid eye movement sleep).[114] Hypercapnic cerebrovascular reactivity also is reduced in patients with preexisting cerebrovascular diseases.[115]

Neurologic Responses. Hypercapnia decreases cerebral metabolic rate for glucose and interferes with cerebral energy

production.[116] The cerebral metabolic rate for oxygen is maintained, or slightly increased, provided that Pa_{CO_2} is less than 90 to 100 mm Hg.[116] For higher values of Pa_{CO_2}, cerebral metabolic rate for oxygen decreases.[116] Hypercapnia has a dual effect on neuron excitability: stimulatory at low concentrations and inhibitory at high concentrations.[72] In humans, very high concentrations (30%) can produce surgical anesthesia, which can be associated with seizures.[72,102,107]

CLINICAL PRESENTATION OF HYPERCAPNIA

The clinical manifestations of hypercapnia result from a complex interaction of several factors, including severity of hypercapnia, comorbidities, and the speed at which the increase in CO_2 has occurred. For example, patients receiving chronic oxygen therapy have been reported to function satisfactorily with Pa_{CO_2} values of greater than 100 mm Hg.[72] Therefore, there is no single threshold of Pa_{CO_2} above which mechanical ventilation is mandatory.

Most signs and symptoms of acute hypercapnic respiratory failure, including hyperpnea, dyspnea, tachycardia and hypertension, and diaphoresis, are similar to those of hypoxemia. Some consider it a waste of effort to try to separate which manifestations are related to hypoxemia and which to hypercapnia.[117]

The major clinical features of hypercapnia are those affecting the CNS. One difference between acute hypoxemic and acute hypercapnic respiratory failure is the greater incidence of neurologic manifestations with the latter. Acute hypercapnia can cause fine tremors (of the outstretched hands, head, or legs), asterixis, myoclonic jerks, sustained myoclonus, and seizures.[24,107] It also can cause cognitive disorders, hostility, irritability, paranoid behavior, somnolence, stupor, and coma.[24] In a study of thirty-two episodes of acute respiratory failure, Kilburn[24] reported that the severity of cognitive disorders, asterixis, and somnolence, and the presence of stupor and coma were closely related to the severity of respiratory acidosis—and not to the severity of hypoxemia.

Some patients with severe hypercapnia have papilledema and elevated cerebrospinal fluid pressure probably because of the increase in blood volume within the near-rigid cranial cavity.[72,118] Under conditions of prolonged hypercapnia (several hours), cortical blood flow may return toward baseline over time.[119] The latter is probably mediated by a buildup of brain extracellular bicarbonate and an increase in pH.[119]

Some patients with combined hypoxemic and hypercapnic respiratory failure become more comatose when treated with oxygen (CO_2 narcosis). The mechanisms responsible for oxygen-induced hypercapnia are complex and probably include reduction in ventilation, increased wasted ventilation (alveolar dead space),[120] and the Haldane effect (Pa_{CO_2} increases because of net release of CO_2 from erythrocytes when Sa_{O_2} is increased)[1] (see Fig. 4-11).

Postoperative Respiratory Failure

Postoperative respiratory failure can be defined as the need for intubation and mechanical ventilation in the 48 hours after surgery.[121] Among more than 180,000 patients who underwent major noncardiac surgery, postoperative respiratory failure occurred in 3%.[121] This exceeds the incidence of cardiac arrest or acute myocardial infarction after noncardiac surgery (1.3%).[122] Among 1055 patients, most of whom underwent lower abdominal/inguinal hernia repair or orthopedic limb surgery, 0.1% required intubation within 7 days of surgery.[123]

Pulmonary complications are estimated to account for nearly 25% of deaths within 6 days of surgery.[124] This figure may be an underestimate; many patients with respiratory failure can be kept alive by ventilator support, only to die from nonrespiratory complications (e.g., sepsis and multiorgan failure).[125] Among patients who undergo major noncardiac surgery, mortality is 27% to 42% for those with postoperative respiratory failure versus 1% to 6% for those without postoperative respiratory failure.[121,126,127] Respiratory failure is the most important determinant of postoperative mortality in 40% to 100% of thoracic surgery patients.[125,128,129]

A common cause of postoperative respiratory failure is the development of atelectasis (Fig. 4-17). Atelectasis is the most frequent pulmonary complication after general surgery (particularly thoracic and upper abdominal surgery) (Table 4-4).[125,128,129] Atelectasis occurs in approximately 90% of patients during anesthesia.[130] During uneventful anesthesia, before any surgery is begun, 15% to 20% of the lung base is collapsed.[131] With thoracic surgery and cardiopulmonary bypass, more than 50% of the lung can be collapsed several hours after surgery.[132] After abdominal surgery, atelectasis can persist for several days,[133] and application of lung recruitment maneuvers and PEEP at the conclusion of the procedure do not improve postoperative oxygenation.[134]

One mechanism for the development of atelectasis during general anesthesia is decreased respiratory muscle tone, which is accompanied by cephalad displacement of the diaphragm, 20% reduction in functional residual capacity (60% reduction in obesity), and compression of lung tissue.[125,135] Two other purported mechanisms are impaired function of surfactant and resorption of gas behind occluded airways (particularly with high FI_{O_2}).[131]

Persistent or new atelectasis after anesthesia can be caused by several mechanisms. First, patients undergoing abdominal or thoracic surgery experience a marked reduction in vital capacity and a smaller but clinically important decrease in functional residual capacity.[135] These changes are ascribed to postoperative pain and diaphragmatic dysfunction.[135,136] Abnormal abdominal mechanics reduce end-expiratory lung volume below (the increased) closing volume, leading to absorption of gas from poorly ventilated lung units.[137] Second, the weakened diaphragm no longer acts as a rigid wall between the thoracic and abdominal space.[136] The positive abdominal pressure transmitted to the thoracic cavity

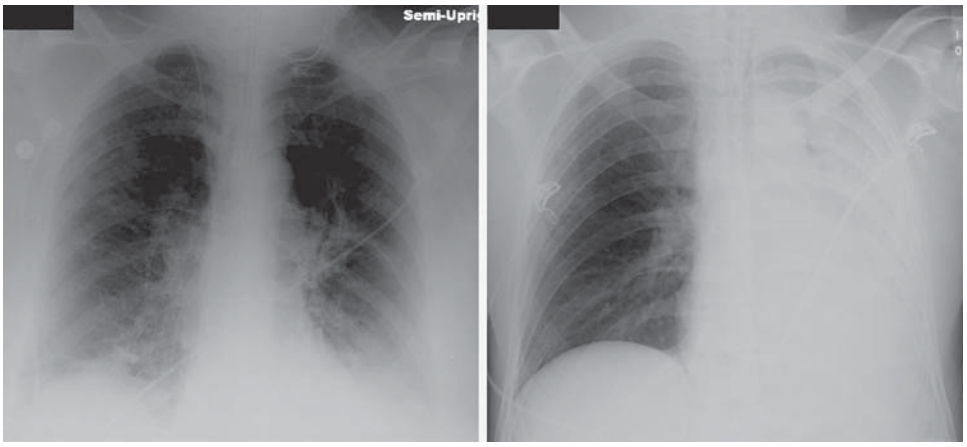

FIGURE 4-17 Postoperative atelectasis. *Left:* Portable anteroposterior chest radiograph showing bibasilar subsegmental atelectasis following hemicolectomy. *Right:* Atelectasis of the entire right lung caused by mucus plugging following drainage of submandibular and pterygomandibular space abscesses.

increases pleural pressure and causes compression atelectasis—particularly in the dependent thorax.[131,138] Third, mucociliary clearance is impaired.[139,140] Fourth, narcotics[141] and pain[142] suppress periodic deep breaths. Lack of intermittent deep breaths favors alveolar collapse by precluding alveolar recruitment and decreasing active forms of alveolar surfactant.[143] Fifth, narcotics[141] and pain[142] also suppress cough and interfere with the ability to clear secretions.[144] In a prospective study of 361 patients undergoing elective lung surgery (including pneumonectomy, lobectomy, wedge and segmental resection, and bullectomy), Bonde et al[144] reported that complications related to retention of secretions (i.e., atelectasis, pneumonia, and respiratory failure) occurred in 30% of patients.[144] On multivariate analysis, being a current smoker, having ischemic heart disease, and the absence of regional analgesia or failure of regional analgesia (thoracic epidural or extrapleural intercostal nerve infusion block) increased the risk of secretion retention.[144] Of twelve in-hospital deaths, ten were considered complications of secretion retention. Sixth, risk of atelectasis is increased with routine use of nasogastric tubes.[123,145,146] Seventh, preexisting pulmonary disease[147] and current smoking[148]—associated with increased postoperative secretions[144]—increase the risk of atelectasis. The end result of atelectasis can be hypoxemic respiratory failure, hypercapnic respiratory failure, or both, and pneumonia and sepsis (Fig. 4-18).[137,149] Development of mucous plugging with lobar or multilobar collapse of the lung is a less-common cause of atelectasis than the development of subsegmental atelectasis (see Fig. 4-17).

Preoperative assessment is useful in identifying patients at increased risk after thoracic and nonthoracic surgery.[123,126,150] In a prospective study of 272 patients undergoing nonthoracic surgery, McAlister et al[150] identified three independent risk factors for postoperative complications: age 65 years or older, smoking of 40 pack-years or more, and maximum laryngeal height of 4 cm or less.

In a subsequent study of 1055 patients undergoing nonthoracic surgery, these investigators reported four independent risk factors for postoperative complications: age 65 years or older, positive cough test (recurrent coughing after asking a patient to cough once), perioperative nasogastric tube, and duration of anesthesia of 2.5 hours or longer.[123] In a prospective study of more than 180,000 patients undergoing major noncardiac surgery, Arozullah et al[126] reported that type of surgery, albumin and blood urea nitrogen levels, functional status, COPD, and age could be used to generate an index to identify patients at risk for postoperative respiratory failure. These results were prospectively validated by the same investigators in a second study comprising more than 180,000 patients undergoing major noncardiac surgery.[121] Solid data on the usefulness of respiratory physiotherapy, including incentive spirometry, inspiratory muscle training, and noninvasive ventilation to *prevent* pulmonary complications, after cardiac or upper abdominal surgery are lacking.[151]

TABLE 4-4: CAUSES OF POSTOPERATIVE RESPIRATORY FAILURE

Intrapulmonary causes
Atelectasis
Aspiration
Pneumonia
Acute respiratory distress syndrome/acute lung injury
Volume overload/congestive heart failure
Pulmonary embolism (thrombus, air, fat)
Bronchoconstriction (asthma/COPD)
Pneumothorax
Extrapulmonary causes
Shock
Sepsis
Decreased respiratory motor output
Phrenic nerve injury
Diaphragmatic dysfunction
Upper airway obstruction
Obstructive sleep apnea

Abbreviation: COPD, chronic obstructive pulmonary disease.

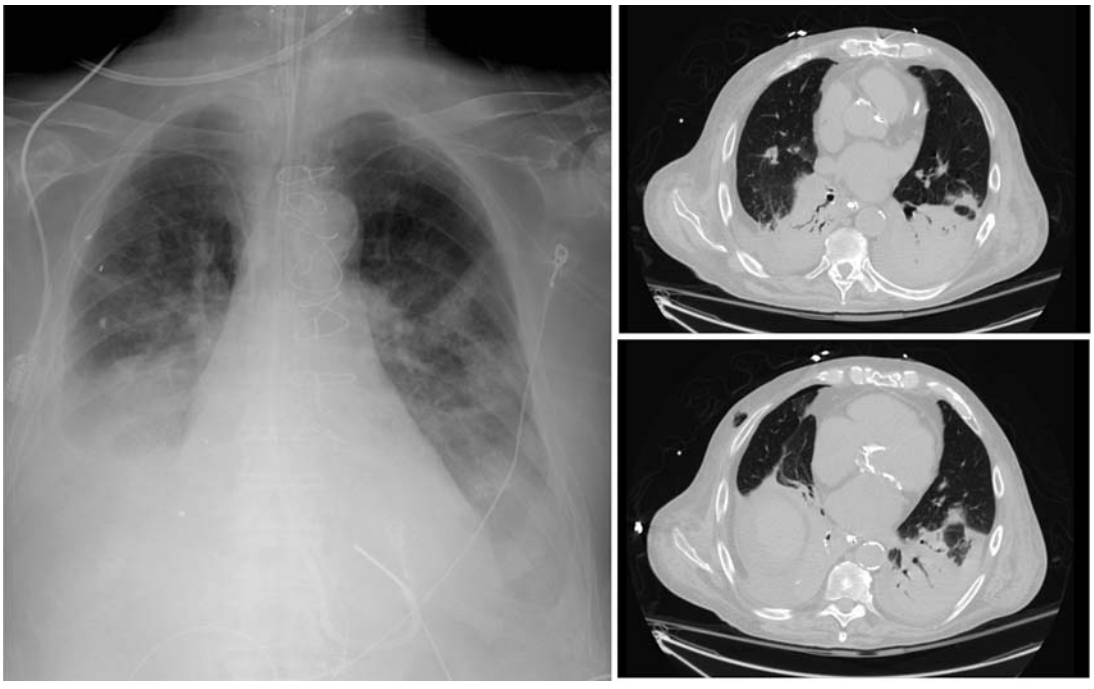

FIGURE 4-18 *Intrapulmonary* and *extrapulmonary* causes of postoperative respiratory failure. Eighty-year-old man with COPD and aortic valve replacement underwent small bowel resection and repair of traumatic diaphragmatic hernia. Six days after surgery he developed respiratory distress caused by atelectasis, atrial fibrillation, volume overload, and aspiration. Following intubation, chest radiograph *(left)* demonstrated discoid atelectasis in the left upper lung zone, pleural effusions, and pulmonary infiltrates. Computed tomography *(right)* revealed air space opacities suggestive of pneumonia and lower-lobe atelectasis.

Patients undergoing cardiac surgery are especially prone to postoperative complications because they are subjected to prolonged anesthesia and, commonly, hypothermia.[152,153] Patients also often require therapy for hypotension or hypertension, as well as fluid resuscitation (including blood transfusions).[152,153] Cardiac surgery can temporarily increase respiratory load.[154–156] At the end of coronary bypass surgery, lung compliance is less and lung resistance greater after chest closure than before surgery.[154] An increase in lung water after cardiopulmonary bypass, especially if the lungs remain collapsed during surgery, contributes to the worsening mechanics. In eight patients undergoing valvular surgery, compliances of the chest wall and lung were less at 4 hours after surgery than before surgery (Fig. 4-19).[155] By 7 hours, chest wall compliance was back to baseline, and lung compliance was higher than before surgery.[155] The investigators speculated that the initial decrease in lung compliance is caused by interstitial fluid secondary to increased vascular permeability.[155] The subsequent increase in lung compliance may result from mobilization of fluid that had accumulated before surgery (as a consequence of valvular disease) and as a result of extracorporeal circulation (increased permeability). Severe restrictive pulmonary defect is the rule,[157,158] and venous admixture (or sum of true shunt and $\dot{V}_A/\dot{Q}$ mismatch) is increased.[158] At the end of surgery, many patients are transferred to the ICU while fully ventilated. Patients then are given the time to rewarm, to metabolize the medications received during anesthesia, and to receive therapy for any hemodynamic derangements that are present.

From the 1960s to 1990s, prolonged controlled mechanical ventilation was the standard of care following cardiac surgery.[159–161] This strategy was justified by the use of high-dose

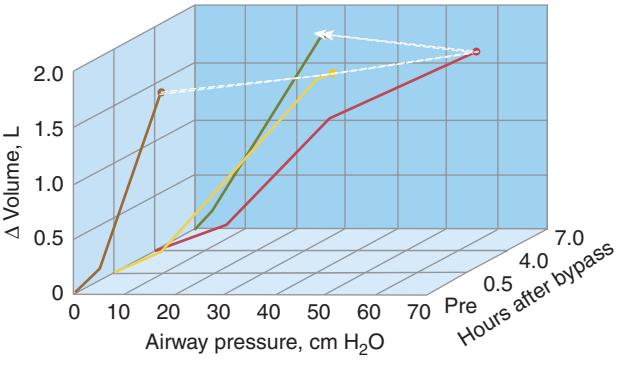

FIGURE 4-19 Cardiopulmonary bypass causes a reversible impairment in respiratory mechanics. Static inflation volume-pressure (V-P) curve of the respiratory system in a patient before cardiopulmonary bypass (*Pre*) and 0.5, 4.0, and 7.0 hours later. Compared with before bypass (*orange curve*), the slope of the V-P curve is less steep 0.5 hours later (*yellow curve*), and less steep again at 4 hours (*red curve*). At 7 hours, the slope of the V-P curve has returned to baseline (*green curve*). An increase in lung water after bypass contributed to the temporary worsening of compliance. *Δ Volume*, changes in lung volume relative to the elastic equilibrium volume of the respiratory system. (Data from Ranieri et al.[155])

narcotic anesthesia and concerns about myocardial ischemia in the early postoperative period.[161–163] Since the early 1990s, under pressure of cost containment and improved resource utilization,[164] early extubation strategies have been implemented successfully in uncomplicated cardiac surgery cases.[152,153,165] Early extubation is achieved by modifying intraoperative anesthetic techniques (e.g., usually a decrease in total opioid administration, use of ultrashort-acting opiates, and use of inhaled techniques[153,166,167]), minimizing sedation during the postoperative ICU stay,[153] and improving postoperative pain control.[168] Recovery to spontaneous respiration and extubation is shorter with rapid tracheal extubation strategies than with conventional strategies—median time of approximately 4 and 7 hours, respectively.[152,153] Approximately 20% to 30% of patients, however, do not tolerate (or are not candidates for) rapid tracheal extubation strategies because of postoperative complications (e.g., bleeding, myocardial ischemia, myocardial infarction, refractory hypoxemia, or neurologic complications).[152,153] Early extubation may improve cardiac output[169] and renal perfusion[162,170] and reduce cardiopulmonary morbidity,[171] as well as decrease hospital stay without adverse outcome.[165,166]

In addition to early extubation (extubation achieved in less than 6 hours after surgery[165]), immediate extubation in the operating room has been reported after coronary bypass grafting with or without valve replacement,[161,167,172,173] single-lung transplantation,[174] and two-stage esophagectomy.[175] Recently, coronary bypass grafting with high thoracic epidural anesthesia in the awake and spontaneously breathing patient has been achieved successfully.[176] This latter strategy remains highly controversial.[177]

Shock

Shock can be defined as a "state in which a profound and widespread reduction of effective tissue perfusion leads to reversible, and, if prolonged, irreversible cellular injury."[178] Based on hemodynamic profile, shock is classified into four categories: cardiogenic, hypovolemic, extracardiac obstructive, and distributive.[178]

PHYSIOLOGIC EFFECTS OF SHOCK

All forms of shock exhibit common cellular metabolic processes that typically lead to cell injury, organ failure, and eventually, death.[178,179] These processes are caused by multiple interrelated factors, including cellular ischemia, circulating or local inflammatory mediators, and free radical injury.[178,179]

Shock elicits at least three respiratory responses: increase in dead space ventilation, respiratory muscle dysfunction, and pulmonary inflammation. The increase in dead space ventilation is an early accompaniment of shock.[180–182] It results from a fall in pulmonary perfusion.[178] (The terminology of dead space is confusing. *Anatomic dead space* is made up of the conducting airways (nose, mouth, pharynx, larynx, trachea, bronchi, and bronchioles). *Alveolar dead space* is made up of alveoli that receive some or no blood flow, which does not match ventilation (units with very high $\dot{V}_A/\dot{Q}$ ratio). *Physiologic dead space* is the sum of anatomic dead space and alveolar dead space.) $\dot{V}_E$ increases to achieve normocapnia.[182,183] $\dot{V}_E$ also may further increase through other mechanisms. First, baroreflex deactivation (secondary to hypotension) amplifies the ventilatory response to stimulation of the peripheral chemoreceptors.[184] Second, direct stimulation of the aortic chemoreceptors occurs as a result of decreased oxygen delivery.[185] (This point, although clearly demonstrated in the cat,[185] remains controversial in humans.[75]) Third, cerebral hypoperfusion causes intracellular hypercapnia and acidosis[72] and, in turn, induces further hyperventilation unless the neurons are depressed (e.g., by hypoxia, lack of substrates, or excessive accumulation of metabolic products).[72] Fourth, increased respiratory drive occurs as a result of peripheral stimulation of pulmonary J receptors.[178] Fifth, increased respiratory drive results from vestibular activation during orthostasis (vestibulorespiratory reflex).[186] Sixth, $\dot{V}_E$ increases to compensate for lactic acidosis,[187] which results in part from the overworked and underperfused respiratory muscles.[182,188,189] The increase in $\dot{V}_E$ accompanying these responses may enhance venous return (through the respiratory pump) and vasoconstriction (through reduced Pa_{CO_2}), helping the cardiovascular system to cope with hypovolemia.[190]

Respiratory muscle dysfunction is one result of the associated cellular dysfunction and injury.[136,191] Many mechanisms contribute to this dysfunction in septic shock, including failure of neuromuscular transmission (because of elevated of muscle membrane potential and failure of excitation–contraction coupling), the cytotoxic effect of nitric oxide and its metabolites, free radicals, ubiquitin-proteasome proteolysis, and, possibly, a decrease in nicotinic acetylcholine receptors.[136,192] Local dysregulation of the circulation and of the Krebs cycle also may contribute.[136] Many pathways purported to be responsible for respiratory muscle dysfunction in sepsis are also activated in cardiogenic and hemorrhagic shock.[193–198]

Laboratory animals with cardiogenic[199] and septic shock[192,200] die of respiratory failure. Death is not caused by pulmonary disease per se but by an inability of the respiratory muscles to maintain adequate ventilation. In dogs with cardiogenic shock, institution of mechanical ventilation decreases the metabolic needs and thus the blood flow to the respiratory muscles (from 21% to 3% of the total cardiac output).[201] A nonrandomized study by Kontoyannis et al[202] in twenty-eight patients with cardiogenic shock provides support for the view that hemodynamic instability is an indication for mechanical ventilation. Compared with nonventilated patients, ventilated patients were weaned from an intraaortic balloon pump more often, and their survival was greater.[202]

The failure to reverse shock and treat the underlying cause promptly predisposes to ARDS (see Chapter 29). Pulmonary vascular resistance increases during shock, including septic shock (in which peripheral vascular resistance is usually decreased).[203]

Hypovolemic, distributive, and extracardiac obstructive shock result in decreased diastolic filling. Low-pressure stretch receptors located in right atrium and pulmonary artery consequently signal the medullary vasomotor centers, triggering sympathetic discharge.[178,204] High-pressure baroreceptors in the aortic arch contribute (negative feedback to the tonic discharge of the medullary vasoconstrictor centers) to the vasomotor response of shock as long as the mean arterial pressure is no lower than 80 to 90 mm Hg.[205] When mean pressure is less than 80 to 90 mm Hg, the aortic baroreceptor response is eliminated (baroreceptor deactivation).[178,205] Likewise, the carotid baroreceptors contribute (negative feedback) to the vasomotor response as long as the mean pressure is no lower than 60 mm Hg.[205] When mean pressure is less than 60 mm Hg, the carotid baroreceptor response is eliminated.[205] When mean pressure is less than 50 to 60 mm Hg, the peripheral chemoreceptors (sensitive to Pa_{O_2}, Pa_{CO_2}, and pH) dominate.[178] The most powerful stimulus to sympathetic tone during severe shock, however, is the ischemic response of the CNS.[205] When mean pressure falls below 50 to 60 mm Hg, the medullary chemoreceptors become active.[205] Maximal sympathetic stimulation is induced by these receptors when mean pressure is 15 to 20 mm Hg, resulting in maximal cardiovascular stimulation.[205] The Cushing response to increased intracranial pressure is an example of this reflex operating in a different setting.[178] Increased sympathetic outflow from the CNS is aimed at supporting oxygen delivery to vital organs. Other compensatory responses include releases of adrenocorticotropic hormone, antidiuretic hormone, and aldosterone, which contribute to sodium retention and maintenance of cardiovascular catecholamine responsiveness.[178,179,206]

CLINICAL PRESENTATION OF SHOCK

Patients in shock or in the process of developing it may report dyspnea. Patients are usually tachypneic and tachycardic; they have primary respiratory alkalosis or a metabolic acidosis with some degree of respiratory compensation. Tachypnea, combined with low tidal volume, worsens dead space ventilation. The skin of patients in septic shock is initially warm and dry. It is typically cold and clammy when cardiac output is low. Livedo reticularis is sometimes seen in patients who have profound hypotension, necessitating the use of high-dose pressors (Fig. 4-20). Shock is usually not an all-or-none phenomenon that occurs abruptly after injury or infection. Instead, homeostatic compensatory mechanisms are engaged.[178,179] Early in the course, subtle signs of

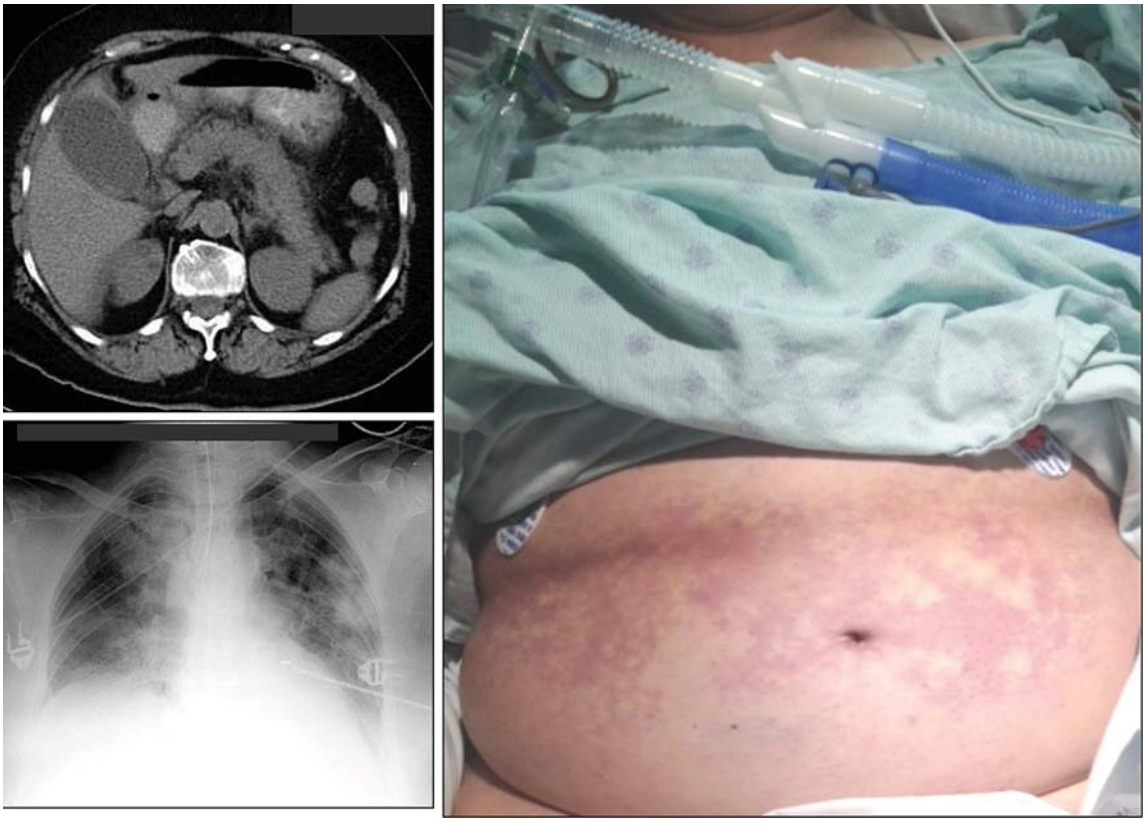

FIGURE 4-20 Livedo reticularis in shock. A 69-year-old woman developed severe gallstone pancreatitis *(left upper panel)* complicated by acute respiratory distress syndrome (ARDS) *(left lower panel)* and shock resistant to high-dose vasopressors. *Right:* A few hours after institution of mechanical ventilation the patient developed diffuse livedo reticularis of the skin, which is characterized by pale, ischemic, hypoperfused areas interspersed with erythematous areas of increased perfusion.

hemodynamic stress include tachycardia and decreased urine output. During early shock, assessment based on vital signs, central venous pressure, and urinary output may fail to detect global tissue hypoxia.[207] If the precipitating insult is too great or progresses quickly, compensatory mechanisms fail, and overt shock follows.[178]

Compensatory mechanisms tend to protect the CNS from the ill effects of decreased cerebral perfusion. In the absence of cerebrovascular compromise, ischemic injury is unusual if mean arterial pressure is 50 to 60 mm Hg or higher.[178] Before ischemic injury, consciousness may become altered, depending on perfusion deficit. Contributory factors include electrolyte disturbances, hypoxemia, and hypercapnia.[178] Sepsis-related encephalopathy can occur at higher arterial pressures (secondary to inflammatory mediators); it is associated with increased mortality.[208] Altered consciousness by itself may be an indication for intubation.

Intubation versus Mechanical Ventilation

In some instances, patients require endotracheal intubation to maintain airway patency because of upper airway obstruction, an inability to protect the airway from aspiration, or to manage secretions. Not all intubated patients necessarily require ventilator support.

UPPER AIRWAY OBSTRUCTION

Upper airway obstruction is one of the most urgent and potentially lethal medical emergencies. Complete airway obstruction lasting for as little as 4 to 6 minutes can cause irreversible brain damage.[209] The upper airway, which encompasses the passage between the nares and carina,[210] can be obstructed for functional or anatomic reasons. Among the first are vocal cord paralysis and laryngospasm.[210–213] Among the second are trauma, burn, infections, foreign bodies, and tumors.[209,210] Functional and anatomic obstruction can occur postoperatively in patients with redundant pharyngeal soft tissue (sleep apnea) and loss of muscle tone related to postanesthetic state.[210–212]

The first warning of airway obstruction in an unconscious patient may be failure of a jaw-thrust maneuver to open the airway or an inability to ventilate with a bag valve.[209] In a conscious patient, respiratory distress, stridor, altered voice (aphonia or dysphonia), snoring, dysphagia, odynophagia, prominence of neck veins, and neck and facial swelling all may indicate impending airway obstruction.[209,210] Patients may bring their hands to their neck, a sign of choking.[210] Other signs include suprasternal and intercostal indrawing and reduced or absent air movement on auscultation. Wheezing may be present (or absent). Thoracoabdominal paradox may be prominent. Sympathetic discharge is high. Patients are diaphoretic, tachycardic, and hypertensive. As asphyxia progresses, bradycardia, hypotension, and death ensue.[210]

Upper airway obstruction can be complicated by pulmonary edema (Fig. 4-21)[210,211]—incidence of 11% in one adult series[214]—or pulmonary hemorrhage.[212] Increased venous return (more negative intrathoracic pressure and catecholamine-induced venoconstriction) contributes to pulmonary edema, but it cannot be the sole mechanism;[215] as intrathoracic pressure becomes more negative, venous return to the right ventricle becomes flow-limited.[216] Other factors contributing to pulmonary edema include decreased left-ventricular preload (leftward shift of interventricular septum), increased left-ventricular afterload (increased negative intrathoracic pressure and catecholamine-induced elevation of systemic vascular resistance), pulmonary vasoconstriction (hypoxemia and acidosis), and possibly, stress failure of the alveolar-capillary membrane.[212,217]

Whether pulmonary edema develops during (or after) relief of upper airway obstruction may depend on whether the obstruction is fixed or variable.[211] Fixed upper airway obstruction results in vigorous inspiratory efforts (Mueller maneuver) followed by vigorous expiratory efforts (Valsalva

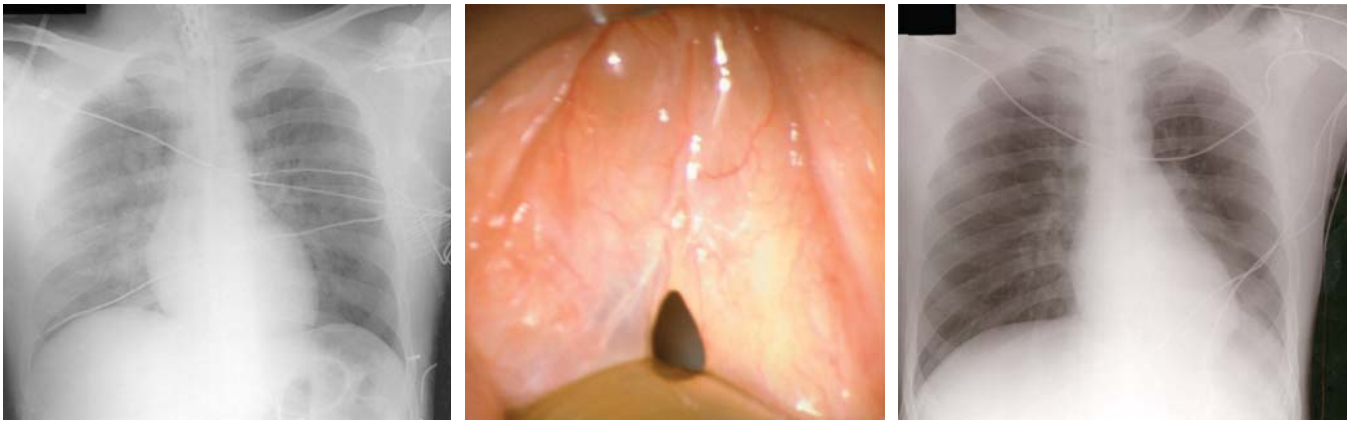

FIGURE 4-21 Pulmonary edema caused by upper airway obstruction. *Left:* Portable anteroposterior chest radiograph of a 35-year-old man who developed pulmonary edema secondary to laryngeal edema. *Middle:* Laryngeal edema demonstrated by direct laryngoscopy. *Right:* Radiograph following resolution of pulmonary edema. (Central panel used, with permission, from Wittekamp et al.[213])

maneuver).[211,214] Exhalation against an obstructed airway raises intrathoracic and alveolar pressures. The positive expiratory pressure decreases pulmonary vascular filling and opposes the hydrostatic forces that favor transudation of fluid into the alveoli during inhalation.[214] With a sudden relief of obstruction, positive expiratory pressure is lost; consequently, there is a massive transudation of fluid from the pulmonary interstitium into the alveoli (pulmonary edema) over minutes to hours. In contrast to fixed obstruction, variable extrathoracic upper airway obstruction hinders inhalation. Exhalation usually is unaffected. In this situation, the hydrostatic forces, which favor transudation of fluid into the alveoli during inhalation, are unopposed, leading to edema before relief of the obstruction.[211]

Upper airway obstruction may worsen suddenly because resistance varies with the fourth power of the radius. A slight change in airway anatomy may increase resistive load dramatically.[210] For example, manipulation of the upper airway by an inexperienced clinician may induce edema, which can increase airway resistance markedly and induce asphyxia.

An initial assessment is undertaken to determine severity of airway compromise. If compromise is judged severe, the airway should be secured immediately. If ventilation is adequate, more detailed assessment is wise.[209] Arterial blood gases are not particularly helpful because they are not specific to airway patency.[209] They may show little change until a patient is in extremis.[209]

Steps to relieve airway obstruction include use of pharyngeal airways, endotracheal intubation, cricothyrotomy, tracheotomy, endoscopy, intubation over a fiber-optic bronchoscope, and medications (e.g., epinephrine, norepinephrine, antihistamines, steroids, and antibiotics).[218] In general, pharmacotherapy cannot reverse mechanical obstruction. Use of helium-oxygen mixtures should not engender a false sense of security.[218]

The nature of respiratory noises helps to localize lesions.[209] Stridor is an inspiratory sound typically caused by a lesion above the thoracic inlet (usually glottic or supraglottic). Wheezing is generated below this level.[209] Snoring, a feature of obstructive sleep apnea, can be life-threatening. A patient with an obstructed airway should not be sedated until the airway has been secured; minimal sedation may precipitate acute respiratory failure.

Cricothyrotomy and tracheotomy can be performed at the bedside or in the operating room. If time permits and the patient is conscious and moving sufficient air to speak, it may be best to transport the patient to the operating room.[218] Although percutaneous tracheotomy is gaining in popularity, it is best performed in an already intubated patient and not as an emergency procedure.[218]

INABILITY TO PROTECT THE AIRWAY FROM ASPIRATION

Patients with severe bulbar weakness or decreased consciousness may be unable to protect the airway against aspiration.[219,220] The lack of a gag reflex or cough on suctioning suggests impaired protective reflexes.[221] If the cervical spine is stable, the head should be flexed while checking for airway obstruction. Inability to maintain a patent airway is an indication for elective intubation.[221]

Patients who require an oral airway or special appliances may require prophylactic intubation; such patients are unstable and can asphyxiate or vomit and aspirate suddenly.[221] Ideally, patients with depressed consciousness should be assessed while asleep, a time during which they are at greatest risk of obstruction.[221]

Severe head injury is a condition requiring intubation for airway protection. In the past, controlled hyperventilation (Pa_{CO_2} of 25 to 35 mm Hg) was delivered in these patients with the goal of reducing intracranial pressure. Such a strategy, however, has proven harmful and is no longer recommended.[222] It is unknown whether the use of short periods of hyperventilation to suddenly lower intracranial pressure are harmful or not.

SECRETIONS

Occasionally, endotracheal intubation or tracheostomy may be required to manage a large amount of secretions or to remove secretions in severely debilitated patients who themselves cannot clear them.[59,144]

Many patients with the preceding conditions are capable of maintaining adequate gas exchange following endotracheal intubation. Yet most intensivists still connect such patients to a ventilator. This decision commonly is taken independently of any consideration about the work of breathing imposed by an endotracheal tube.[223]

GOALS OF MECHANICAL VENTILATION

The fundamental goal of mechanical ventilation is to keep a patient alive and free from iatrogenic complications so that the catastrophic precipitating event(s) may resolve. Attention should be directed to the primary disorder.

Reversal of Apnea

The goal of mechanical ventilation in the apneic patient is to restore ventilation.

Reversal of Respiratory Distress

For obvious ethical reasons, no human studies have addressed the natural course of acute respiratory failure in the presence of increased work of breathing or, for that matter, with any other type of respiratory failure. Animal data indicate that increased loads can cause respiratory muscle damage, CO_2 retention, and as a terminal event respiratory muscle fatigue.[136] Increased load may be responsible for

respiratory muscle damage in patients with COPD[224] and in patients dying while supported by mechanical ventilation.[225] In sepsis, increased respiratory efforts are particularly damaging to the respiratory muscles.[226]

Despite intense research, the role of contractile fatigue in the development of respiratory failure in patients is unknown.[136] Diaphragmatic contractility has been quantified objectively (phrenic nerve stimulation) in only one study where patients developed acute respiratory distress (during weaning from mechanical ventilation).[5] No change in diaphragmatic contractility was documented.[5] It is not known if the latter observation applies to patients in respiratory distress who have yet to undergo mechanical ventilation.

It seems self-evident that connecting a patient to a ventilator and providing ventilator assistance should unload the respiratory muscles and, possibly, reduce muscle stress. To date, however, we do not know the desirable level of unloading (and for how long) for a specific patient. Insufficient unloading can be dangerous to the respiratory muscles, as can excessive unloading (see Chapter 43).[227]

Although most patients in acute respiratory failure have increased work of breathing, this may not be the sole problem. Most patients also have abnormal gas exchange, impaired muscle perfusion, and sepsis-induced muscle dysfunction.[6,228,229] In patients with increased work of breathing, unloading by the ventilator may appreciably reduce $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$.[8,54] These reductions, in turn, may improve concurrent hypoxemia and hypercapnia.

Reversal of Severe Hypoxemia

Mechanical ventilation is commonly commenced with 100% oxygen. The response helps to define the underlying pathophysiology and thus aids in differential diagnosis and therapy (see Figs. 4-9 and 4-12). For example, if 100% oxygen fails to increase Pa_{O_2} in a patient with an exacerbation of COPD, the underlying problem is not pure $\dot{V}_A/\dot{Q}$ mismatch (as is typical with acute bronchitis); instead, the patient has coexisting shunt. Common causes of shunt include pneumonia, congestive heart failure, atelectasis, and pulmonary embolism. (For a discussion of oxygen toxicity, see Chapter 45.)

Patients with increased shunt commonly exhibit considerable improvement in oxygenation with application of PEEP. The improvement results from a decrease in shunt[230] secondary to recruitment of previously atelectatic areas and redistribution of extravascular lung water from alveoli to peribronchial and perivascular spaces.[231] If cardiac output decreases (with PEEP), this can contribute to the decrease in shunt.[230,232]

PEEP causes an increase in dead space through several mechanisms. First, an increase in lung volume exerts radial traction on the airways, increasing their volume with a consequent increase in *anatomic dead space*. Second, increased airway pressure tends to divert blood flow from ventilated lung units by compressing capillaries. The consequent development of areas of high $\dot{V}_A/\dot{Q}$ ratio (or even unperfused areas) produces an increase in *alveolar dead space*. Such dead space is especially common in the uppermost lung units, where pulmonary artery pressure is relatively low because of the hydrostatic effect.[61,233] If the capillary pressure falls below airway pressure, the capillaries may collapse completely and the lung units become unperfused (Fig. 4-22).[233] Two factors encourage collapse: very high airway pressure and low venous return.

Dantzker et al[230] showed that increasing levels of PEEP can induce two distinct patterns of $\dot{V}_A/\dot{Q}$ distribution. Some patients experienced no change in the pattern of $\dot{V}_A/\dot{Q}$ relationships (Fig. 4-23). Other patients experienced broadening of the ventilation dispersion—increases of areas with

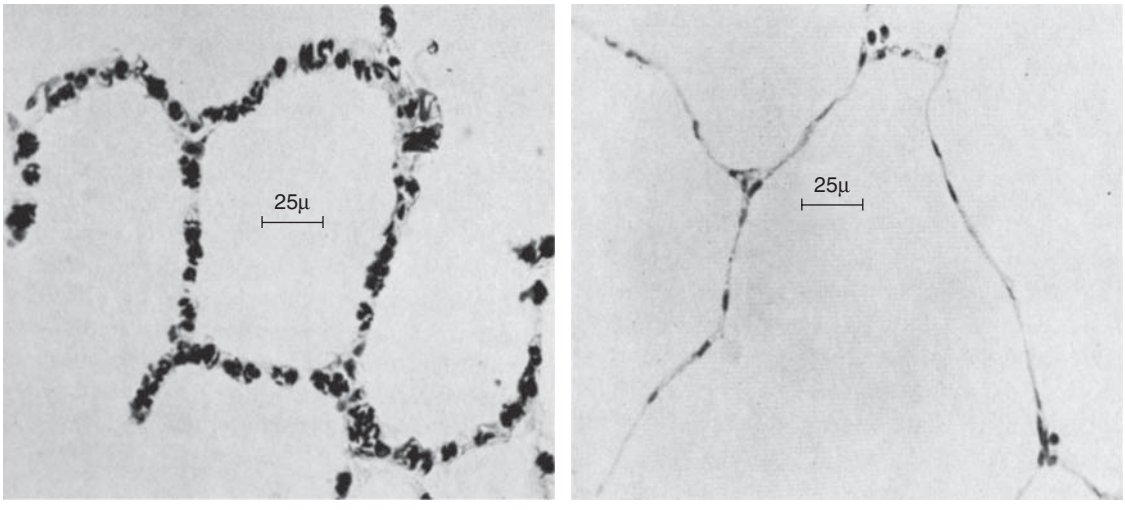

FIGURE 4-22 Effect of an elevated airway pressure on the structure of pulmonary capillaries. *Left:* Normal appearance. *Right:* An increase in alveolar pressure above capillary pressure produces capillary collapse. (Used, with permission, from Glazier et al.[233])

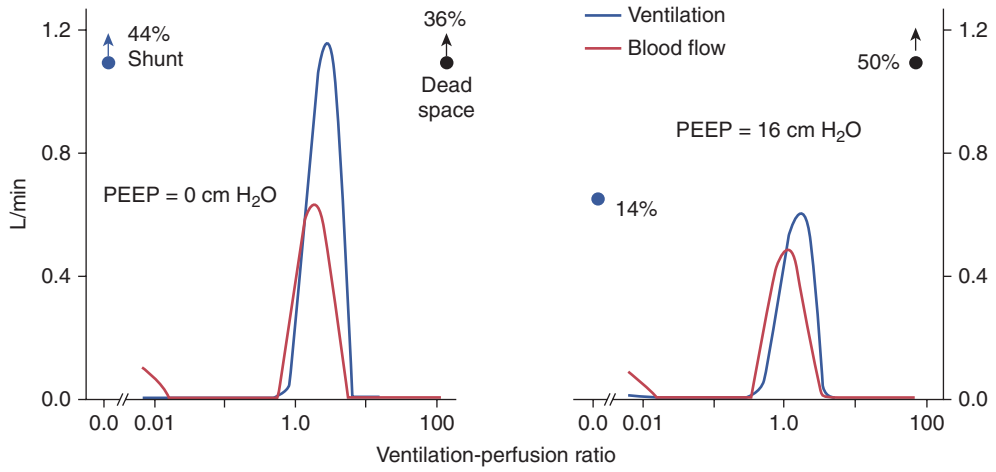

FIGURE 4-23 Effect of positive end-expiratory pressure (PEEP) on shunt and dead space in a patient with acute respiratory distress syndrome. A progressive increase in PEEP from 0 to 16 cm H_2O caused a decrease in shunt from 44% to 14% of the cardiac output and an increase in dead space from 36% to 50% of the tidal volume. The shape of the distribution of ventilation and perfusion did not change. (Modified, with permission, from Dantzker et al.[230])

high $\dot{V}_A/\dot{Q}$ ratios and alveolar dead space (Fig. 4-24). The improvement in gas exchange with PEEP is even greater when pressors are used to prevent the expected decrease in cardiac output during PEEP.[234]

In some patients, PEEP causes no improvement or even a decrease in Pa_{O_2}. This effect is the result of increased dead space ventilation, diversion of blood flow from well-ventilated to unventilated regions, and decreased cardiac output (especially if circulating blood volume is depleted).[61] Lack of improvement in oxygenation with PEEP also may result from a patent foramen ovale because PEEP can increases the right-to-left shunt.[235]

Because PEEP can decrease cardiac output,[230,236] its net effect should be judged in terms of oxygen delivery. Mixed venous P_{O_2}[207,236] has been used as a surrogate for oxygen delivery. Other potential hazards of PEEP include reduced splanchnic and renal blood flow, barotrauma, and ventilator-induced lung injury (see Chapter 10).

In addition to mechanical ventilation, patients with hypoxemic respiratory failure may require other therapies, such as antibiotics (pneumonia), diuretics, and inotropic support (heart failure). Ancillary strategies to reverse hypoxemia include exogenous surfactant, nitric oxide supplementation and prone position.[237] These strategies can increase oxygenation in patients with ARDS, but none has improved patient outcome.

Theoretically, patients with hypoxemia secondary to $\dot{V}_A/\dot{Q}$ mismatch can be managed by increasing FI_{O_2}

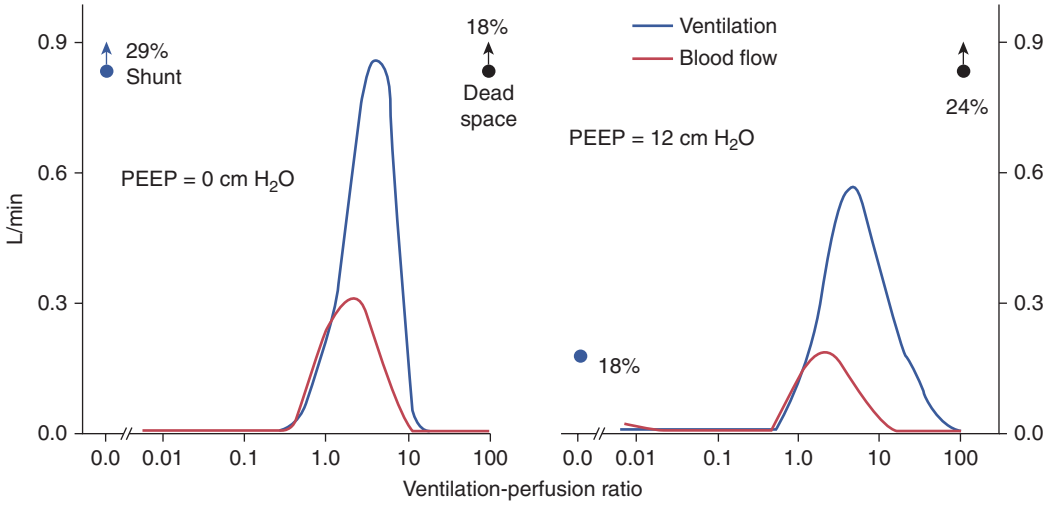

FIGURE 4-24 Effect of positive end-expiratory pressure (PEEP) on shunt and dead space in a patient with acute respiratory distress syndrome. An increase in PEEP from 0 to 12 cm H_2O produced a decrease in shunt (from 29% to 18%) and increase in dead space (from 18% to 24%). Also apparent is a widening of the dispersion in ventilation with the development of units with very high $\dot{V}_A/\dot{Q}$; these may have resulted from diversion of blood flow or increased ventilation of these areas of the lung. (Modified, with permission, from Dantzker et al.[230])

without mechanical ventilation (see Fig. 4-12). In reality, such patients always have increased ventilatory requirements (see Fig. 4-10), which may demand ventilator support. Many patients with $\dot{V}_A/\dot{Q}$ inequality requiring mechanical ventilation are hyperinflated (e.g., COPD or status asthmaticus). Hyperinflation decreases the efficiency of the respiratory muscles in generating pressure, which contributes to the respiratory distress.[136]

In a study of seven patients with exacerbations of COPD, mechanical ventilation improved $\dot{V}_A/\dot{Q}$ mismatch by redistributing blood flow away from low $\dot{V}_A/\dot{Q}$ areas.[238] Dispersion of the distribution of ventilation also improved. Dead space or ventilation of high $\dot{V}_A/\dot{Q}$ units did not change.[238] Patients with increased $\dot{V}_A/\dot{Q}$ mismatch associated with COPD or ARDS may benefit from careful application of PEEP (see Chapter 10). Use of PEEP in patients with status asthmaticus is fraught with danger (see Chapter 30).

Reversal of Severe Hypercapnia

Severe hypercapnia depresses the CNS and decreases respiratory motor output.[239] A viscous cycle can arise: Hypercapnia depresses motor output leading to more hypercapnia.[240,241] Hypercapnia can decrease diaphragmatic contractility, although not consistently.[136] Acidosis may be more important than hypercapnia in depressing respiratory muscle contractility.[136]

The goal of mechanical ventilation in patients with hypercapnic respiratory failure is to improve $\dot{V}_A$. Ventilator strategies need to be tailored to the specific setting. In hypercapnic patients with status asthmaticus or COPD, the prolonged respiratory time constant poses a significant challenge. If the ventilator is set to deliver small tidal volumes at high respiratory frequencies, the prolonged time constant may interfere with lung emptying, and hyperinflation may ensue. Moreover, small tidal volumes may not achieve adequate alveolar ventilation because physiologic dead space is increased. Larger tidal volumes may achieve adequate alveolar ventilation but require longer expiratory times than do smaller tidal volumes. A common strategy to ensure sufficient time for exhalation is to increase inspiratory flow. The increase in flow decreases the time of mechanical inflation and, if respiratory rate remains constant, prolongs time available for exhalation. An increase in inspiratory flow, however, is commonly associated with an increase in respiratory rate.[242,243] Yet, despite the reduction in the respiratory cycle, the decrease in inspiratory time is accompanied by an increase in time available for exhalation—and a decrease in inspiratory effort.[243]

Neuromuscular disorders, such as Guillain-Barré syndrome, myasthenia gravis, and spinal cord injury, can cause hypercapnic respiratory failure.[136] These patients usually have normal lung mechanics, unlike patients with COPD or asthma. The normal time constant allows for greater flexibility in the setting of the ventilator.

Overzealous ventilation can cause serious complications, including life-threatening alkalosis, decreased cerebral perfusion, and cardiovascular instability. Patients previously hypercapnic are especially vulnerable to these complications. When severe, alkalosis is occasionally associated with coronary artery spasm,[244] confusion, myoclonus, asterixis, and seizures.[245]

Respiratory alkalosis reduces ionized calcium. For each 0.1-unit rise in pH, ionized calcium falls by 0.05 mmoL/L.[246] These changes are too modest and inconsistent[247] to account for the increased central and peripheral excitability associated with alkalosis. Paresthesias, carpal-pedal spasm, and tetany, seen in acute hyperventilation, are caused by the direct effects of respiratory alkalosis on neurons.[248] Other effects of alkalosis include increase in hemoglobin affinity for oxygen and, in the presence of increased shunt, a possible worsening of $\dot{V}_A/\dot{Q}$ relationship (secondary to a decrease in hypoxic pulmonary vasoconstriction).[249] Precipitous decrease in Pa_{CO_2} reduces blood flow to the CNS,[250] which may contribute to confusion and loss of consciousness in patients with hyperventilation.[245]

The most common hemodynamic instability associated with overzealous ventilator management of the hypercapnic patient (prolonged time constant) is hypotension. Hypotension often results from an increase in intrinsic PEEP after intubation—although a decrease in sympathetic tone caused by the decrease in Pa_{CO_2} and administration of sedation may be contributory factors. In this setting, the circulation usually is restored promptly by stopping ventilation for 30 seconds (or more) and then resuming less vigorous ventilation.

In the 1940s and 1950s, it was reported that rapid CO_2 washout after hypercapnia could cause hypotension (removal of cyclopropane anesthesia in humans)[251,252] and life-threatening ventricular arrhythmias (dog experiments).[253,254] Hyperkalemia appeared to be involved.[253,254] More recent series in patients, however, have not substantiated the earlier studies.[102,255] For example, Prys-Roberts et al[102,255] reported no electrocardiographic alterations when Pa_{CO_2} was reduced from approximately 80 mm Hg to less than 20 mm Hg over 5 minutes in anesthetized patients. Some practitioners suggest that supraventricular and ventricular arrhythmias associated with alkalemia[256] may occur only in patients with ischemic heart disease.[257] Whether reductions in ionized magnesium could contribute to cardiac irritability remains unclear.[247]

Excessive ventilation, over time, causes bicarbonate wasting by the kidney. In patients who retain CO_2 when clinically stable, this renal wasting (of bicarbonate) will increase ventilatory demands during weaning.

Goals of Mechanical Ventilation in Postoperative Respiratory Failure and Trauma

Patients developing postoperative hypoxemia usually are treated with supplemental oxygen and chest physical therapy (including incentive spirometry).[258–260] In approximately

10% of patients undergoing major elective abdominal surgery, supplemental oxygen and chest physical therapy do not prevent respiratory failure.[258] Squadrone et al[258] undertook a randomized study in more than 200 patients who had undergone major elective abdominal surgery and who developed hypoxemia within 1 hour of the operation. They compared the incidence of intubation in patients receiving standard treatment (50% oxygen and chest physical therapy) and patients who also received 7.5 cm H_2O CPAP (delivered noninvasively with a helmet). Compared with the control group, patients receiving CPAP had lower rates of intubation (1% vs. 10%) and complications (e.g., pneumonia, infection, and sepsis). The CPAP group spent fewer days in the ICU. Exclusion criteria included history of COPD, asthma, sleep apnea, heart failure, hypercapnia, and respiratory acidosis. Thus, these results[258] may not apply to those patients who are at greatest risk of postoperative atelectasis.

Bonde et al[149] undertook a prospective, randomized study in 102 patients undergoing elective lung surgery who were considered at high risk for retention of secretions.[144] Minitracheotomy (4-mm percutaneous cricothyroidotomy device) was performed at the conclusion of surgery in one group. Sputum retention was 30% in a conventionally treated group and 2% in the minitracheotomy group ($p < 0.005$).[149] Atelectasis was less common in the minitracheotomy group. Incidences of pneumonia, respiratory failure, myocardial infarction, and death were not affected by minitracheotomy.[149] Significant complications of minitracheotomy have been reported, however.[261,262] Therefore, its routine use, even in patients at risk of secretion retention, needs to be considered on a case-by-case basis.

Some patients with multiple trauma present with a flail chest. Many such patients may have respiratory failure secondary to underlying lung damage or other pathophysiology and may require mechanical ventilation. Flail chest on its own, however, is not an indication for mechanical ventilation.[263] In one randomized study of patients with flail chest who were hypoxemic and in respiratory distress, noninvasive CPAP decreased mortality and nosocomial infection as compared with patients who underwent endotracheal intubation and ventilation.[264]

Goals of Mechanical Ventilation in Shock

In hemodynamically unstable patients, tissue perfusion, including that of the CNS, is compromised.[179,207] Two main goals are to establish an adequate airway and reduce $\dot{V}_{O_2}$.[178] By resting the respiratory muscles and allowing for sedation, mechanical ventilation can reduce $\dot{V}_{O_2}$[265,266] and decrease sympathetic tone.[54] These effects may improve tissue perfusion,[201,267] which may explain why ventilator support improves outcome in animals[199] and patients in shock.[202] It is important to achieve good patient–ventilator synchronization;[268,269] otherwise, work of breathing increases, which diverts blood to the respiratory muscles and away from other vulnerable tissue beds.

DELIVERY OF MECHANICAL VENTILATION: INVASIVE VERSUS NONINVASIVE MECHANICAL VENTILATION

Solid experimental data support the use of noninvasive ventilation in patients with acute respiratory failure caused by severe exacerbations of COPD (limited to patients deemed not to require immediate intubation).[270] Noninvasive ventilation is probably superior to invasive ventilation in patients with cardiogenic pulmonary edema complicated with hypercapnia[271] and in immunocompromised patients with early hypoxemic respiratory failure.[270]

Sinuff et al[272] studied the use of a practice guideline for noninvasive ventilation in patients admitted to hospital for an exacerbation of COPD or congestive heart failure. The developers of the guideline pointed out that data from randomized trials do not support use of noninvasive ventilation in other disease states. Before introduction of the guideline, 65% of patients with diseases other than COPD or cardiogenic pulmonary edema were managed without endotracheal intubation. After introduction of the guideline, 100% of these patients were intubated; mortality also tended to increase (from 20.5% to 34.3%). This study raises the possibility that introduction of a practice guideline may cause an increase in morbidity and mortality.[272,273] A practice guideline could discourage physicians from the use of noninvasive ventilation in subgroups of patients who are likely to benefit from its use simply because benefit has not yet been demonstrated in a randomized trial and thus has not been incorporated into the practice guideline. In an accompanying editorial, Hill[273] commented: "The concern is that by classifying a sizable category of patients as 'not meeting noninvasive positive pressure ventilation criteria,' the authors could have unintentionally encouraged endotracheal intubation in this subgroup, possibly contributing to morbidity and mortality."

Chapters 18 and 34 provide detailed discussion of noninvasive ventilation.

INDICATIONS FOR MECHANICAL VENTILATION AND NOSOLOGY

Indications: True versus Stated

In publications on mechanical ventilation, listed indications commonly include acute respiratory failure, exacerbation of chronic respiratory failure (secondary to infection, bronchoconstriction, heart failure), coma, and neuromuscular disease. Many patients, however, have these same conditions but do not require ventilator assistance. Consider COPD, one of the most common indications for mechanical ventilation. At any point in time, much, much less than 1% of patients with COPD are receiving mechanical ventilation. This small

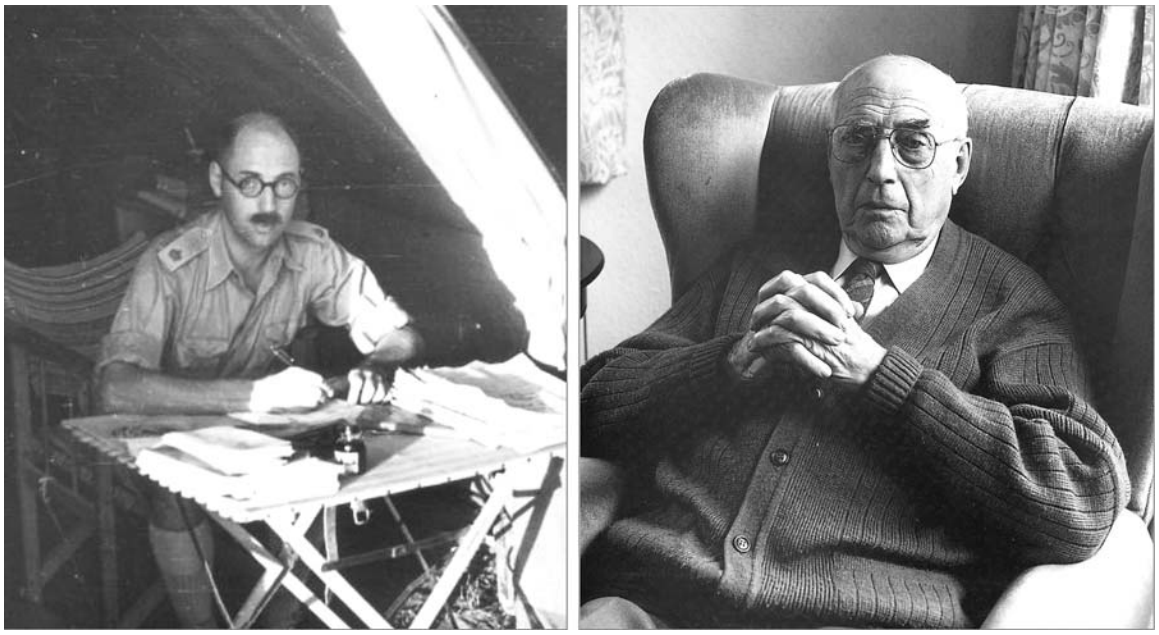

FIGURE 4-25 Guy Scadding was one of the founders of the British Thoracic Society and first editor of *Thorax*. He served in the Royal Army Medical Corps during World War II *(left)*, and is sometimes credited with changing the outcome of the war through his successful treatment of the pneumonia that Winston Churchill developed in Tunisia in December 1943.[274] Scadding wrote extensively on use of medical semantics and nosology. (Used, with permission, from Scadding[275] and Sinclair et al.[276])

subset is commonly identified as those with acute respiratory failure. But the definition of acute respiratory failure is vague and the criteria loose. The usual defining criterion is a Pa_{O_2} of less than 60 mm Hg (sometimes combined with a Pa_{CO_2} of >50 mm Hg). It is patently absurd to suggest, however, that all patients with a Pa_{O_2} of 59 mm Hg (or lower) need ventilator assistance and that all patients with a Pa_{O_2} of 61 mm Hg (or higher) can be managed without it.

As such, the usually stated indications for mechanical ventilation are elastic, lacking meaningful boundaries. What, then, is the real reason to institute it? We believe that the most honest description of a physician's judgment at this juncture is: "The patient looks like he (or she) needs to be placed on the ventilator." That is, a physician institutes mechanical ventilation based on his or her gestalt of disease severity as opposed to slotting a patient into a particular diagnostic pigeonhole.

At first blush, this admission makes the undertaking of mechanical ventilation appear less scientific than other areas of medicine. Students of medicine are taught to make a diagnosis before initiating treatment. The usual teaching is that an accurate diagnosis will make the appropriate treatment relatively obvious. But this medical model is plausible only for diseases where the precise etiology is known (such as a microbial agent). The medical model is also more ideal than real. To understand the limitations of this model—and the apparent lack of science concerning ventilator indications—the reader needs to grapple with nosology, the discipline that names and classifies diseases. Guy Scadding (1907–1999)[274–276] wrote more lucidly on nosology than most; he made explicit the factual implications of medical usage of disease names. The account in this chapter borrows extensively from his writings (Fig. 4-25).

Nosology

The first attempt to introduce a systematic and consistent nomenclature for diagnostic terms was made in the mid-nineteenth century.[277] Diseases were no longer viewed in terms of a galenic humoral disequilibrium. Instead, they were regarded as discrete entities—real things. This ontologic model grew out of the increasing use of autopsy, which was seen to uncover the true reasons for the corporeal changes induced by disease.[278] Ideally, each disease category would be identified through elicitation of pathognomonic signs on physical examination and the finding of a defining lesion on autopsy. This thinking is conveyed in the quip circulated by nineteenth-century physicians: If you were suffering from some mysterious illness, the best thing to do was go to Vienna (then the Mecca of medical science)[279] and be diagnosed by Skoda and autopsied by Rokitansky.

Disease Definition and Characteristics

How is disease defined? A *disease* is "the sum of abnormal phenomena displayed by a group of patients in association with a specified common characteristic (or set of characteristics) by which these patients differ from the norm (of healthy people) in such a way as to place them at a biological disadvantage."[280]

There are four main classes of characteristics by which diseases can be defined:

1. *Syndrome.* Historically, diseases are defined initially by way of a description of symptoms and signs; when these constitute a recognizable pattern, they are referred to as a *syndrome* (e.g., ARDS).
2. *Disorders of structure (morbid anatomy).* When a specifiable disorder is found to be associated constantly with a morbid-anatomic change, it tends to be named in these terms (e.g., the switch from jaundice to hepatitis).
3. *Disorders of function (pathophysiology).* When a disorder is found to be associated constantly with a specific abnormality of function, the abnormality may be used to name the disorder (e.g., hypothyroidism).
4. *Causation (etiology).* When the cause of a disease is discovered, the disease generally is redefined in causal terms (Legionnaire disease). Scadding[280] refers to another category, "clinical entity," that always needs an ad hoc explanation; he says, "It often seems to be the refuge of one who has not succeeded in clarifying his or her thoughts, but is nevertheless determined to put them into words."

In general, the direction of scientific advance follows the preceding sequence, although many conditions are never described in etiologic terms. The primary purpose of applying a name to a disorder is to provide a brief statement of the medical understanding of its nature (from syndrome to etiologic mechanism) and to serve as a verbal device for ease of communication. The American-European consensus definition of ARDS,[281] for example, has served as the basis of patient recruitment for most of the recent trials of mechanical ventilation in ARDS. Yet, as discussed in detail by Marini (see Chapter 31), this definition lacks scientific rigor. Nevertheless, in everyday practice, the term *ARDS* helps a clinician to predict prognosis and prescribe treatment. Moreover, in emergency settings (such as the ICU), problems are discussed and major decisions often are made without making any explicit diagnosis. Indeed, this is the rule rather than the exception when instituting mechanical ventilation. An experienced critical care physician can identify a patient who will die if left untreated but who might live if managed by mechanical ventilation—even though the physician is unable to identify the etiology of that patient's illness. Nevertheless, in such situations where physicians cannot put forward a defensible diagnosis, they still apply descriptors (at Scadding's level of "clinical entity"), such as "the patient is tiring out," to justify their judgment that mechanical ventilation is indicated.

Definitions: Essentialist and Nominalist

What are the factual implications of the naming of a disease? Diseases are defined in essentialist or nominalist terms. An *essentialist definition* tries to describe the true essence of an entity: the essential quality (invariable and fixed properties) that makes a given entity the type of thing it is—the "whatness" of an entity. (The study of the essence of things is called *ontology.*[282]) Essentialist ideas about diseases are implicit in everyday speech.[283] For example, a patient presents with a cough and mucoid sputum. The doctor makes a diagnosis of chronic bronchitis. The patient then thinks that chronic bronchitis is causing his or her cough. Given that chronic bronchitis is defined as a productive cough, the patient's reasoning is circular.

Such usage lays a linguistic trap: Many laypeople and some doctors think that the names of diseases refer to active agents that cause the illness. To talk of diseases as if they existed as real entities is plausible (at first sight) only in relation to diseases that are defined in etiologic terms.[284] Even then we must not confuse an etiologic agent with the disease itself. The disease is the effect on the affected person; diseases have no existence apart from patients. We treat patients, not diseases. When we speak of treatment of a disease, we are employing an ellipsis for treatment of patients with that disease.[280] All this brings to mind Osler's admonition: "It is much more important to know what sort of patient has the disease than to know what sort of disease the patient has."[278]

A *nominalist definition* recognizes that the task of revealing the essence of the *definiendum* is impossible.[285,286] Instead, it simply uses words to state the set of characteristics that are used to identify a member of a class (make a diagnosis). Such a definition makes it possible to determine whether a particular example (clinical picture) falls into a category to which a name (a disease) is applied.[287] A nominalist definition avoids the essentialist fallacy of regarding diseases as causes of illness; instead, it is simply naming a class of entities or events.

The nominalist–essentialist distinction becomes clearer if we consider the definition of acute respiratory failure. Karl Popper, who condemned essentialist definitions, observed that a good definition in science should be read from right to left, not left to right.[288] Consider the sentence, "Acute respiratory failure is the presence of a Pa_{O_2} of less than 60 mm Hg, with or without a Pa_{CO_2} of greater than 50 mm Hg, together with physical findings indicative of increased work of breathing." Reading from right to left, the sentence provides a "nominalist" answer to the clinician's question, "What shall we call the presence of a Pa_{O_2} of less than 60 mm Hg, with or without a Pa_{CO_2} of greater than 50 mm Hg, together with physical findings indicative of increased work of breathing?" rather than providing an "essentialist" answer to the question, "What is acute respiratory failure?" That is, the term *acute respiratory failure* is handy shorthand for the longer, more cumbersome description. Nothing more. The term *acute respiratory failure* contains no information about medicine, and nothing is to be gained from analyzing it.

Diagnostic Process, Treatment, and Value Judgment

The process of making a diagnosis goes through two broad steps. First, the physician undertakes an initial review of the clinical features, looking for a pattern that suggests one or

more diseases. For example, a clinician notes eyelid retraction, tracheal tug, sternomastoid contraction, tachypnea, and monosyllabic speech. The physician concludes that the patient is in acute respiratory distress (an "entity" rather than a disease). Second, the physician undertakes a directed search for the defining characteristics (pathognomonic findings) of each of a number of suspected diseases.[289] Let us consider a patient who exhibits all the above-listed features of acute respiratory distress. On learning that the patient had been extubated a half hour previously, the physician suspects laryngeal edema and carefully listens for stridor. In a second patient, a physician's initial assessment again may reveal the general features of acute respiratory distress. On learning that this patient also has fever, chills, and rust-colored sputum, the physician suspects pneumonic consolidation. The physician then undertakes careful palpation (for tactile vocal fremitus), percussion (for dullness), and auscultation (for whispering pectoriloquy, egophony, and bronchial breathing).

The clinical diagnostic criteria are the descriptive features that best discriminate between one disease and other diseases with which it might be confused. In the best-case scenario, the clinical diagnostic criteria are made up largely of defining characteristics. None of the features is conclusive, but together they produce a degree of probability that justifies a diagnosis on which practical management may be based.[287] It is possible to state defining characteristics in objective, demonstrable terms when a disease is defined etiologically or as a disorder of structure or function.[280] The same is also possible for a disease defined syndromically if the description of the syndrome includes objectively demonstrable elements. For example, as entry criteria for a research study, respiratory distress might be defined (arbitrarily) as meeting three of the following four elements: respiratory rate greater than 33 breaths/min, a Pa_{O_2}/FI_{O_2} ratio of less than 300, phasic sternomastoid contraction, and nasal flaring. That is, in the context of this study, respiratory distress can be defined without making subjective value judgments.

When making decisions about the treatment of an individual patient, however, it is not possible to avoid subjective value judgments (things being assessed on a scale of goodness or badness). Ultimately, the decision of whether to institute mechanical ventilation (or not) boils down to a value judgment by the patient's physician. In some instances this decision will be preceded by a physician's making of a diagnosis. In many cases, however, physicians institute mechanical ventilation without having formulated a precise diagnosis. Along the same lines, Gross[290] has argued that it is unlikely that management of asthma would be improved were it possible to articulate a more widely accepted definition of this disease.

Factual Implications of Disease Terminology

Nosology is rarely discussed at medical conferences.[277] Questions on terminology are regarded as recondite and pedantic, eliciting yawns from the audience. When a speaker is asked to define the clinical entity about which he or she is speaking, the speaker may appear puzzled—believing that everyone surely knows what the term means. The audience becomes restless, seeing the question as a philosophical diversion that distracts from the hard scientific facts that the speaker is trying to discuss. Yet it makes little sense for a speaker to present detailed data analysis on a condition that the speaker cannot define. Likewise, readers should treat with a jaundiced eye statistics in surveys that list precise diagnoses for which mechanical ventilation was used. The ghost of such unrealistic (and unattainable) precision also hovers over lists of reasons for why patients were intubated in reports on controlled trials of noninvasive ventilation versus conventional therapy.

The application of precise mathematical methods to vague and ill-defined concepts gives them a false air of respectability that cloaks ignorance and perpetuates confusion.[284] It is unfortunate that the more fundamental the concept to which a word refers, the less careful we tend to be about the use of a clear definition.[291]

CONTRAINDICATIONS TO MECHANICAL VENTILATION

Complications associated with mechanical ventilation can be lethal (see Chapters 43 to 47). Thus, mechanical ventilation should be used only when it is clearly needed. Intubation is not the first approach for most patients with an exacerbation of COPD; instead, noninvasive ventilation is the first choice. The same sequence probably holds for selected patients with congestive heart failure or immunocompromise. Mechanical ventilation should not be instituted when a mentally competent patient or a surrogate designated to make decisions on behalf of a noncompetent patient refuses it. If time permits, the patient and family should be instructed about the likely impact of mechanical ventilation on prognosis. For instance, hospital mortality of patients with idiopathic pulmonary fibrosis requiring mechanical ventilation is 68%[292] to 100%,[293] and 92% of the survivors are dead within 2 months of hospital discharge.[292]

CONCLUSION

When we started to write this chapter, we expected to end it by formulating a set of concrete recommendations as to when mechanical ventilation should be instituted. Readers willingly wade their way through complex pathophysiologic concepts if they believe the material enhances their understanding of a clinical topic. At the end, however, they expect to see the complexity reduced to a set of concrete recommendations, preferably conveyed as a list of entities with numerical values attached. That final step is not possible with this chapter. More than is the case for any other chapter in this book, it is not possible to articulate the indications for mechanical ventilation in the form of a list of items.

If it is not possible to formulate a list, then what? When you, dear reader, are in severe respiratory distress and a physician is standing at your bedside deciding whether or not to ventilate (and possibly intubate) you, what type of physician are you hoping will make this decision? We can speak only for ourselves. The physician we want is a person deeply versed in pathophysiologic concepts, skilled in the art of physical examination, with extensive experience of cases similar to our own illness, and blessed with good clinical judgment. We expect that physician to base the decision (on which our life depends) on his or her clinical gestalt. And we recognize that the physician may not be able to articulate the precise reasons behind this decision in the form of words.

Why can't our ideal physician express these thoughts in explicit terms? A wise physician standing at a patient's bedside senses a great deal of worthwhile information—much more than can be expressed in words. In short, there is a very large tacit coefficient to clinical knowledge—physicians *know* much more than they can communicate verbally.[294] There is an enormous difference between the assessment made by an experienced physician standing at a bedside and the assessment the same physician makes on hearing information (about the same patient) relayed over the telephone by a junior resident. An experienced and wise physician employs intuition rather than explicit rules in deciding what is best for a particular patient in a particular setting. A physician who regards such intuition as unscientific betrays a fundamental misunderstanding of the epistemology of science.[286]

Our failure to formulate a list of indications does not mean that we advocate a laissez-faire approach to instituting mechanical ventilation. Earlier we mentioned the absurdity of saying that mechanical ventilation is always indicated for acute respiratory failure, defined as a Pa_{O_2} of less than 60 mm Hg. This does not mean that we consider Pa_{O_2} unimportant. On learning that a patient has a sustained Pa_{O_2} of 40 mm Hg, a physician will take immediate steps to institute assisted ventilation. But it is not possible to pick a Pa_{O_2} breakpoint (between 40 and 60 mm Hg) below which the benefits of mechanical ventilation decidedly outweigh its hazards. It is futile to imagine that decision making about instituting mechanical ventilation can be condensed into an algorithm with numbers at each nodal point. In sum, an algorithm cannot replace the presence of a physician well skilled in the art of clinical evaluation who has a deep understanding of pathophysiologic principles.

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IV

CONVENTIONAL METHODS OF VENTILATORY SUPPORT

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SETTING THE VENTILATOR

5

Steven R. Holets
Rolf D. Hubmayr

The choice of ventilator settings should be guided by clearly defined therapeutic end points. In most instances, the primary goal of mechanical ventilation is to correct abnormalities in arterial blood-gas tensions. In most patients, this is accomplished easily by adjusting the minute volume to correct hypercapnia and by treating hypoxemia with oxygen (O_2) supplementation. Because the volume, frequency, and timing of gas delivered to the lungs have important disease-specific effects on cardiovascular and respiratory systems functions, the physician must avoid simply managing the blood-gas tensions of the ventilator-dependent patient. After a brief review of the capabilities of modern ventilators, this chapter discusses the mechanical determinants of patient–ventilator interactions and defines therapeutic end points in common respiratory failure syndromes. These sections provide background for the major thrust of the chapter, which is to detail the physiologic consequences of positive-pressure ventilation and to develop recommendations for ventilator settings in various disease states based on this knowledge.

CAPABILITIES OF MODERN VENTILATORS

The incorporation of microprocessors into ventilator technology has made it possible to program ventilators to deliver gas with virtually any pressure or flow profile. Significant advances have been made in producing machines that are more responsive to changes in patient ventilatory demands, and most full-service mechanical ventilators display diagnostic information contained in airway pressure (Paw), volume (V), and flow ($\dot{V}$) waveforms. Because of these added capabilities, the practitioner is being challenged with a staggering array of descriptive acronyms for so-called new modes of ventilation. To avoid unnecessary confusion, it is useful not to focus on specific modes for the moment but rather to consider three general aspects of ventilator management: (a) the choice of inspired-gas composition, (b) the means to ensure the machine's sensing of the patient's demand, and (c) the definition of the machine's mechanical output.

Choice of Inspired-Gas Composition

Practically speaking, decisions regarding the composition of inspired gas concern only the O_2 concentration (see "Acute Lung Injury and Hypoxic Respiratory Failure" below). Although there may be occasions when the care provider considers supplementing the inspired gas with nitric oxide, the efficacy of nitric oxide therapy for most forms of hypoxic respiratory failure remains to be established.[1] There has been growing interest in the biologic effects of hypercapnia on gas exchange, vascular barrier properties, and innate immunity.[2–7] Therapeutic hypercapnia, that is, the deliberate supplementation of inspired gas with carbon dioxide (CO_2), however, cannot be recommended at this point in time. On extremely rare occasions, it may be appropriate to use a helium-oxygen mixture in an attempt to lower the flow resistance across a lesion in the distal trachea or mainstem bronchi, and there has been some interest in the use of helium in asthma.[8] Currently, these approaches must be considered experimental.

Machine's Sensing of Patient's Demand (Ventilator Triggering)

Ideally, a mechanical ventilator should adjust not only its rate but also its instantaneous mechanical output in response to changing patient demands. Conventional modes of ventilation cannot do so; instead, such modes execute a predefined pressure or flow program after an effort has been sensed.

Volume preset controlled mechanical ventilation (CMV) refers to a mode during which rate, tidal volume (V_T), inspiratory-to-expiratory timing (I:E ratio), and inspiratory flow profile are determined entirely by machine settings and cannot be altered by either the rate nor the amplitude of the patient's effort. Occasionally, investigators refer to ventilation as "controlled" when spontaneous respiratory muscle activity has been abolished by mechanical hyperventilation or by pharmacologic means (e.g., sedation and neuromuscular blockade).

Assist-control ventilation (ACV) gives the patient the option of initiating additional machine breaths when the rate, set by the physician, is insufficient to meet the patient's rate demand. ACV differs from intermittent mandatory ventilation (IMV) in that all delivered breaths execute the same pressure or flow program, depending on the choice of primary mode. The ACV feature has lured many providers into the erroneous assumption that the primary machine rate setting is unimportant (see "Acute Lung Injury and Hypoxic Respiratory Failure: Respiratory Rate" below).

Traditionally, machine algorithms for detecting patient effort have keyed on the airway pressure signal.[9] Because the inspiratory port of ventilators is closed during machine expiration, any inspiratory effort that is initiated near relaxation volume (Vrel) causes a fall in Paw. When Paw reaches a predefined trigger threshold (usually set 1 to 2 cm H_2O below the end-expiratory pressure setting), the machine switches from expiration to inspiration. In the presence of dynamic hyperinflation, the inspiratory muscles must generate considerably more pressure than the set airway trigger pressure before a machine breath is delivered[10] (see "Obstructive Lung Diseases" below).

Particularly in older ventilator models and in less-sophisticated portable machines intended for home use, it used to be common to find delays of up to 0.5 second between the onset of inspiratory muscle activity and machine response. In most ventilators used today, such delays are less than 100 milliseconds.[11] Sensing delays are common when the Paw is monitored in the machine rather than near the patient–ventilator interphase. In the former case, the ventilator tubing acts as a capacitor, delaying the transmission of pressure from the intrathoracic airway to the pressure transducer. Additional delays can be attributed to dynamic hyperinflation and physical constraints on the opening and closing of demands valves. Considering that most ventilator-dependent patients generate between 4 and 8 cm H_2O pressure in 100 milliseconds,[10,12] delays can cause significant effort expenditure and discomfort. More importantly, patients may terminate seemingly ineffective inspiratory efforts prematurely only to initiate another effort of greater amplitude shortly thereafter. This leads to discrepancies between patient and machine rate.[13,14] Discrepancies are seen often in weak or heavily sedated patients with severe hyperinflation and high intrinsic respiratory rates.[13,15]

Flow-triggering algorithms are alternatives or adjuncts to Paw-based triggering. During "flow triggering," a base flow of gas is being delivered to the patient during the expiratory as well as the inspiratory phases of the machine cycle.[9] Unless the patient makes an inspiratory effort, gas bypasses the endotracheal tube and is discarded through the expiratory machine port. In the absence of patient effort, expiratory flow is equal to inspiratory base flow. In the presence of an inspiratory effort, gas enters the patient's lungs and is thereby diverted from the expiratory machine port. A discrepancy between inspiratory and expiratory base flow is sensed, and the ventilator switches phase. Because "flow triggering" alleviates the need to rarefy gas against an occluded demand valve, initially it was considered superior to pressure-based trigger algorithms.[9,16] Because most new-generation ventilators have combined pressure and flow-sensing capabilities, these distinctions no longer apply.

Options for Defining the Machine's Mechanical Output

The mode of mechanical ventilation often refers to the shape of the inspiratory pressure or flow profile and determines whether a patient can augment V_T or rate through his or her own efforts.

Volume-Preset Mode

In conventional volume-preset mode, each machine breath is delivered with the same predefined inspiratory flow-time profile. Because the area under a flow-time curve defines volume, V_T remains fixed and is uninfluenced by the patient's effort. Volume-preset ventilation with constant (square wave) or decelerating inspiratory flow is the most widely used breath-delivery mode. Breath delivery with flows that decrease with increasing lung volume are effective in reducing peak Paw. It is not clear, however, whether they protect the lungs from overdistension injury any more than square wave flow profiles.

The mechanical output of a ventilator operating in the volume-preset mode is uniquely defined by four settings: (a) the shape of the inspiratory flow profile, (b) V_T, (c) machine rate, and (d) a timing variable in the form of either the I:E ratio, the duty cycle (T_I/T_{TOT} [inspiratory time/total respiratory time]), or the T_I. In some ventilators, timing is set indirectly through the choice of peak or mean inspiratory flow (V_T/T_I). Figure 5-1 illustrates the relationships among these and other breathing-pattern parameters of significance.

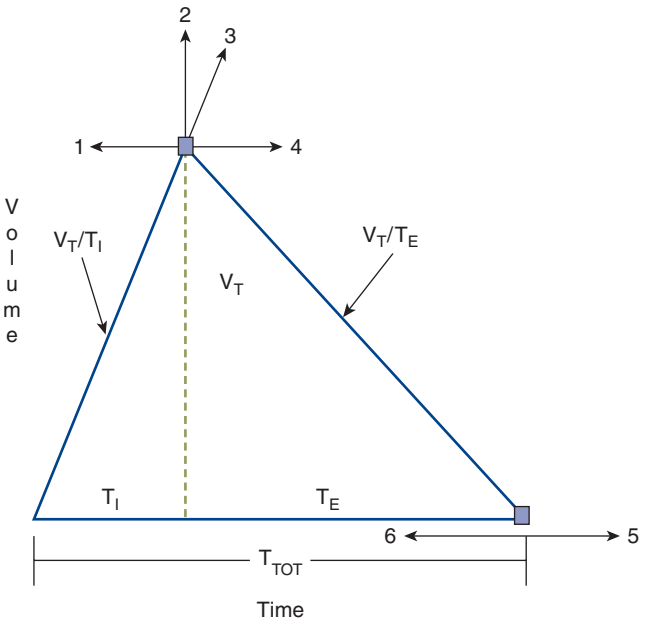

FIGURE 5-1 Idealized spirogram of a breath delivered during volume-preset mechanical ventilation. Examples 1 through 6 indicate specific changes in ventilator settings and illustrate the consequences on flow and timing variable. (For abbreviations, see Table 5-1.) (1) Increasing mean inspiratory flow (V_T/T_I) at a constant machine rate setting results in a reduced I:E ratio and vice versa. T_I, T_I/T_{TOT}, and mean expiratory flow (V_T/T_E) decline. (2) Increasing V_T at constant T_I/T_{TOT} or I:E setting increases mean inspiratory flow and requires an increase in mean expiratory flow. Remember that mean inspiratory flow equals peak inspiratory flow when delivery modes with constant square wave flow profiles are used. (3) Increasing V_T at a constant mean inspiratory flow setting increases T_I, T_I/T_{TOT}, I:E ratio, and mean expiratory flow. (4) Decreasing mean inspiratory flow at a constant machine rate setting results in an increase in the I:E ratio and vice versa. T_I, T_I/T_{TOT} and mean expiratory flow rise. (5) Reducing the machine backup rate (f_M) at a fixed I:E ratio or T_I/T_{TOT} setting always prolongs T_I and lowers mean inspiratory flow. The timing effects of reducing f_M at a fixed inspiratory-flow setting cannot be predicted without knowledge of the patient's actual trigger rate. (6) Increasing f_M at a fixed I:E ratio or T_I/T_{TOT} setting always raises inspiratory flow. The timing effects of increasing f_M at a fixed inspiratory-flow setting cannot be predicted without knowledge of the patient's actual trigger rate.

Pressure-Preset Mode

During pressure-preset ventilation, the ventilator applies a predefined target pressure to the endotracheal tube during inspiration. The resulting V_T and inspiratory flow profile varies with the impedance of the respiratory system and with the strength and duration of the patient's inspiratory efforts. Therefore, when the lungs or chest wall become stiff, airway resistance increases, the patient's own inspiratory efforts decline, or T_I decreases, V_T decreases. An increase in respiratory system impedance can lead to a dangerous fall in minute ventilation ($\dot{V}_E$), hypoxemia, and CO_2 retention, but in contrast to volume-preset modes, it does not predispose the patient to an increased risk of barotrauma. On the other hand, pressure-preset modes are no safeguard against ventilator-induced lung injury because large fluctuations in respiratory impedance or patient effort would result in large V_T fluctuations directly undermining the primary objective of lung-protective mechanical ventilation (see section on Acute Lung Injury and Hypoxic Respiratory Failure).

Pressure-support ventilation (PSV), pressure-controlled ventilation (PCV) and airway pressure release ventilation (APRV) are the most widely used forms of pressure-preset ventilation. In contrast to PCV, PSV requires the patient's effort before a machine breath is delivered. Consequently, PSV is not suitable for the management of patients with central apneas. During PCV, the physician sets the machine rate, the T_I, and thus the I:E ratio. In PSV, phase switching is linked to inspiratory flow, which, in turn, depends on the impedance of the respiratory system, as well as on the timing and magnitude of inspiratory muscle pressure output.[11,14] APRV is akin to PCV with a long duty cycle, but with one important distinction: patients are able to take spontaneous breaths throughout all phases of the machine cycle.

PSV remains a popular weaning mode for adults. Its popularity is based on the premise that weaning from mechanical ventilation should be a gradual process and that the work of unassisted breathing through an endotracheal tube is unreasonably high and could lead to respiratory muscle failure in susceptible patients. Actual measurements of pulmonary resistance and work of breathing before and after extubation do not support this reasoning,[17,18] and several large clinical trials have established equivalence between PSV and T-piece weaning (unassisted breathing from a bias-flow circuit).[19–21] In the PSV mode, a target pressure is applied to the endotracheal tube, which

TABLE 5-1: LIST OF ABBREVIATIONS

τ	Time constant
AC	Assist-control mode
ARDS	Adult respiratory distress syndrome
CMV	Controlled mechanical ventilation
CPAP	Continuous positive airway pressure
Ers	Elastance of the respiratory system
Edi	Electromyographic tracing of the diaphragm
F	Force
f_A	Actual breathing rate
FEF_{25-75}	Forced expiratory flow in the mid vital capacity range
FI_{O_2}	Fractional inspired oxygen concentration
f_M	Machine backup rate
I:E ratio	Inspiratory-to-expiratory time ratio
IMV	Intermittent mandatory ventilation
Pa_{CO_2}	Arterial CO_2 tension
Pa_{O_2}	Arterial O_2 tension
Paw	Airway pressure
PCV	Pressure-controlled ventilation
PEEP	Positive end-expiratory pressure
$PEEP_E$	Extrinsic positive end-expiratory pressure
PEEPi	Intrinsic positive end-expiratory pressure
Pel	Elastic recoil pressure
P_{tp}	Transpulmonary pressure
Pmus	Inflation pressure exerted by inspiratory muscles
Pres	Resistive pressure
Prs	Recoil of respiratory system
PSV	Pressure support ventilation
SIMV	Synchronized intermittent mandatory ventilation
T_E	Expiratory time
T_I	Inspiratory time
T_I/T_{TOT}	Duty cycle
T_{TOT}	Total cycle time
TLC	Total lung capacity
$\dot{V}$	Flow
$\dot{V}/\dot{Q}$	Ventilation-perfusion ratio
$\dot{V}_{CO_2}$	Volume of CO_2 produced in liters per minute
$\dot{V}_E$	Minute ventilation
$\dot{V}_I$	Mean inspiratory flow
V(t)	Instantaneous lung volume
$\dot{V}_E/V_T$	Dead-space-to-tidal-volume ratio
Vee	Volume of lungs at end expiration
Vrel	Relaxation volume
V_T/T_E	Mean expiratory flow
V_T/T_I	Mean inspiratory flow
V_T	Tidal volume
Vtrapped	Volume of gas remaining in the elastic element at the beginning of a new machine inflation
Wel	Elastic work

augments the inflation pressure exerted by the inspiratory muscles (Pmus) on the respiratory system. When inspiratory muscles cease to contract and Pmus falls, inspiratory flow (a ventilator-sensed variable) declines, and the machine switches to expiration. Early PSV modules were designed to generate pressure ramps (square wave inflation pressure) and had relatively rigid flow-based, off-switch criteria. Most recent versions of PSV afford control over the rate of rise in inspiratory pressure and the flow threshold at which inspiration is terminated.[11,14,22]

Synchronized Intermittent Mandatory Ventilation

During synchronized intermittent mandatory ventilation, a specified number of usually volume-preset breaths are delivered every minute. In addition, the patient is free to breathe spontaneously between machine breaths from a reservoir or to take breaths augmented with PSV. Most ventilators allow the operator to choose between volume- and pressure-preset mandatory breaths. Unless the patient fails to breathe spontaneously, machine breaths are delivered only after the ventilator has recognized the patient's effort; that is, ventilator and respiratory muscle activities are "synchronized." Because nowadays all IMV circuits are synchronized, the terms *IMV* and *synchronized intermittent mandatory ventilation* are used interchangeably. Although synchronized intermittent mandatory ventilation remains a viable and popular mode of mechanical ventilation, compared with the alternatives, PSV and T piece, it has clearly proven inferior as a weaning modality.[19,20,23,24] Moreover, the care provider needs to be aware of certain pitfalls when using IMV. Even a small number of volume-preset IMV breaths per minute may make the blood-gas tensions look acceptable in patients who otherwise meet criteria for respiratory failure. One should suspect this in patients with small spontaneous V_T (≤3 mL/kg of body weight), in those with thirty or more inspiratory efforts per minute regardless of whether they trigger a machine breath, and when dyspnea and thoracoabdominal paradox indicate a heightened respiratory effort. One reason that IMV remains popular is because it silences apnea alarms by masking PSV-induced respiratory dysrhythmias, which are common in sleeping and obtunded patients.[25–27]

Dual-Control and Advanced Closed-Loop Modes

Many new-generation mechanical ventilators feature modes with closed-loop feedback control of both pressure and volume.[28,29] While a detailed description of the operating principles of every new mode is beyond the scope of this chapter, it is important to understand the rationale behind dual-control modes and some of their general operating characteristics. The idea behind most dual-control modes is the meeting of a ventilation target while maintaining low inflation pressures. To this end, ventilator output is adjusted based on volume, flow, and pressure feedback. This may occur within each machine cycle or gradually from one cycle to the next. Modes that adjust output within each cycle execute a predetermined pressure-time program as long as the desired V_T is reached. When the V_T target is not reached, inspiration continues at a preselected inspiratory flow rate (volume-limited) until the target volume is attained. *Volume-assured pressure support* and *pressure augmentation* are examples of such modes.[30] Breath-to-breath dual-control modes are pressure-limited and time-cycled or flow-cycled. Ventilator

output is derived from the pressure–volume relationship of the preceding breath and is adjusted within predefined pressure limits to maintain the target V_T. *Adaptive support ventilation, pressure-regulated volume control*, *volume control+*, *autoflow*, *adaptive pressure ventilation*, *volume support*, and *variable pressure support* are examples of breath-to-breath control modes. There is no evidence that the use of dual-control modes improves patient outcomes.[31,32] Moreover, there is a conceptual problem insofar as less complex modes already safeguard against hypoventilation, whereas dual-control modes do little to protect the patient from a potentially harmful increase in the regulated variable, that is, large V_T-mediated lung injury.[33,34]

Neurally adjusted ventilatory assistance (NAVA) and *proportional-assist ventilation* (PAV)[35–37] are the most complex, and arguably the most promising, closed-loop ventilation modes. During NAVA, the diaphragm's electrical activity is recorded with an esophageal probe, and the signal is conditioned and transposed into a positive airway pressure output. During PAV, the ventilator derives its mechanical output from continuously monitored Paw, V, and $\dot{V}$ information, which, in turn, reflects Pmus. The operating principles of PAV will be easier to understand after a review of patient–ventilator interactions (see "The Mechanical Determinants of Patient-Ventilator Interactions" below). Compared to conventional modes of mechanical ventilation, both NAVA and PAV preserve the biologic variability in breathing rate and V_T, which is generally considered lung protective.[38] Moreover, the maintenance of intrinsic respiratory control mechanisms is likely to reduce the probability of exposing the lungs to injurious deformations. Although there is ample literature on the effects of closed-loop modes on patient–ventilator interactions and physiologic end points, there is insufficient clinical experience to judge efficacy of these modes compared to conventional approaches. This is particularly true for NAVA, which was only recently introduced to the world market, but holds particular promise as platform for delivering noninvasive mechanical ventilation and as a support mode for neonates and small infants. Be this as it may, the full-scale migration of closed-loop modes from expert hands into general practice will likely depend on the willingness of providers to acquire the physiologic insights and skills necessary for managing patients who are ventilated with "unconventional" modes.

THE MECHANICAL DETERMINANTS OF PATIENT–VENTILATOR INTERACTIONS

Inspiratory Mechanics

It is useful to think of patient–ventilator interactions in terms of a mechanical or electrical analog system consisting of a resistive element (resistor) and an elastic element (capacitor) in series. The forcing function is defined by the pressure or flow "program" that is executed by the mechanical ventilator.

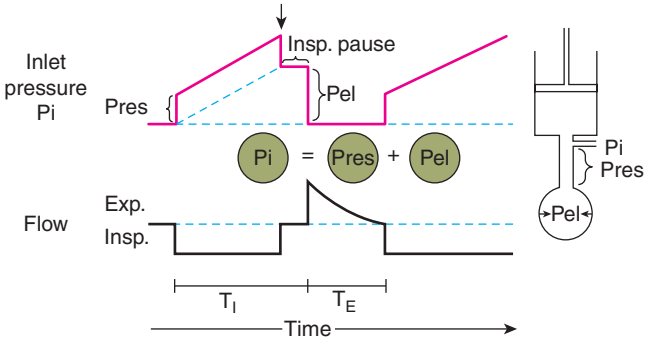

FIGURE 5-2 Components of inlet pressure. The model of the respiratory system at right consists of a resistive element (straight tube) and an elastic element (balloon) connected to a ventilator (piston). During inflation of the model with constant flow *(lower panel)*, there is a stepwise increase inlet pressure (Pi) that equals the loss of pressure across the resistive element (Pres) (*upper panel*). Thereafter, Pi increases linearly and reflects the mechanical properties of the elastic element (Pel). Pi is the sum of Pres and Pel. At end inspiration, when flow has ceased (Insp. Pause), Pi decreases by an amount equal to Pres; Pi equals Pel during Insp. Pause. T_I, inspiratory time; T_E, expiratory time. (Used, with permission, from Hubmayr, et al. Physiologic approach to mechanical ventilation. *Crit Care Med.* 1990;18:103–113.)

In Figure 5-2, a piston pump (the mechanical ventilator) is attached to a rigid tube (the resistive element) and a balloon (the elastic element). An in-series mechanical arrangement means that at any time *t*, the pressure that is applied to the tube inlet $Pi(t)$ (near the attachment to the ventilator) is equal to the sum of two pressures, an elastic pressure $Pel(t)$ and a resistive pressure $Pres(t)$:

$$Pi(t) = Pel(t) + Pres(t) \quad (1)$$

The tube outlet pressure at the junction with the balloon is equal to the pressure inside the balloon, that is, Pel. Pres is the difference in pressure between the tube inlet and the tube outlet. Assuming linear-system behavior, the inlet pressure-time profile can be computed for any piston stroke volume (Vstroke) and flow ($\dot{V}$) setting, provided the resistive properties of the tube (R) and the elastic properties of the balloon (E) are known:

$$Pi(t) = EV(t) + R\dot{V}(t) \quad (2)$$

The elastance (E) is a measure of balloon stiffness and is equal to the Pel-to-V stroke ratio (assuming 0 volume and pressure at the beginning of balloon inflation). Therefore, $Pel(t)$ in Eq. (1) can be replaced with $EV(t)$ in Eq. (2). Because the Ohm law states that the tube resistance (R) is equal to the Pres-to-$\dot{V}$ ratio, $Pres(t)$ in Eq. (1) can be replaced with the product $R\dot{V}(t)$ in Eq. (2).

Equations (1) and (2) are based on the equation of motion, which describes the force (F) that must be applied to a mass (M) in order to move it a certain distance (d) at a rate dd/dt against a spring (elastic) load:

$$F(t) = kd(t) + k'(dd/dt)(t) + k''[d(dd/dt)](t) \quad (3)$$

where k = stiffness of the spring (analogous to E); k' = frictional resistance between mass and supporting surface

(analogous to R); and k'' = inertance, which is proportional to mass.

The first and second derivatives of d (analogous to volume) represent the velocity (dd/dt, analogous to flow) and the acceleration [$d(dd/dt)/dt$] of the mass at time t, respectively. As long as the mass of the moving parts in the model of Figure 5-2 is small, any inertive-pressure component that is dissipated during the acceleration of gas at the beginning of the pump instroke can be ignored. Therefore, the respiratory analog of the equation of motion [Eqs. (1) and (2)] considers only elastic and resistive pressures.

Consider the Pi-time profile of a tube-balloon system with resistance of 10 cm $H_2O \times L/s$ and an elastance of 10 cm H_2O when the piston pump is programmed to deliver a volume of 0.5 L with a constant (square wave) flow of 0.5 L/s. Because flow and R remain constant throughout inflation, Pres is constant at 5 cm H_2O and accounts for the initial step change in inlet pressure at the beginning of inflation. As gas enters the balloon, Pi increases further and reaches a value of 10 cm H_2O at end inflation. At that instant, the tube is occluded (end-inflation hold), causing Pi to drop by an amount equal to Pres (as flow returns to 0). The end-inflation hold pressure is equal to Pel at that volume. Its value of 5 cm H_2O is equal to the product of piston stroke volume (0.5 L) and elastance (10 cm H_2O/L), as follows from Eqs. (1) and (2). Subtracting Pres from Pi(t) yields the Pel per time course during inflation. Pel increases linearly with time and volume. Its rate of rise (dPel/dt) parallels that of Pi and is determined by E and the flow setting of the piston:[39]

$$E \times \dot{V} = (dp/dV) \times (dV/dt) = dP/dt \quad (4)$$

Although changes in inspiratory flow result in proportional changes in dPel/dt, flow has no effect on peak Pel, provided that Vstroke, and thus peak lung volume, is held constant. This is in contrast to peak Pi, which reflects flow-dependent changes in Pres, as well as change in Pel, at end inflation. The relevance of this important property of linear single-compartment systems will become apparent later when the relationships between ventilator settings and barotrauma (balloon yield stress) are discussed (see "Acute Lung Injury and Hypoxic Respiratory Failure" below).

Expiratory Mechanics

In mechanically ventilated subjects, expiration is usually a passive process that is driven by the elastic recoil (Pel) of the respiratory system. Assuming linear pressure-volume and pressure-flow relationships, the instantaneous expiratory flow [$\dot{V}exp(t)$] is given by

$$\dot{V}exp(t) = Pel(t)/R \quad (5)$$

Because $Pel(t)$ is a function of E and of the instantaneous lung volume [$V(t)$], Eq. (5) can be rewritten as

$$\dot{V}exp(t) = E \times V(t)/R = V(t)/R \times C \quad (6)$$

where C (the compliance of the respiratory system) is simply the inverse of the elastance (E). The product of R and C characterizes the time constant (τ) of single-compartment linear systems. The time constant defines the time at which approximately two-thirds of the volume above $Vrel$ has emptied passively. From this it should be clear that patients with increased respiratory system resistances and compliances (e.g., patients with emphysema) are prone to dynamic hyperinflation even if one ignores nonlinear system behavior, such as flow limitation, for the moment.

The volume of gas remaining in the elastic element at the beginning of a new machine inflation ($Vtrapped$) can be calculated as follows:

$$Vtrapped = V_T/(e^{TE/\tau} - 1) \quad (7)$$

In other words, the degree of dynamic hyperinflation is determined by the choice of ventilator settings, specifically mean expiratory flow (V_T/V_E) and the time constant of the respiratory system, which reflects its mechanical constants R and C.[40] These important concepts are expanded on under "Obstructive Lung Diseases" below.

Limitations of Linear Single-Compartment Models

Before linear model principles are applied to the ventilator management of patients, one must be cognizant of the model's limitations. The limitations fall into two general categories: those related to nonlinear respiratory system characteristics and those related to respiratory muscle activation during mechanical ventilation. Sources of nonlinear system behavior include inhomogeneities within the numerous bronchoalveolar compartments (particularly when the lungs are diseased),[41] respiratory system hysteresis from recruitment of alveolar units and time-dependent surface tension phenomena,[42] and phenomena related to dynamic airway collapse and expiratory flow limitation.[43] Coactivation of the respiratory muscles during mechanical ventilation invalidates Eqs. (1) through (7) insofar as they alter the impedance of the respiratory system and change the driving pressure for expiratory flow. If one assumes that the respiratory muscles and the ventilator are arranged in series, then the monitoring of pressure, volume, and flow at the airway opening offers the opportunity to define the magnitude, rate, and duration of respiratory muscle output in mechanically ventilated subjects.[44,45]

DEFINING THERAPEUTIC END POINTS IN COMMON RESPIRATORY FAILURE SYNDROMES

Numerous diseases of cardiopulmonary systems can cause respiratory failure. From a ventilator management perspective, it is useful to group them into those that cause lung failure and those that cause ventilatory pump failure.

The hallmark of lung failure is hypoxemia, which is usually the result of severe ventilation-perfusion mismatch. The hallmark of ventilatory pump failure is hypercapnia. Ventilatory pump failure may be caused by disorders of the central nervous system, peripheral nerves, or respiratory muscles. It also may accompany diseases of the lungs, such as emphysema, once the ventilatory pump fails to compensate for inefficiencies in pulmonary CO_2 elimination. Two classic examples of hypoxic and hypercapnic ventilatory failure that require fundamentally different approaches to mechanical ventilation are the acute respiratory distress syndrome (ARDS) and chronic airflow obstruction. The therapeutic goal in ARDS is to protect the lung from mechanical injury while raising lung volume in an attempt to reduce shunt by reexpanding collapsed and flooded alveoli. In contrast, the therapeutic goal in a patient with hypercapnic ventilatory failure from exacerbation of airways obstruction is to reduce dynamic hyperinflation and to protect the respiratory muscles from overuse.

ACUTE LUNG INJURY AND HYPOXIC RESPIRATORY FAILURE

Acute lung injury (ALI) is a syndrome associated with bilateral pulmonary infiltrates and a gas-exchange impairment severe enough to lower the arterial oxygen tension-to-fractional inspired oxygen concentration ratio (Pa_{O_2}/FI_{O_2}) below 300.[46] Heart failure and moderate to severe preexisting chronic lung disease must be absent. ALI and its more severe form, ARDS, are often complications of systemic illnesses such as sepsis.[47] The impairment on pulmonary gas exchange therefore is accompanied frequently by microcirculatory failure. The general management goal in these disorders is to augment systemic oxygen delivery until the metabolic demands of the organism can be met. This goal requires an integrated approach between cardiovascular and ventilator support.[48]

Ventilator support is often difficult because exceedingly high ventilatory requirements challenge the performance capacity of mechanical ventilators; render patients at risk for barotrauma, ventilator-induced lung injury, and cardiovascular collapse; and often are accompanied by excessive respiratory muscle activity ("fighting the ventilator"). All these conditions on occasion can necessitate heavy sedation and neuromuscular blockade.

Fractional Inspired Oxygen Concentration

The two principal means by which the physician can increase Pa_{O_2} in ARDS are to raise the FI_{O_2} and to elevate the volume about which the lungs are being ventilated. The danger inherent in raising $FI_{O_2}$is oxygen toxicity,[49] whereas manipulating lung and/or V_T may result in ventilator-induced lung injury[34,50] and/or barotrauma.[51] Presented with the choice between two different kinds of adverse reactions, physicians currently tend to be more fearful of mechanical lung injury than of oxygen toxicity. Unfortunately, there are no clinical outcome studies that shed light on the interactions between these two iatrogenic insults. It is common practice to initiate ventilator support with an FI_{O_2} of 1.0 and to ignore the potential for oxygen toxicity during the first few hours of ventilator management. Although, generally speaking, the relative and combined risks of oxygen toxicity and overdistension injury of the lungs remain poorly defined, there are instances in which it seems wise to minimize FI_{O_2}, namely, in patients who have received drugs such as bleomycin or amiodarone, which make the lungs particularly susceptible to reactive O_2 species-mediated injury.[52]

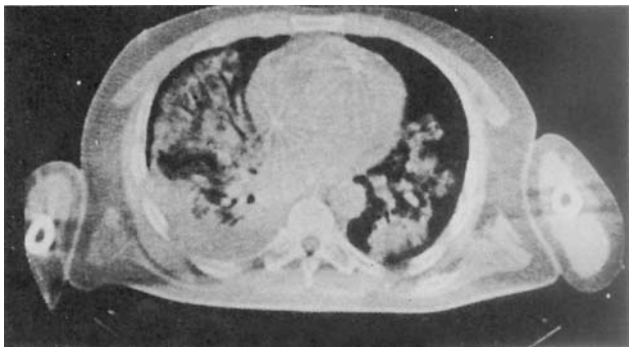

FIGURE 5-3 Computed tomographic (CT) scan of a patient with acute respiratory failure in the supine position. Note the patchy, nonuniform distribution of alveolar edema. (Used, with permission, from Gattinoni L, et al. Body position changes redistribute lung computed-tomographic density in patients with acute respiratory failure. *Anesthesiology.* 1991;74:15–23.)

Manipulating End-Expiratory Lung Volume

The insults to the lungs of patients with hypoxic respiratory failure are often patchy and result in flooding and closure of dependent airspaces (Fig. 5-3).[53,54] Paraspinal regions of the lung appear most susceptible to atelectasis (lack of aeration) because, in the supine posture, they normally empty close to their residual volume and they receive most of the pulmonary blood flow.[55] Therefore, insults to their capillary integrity are most likely to promote alveolar flooding, closure of airspaces by liquid plugs, surfactant inactivation, and gas-absorption atelectasis.[56] The accumulation of airway liquid and foam also generates interfacial forces that are large enough to abrade the epithelial lining of small airways during breathing, causing further injury.[57–61] Ventilator management therefore must be directed toward preventing the repeated opening and closing of unstable lung units, which means reestablishing aeration and ventilation of the flooded lung (Fig. 5-4).[62]

There are several ways to achieve this objective: (a) by raising overall lung volume through the judicious use of extrinsic positive end-expiratory pressure (PEEP), (b) by raising lung volume dynamically through "intentional gas trapping," (c) by increasing V_T, and (d) by taking advantage of the local

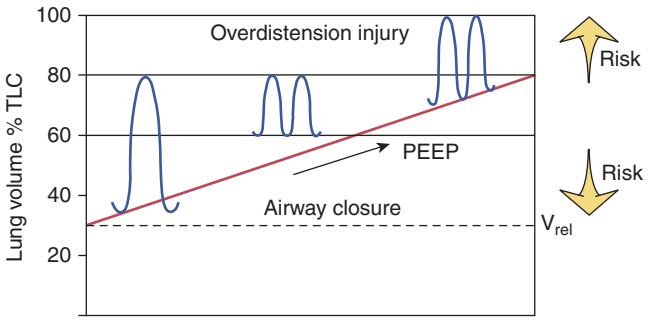

FIGURE 5-4 Schematic of the therapeutic end points of ventilator management in ARDS. Raising peak lung volume toward total lung capacity (TLC) increases the risk of barotrauma. Keeping the minimal volume near relaxation volume (Vrel) raises the likelihood of alveolar derecruitment at end expiration and the need to apply large opening pressures so as to recruit collapsed and flooded lung regions during the subsequent breath.

distending forces generated by an actively contracting diaphragm. Any one of these approaches may be combined with so-called recruitment maneuvers, which consist of sustained (up to 40 seconds) inflations of the lungs to high volumes and pressures.[63–65] The preferred and time-tested approach is the judicious use of extrinsic PEEP. All the other means of raising lung volume are comparatively untested, and in the case of V_T, manipulations can be outright harmful.[33,34] Although there is a strong physiologic rationale to condition (i.e., "open") the lungs with recruitment maneuvers before a PEEP adjustment, most experimental and clinical data indicate that conditioning effects are relatively short-lived.[66–69] Because it is common for patients with ALI to have an increased respiratory rate, a component of dynamic hyperinflation is often present.[70] Despite the short time constant for lung emptying, the use of extrinsic PEEP valves, which in older-generation ventilators represent resistive as well as threshold loads, and ventilator settings that require large mean expiratory flows (V_T/T_E; see "Mean Expiratory Flow: The Hidden Variable" below) contribute to dynamic hyperinflation.

Although the experimental evidence in support of PEEP therapy in injured lungs is overwhelming, its specific application to clinical practice remains controversial. There is general agreement among experts that patients with injured lungs should be ventilated with PEEP settings greater than 5 cm H_2O. The risk, however, of overinflating and thereby damaging well-aerated, generally nondependent lung units and adverse hemodynamic effects set limits to an aggressive recruitment strategy.[71,72] Uncertainty about the topographic distribution of lung parenchymal stress and related stress injury thresholds are partly the reason why there is no consensus as to whether PEEP should be set arbitrarily to 10, 15, or 20 cm H_2O, whether it should be targeted to specific physiologic end points, and, if so, what those end points and their specific target thresholds should be. Several large randomized clinical trials have failed to resolve the controversy about "best PEEP."[73–75] Although none of these trials established superiority of one specific PEEP strategy over another, proponents of aggressive lung recruitment argue that PEEP was not targeted to the appropriate surrogate end points. Specifically, lung recruitment, chest wall recoil, and parenchymal stress were not measured or considered in the choice of PEEP settings.

Tools for assessing recruitment responses include (a) measures of regional lung aeration with computed tomography or electrical impedance imaging of the chest,[76–78] (b) measurement of lung and/or respiratory system pressure–volume relationships,[79–82] and (c) assessment of within-breath oscillations in arterial O_2 tension with indwelling arterial O_2 sensors with fast response times.[83,84] At the bedside, the most readily available PEEP management guides are airway inflation pressure amplitude, ΔP (in case of volume preset ventilation) or V_T (in case of pressure preset ventilation). As long as raising PEEP causes recruitment of previously "closed" lung units without overdistending already open ones, ΔP will decrease, reflecting the corresponding increase in compliance. In relaxed patients who are being ventilated with a pressure preset mode, the PEEP-related effect on lung compliance can be inferred from corresponding V_T changes. Adjusting PEEP until ΔP reaches a minimum, or conversely in the case of pressure preset ventilation until V_T reaches a maximum, is in line with the stress-index hypothesis.[81] The latter states that inflating lungs over the linear range of the respiratory system pressure–volume curve is most lung protective.

Patients who are likely to recruit in response to PEEP and who indeed may benefit from raising PEEP above 10 cm H_2O at the outset are patients with an increased end-expiratory chest-wall recoil pressure, which may or may not be associated with a reduced chest-wall/abdominal compliance[85–87] and patients whose airway and alveolar edema can be redistributed easily.[88,89] In critically ill patients, the most common conditions associated with increased chest-wall recoil are obesity, ileus, and ascites.[84,90] The ability to influence the distribution of edema within and between lung regions is greatest in the early stages of inflammation. In the later stages of ARDS, when the inflammatory exudate turns from liquid to a gel, it becomes much harder to "open" a closed airspace. The likelihood of high PEEP causing recruitment is even less once organizing pneumonia, alveolar remodeling, and fibrosis dominate the pathology.[91,92]

One attempt to identify groups of patients who are more or less likely to respond to PEEP has been to classify their insults as indirect versus direct.[89] Indirect insults such as abdominal sepsis are more likely associated with a favorable PEEP response (possibly because their chest-wall recoil is high and their alveolar exudate is liquid), whereas a direct insult, from a microbial lung infection, for example, tends to be more PEEP resistant (airway secretions tend to be viscous, and the alveolar exudate has the consistency of a gel). There is, however, enough variability in lung and chest-wall mechanics within and across these two patient populations to warrant a case-by-case assessment of pulmonary and hemodynamic responses to PEEP or recruitment maneuvers. Although most clinicians choose PEEP levels according to indices of arterial oxygenation,[75] there is

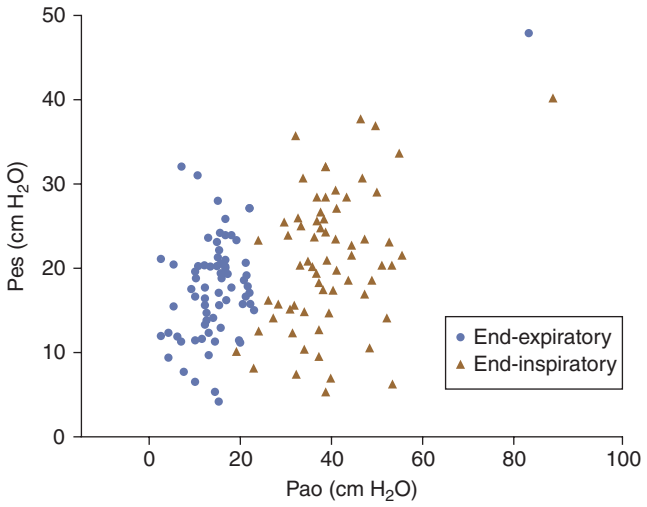

FIGURE 5-5 Relationship between airway pressure (*x axis*) and esophageal pressure (*y axis*) at end-expiration (*solid circles*) and end-inspiration (*open triangles*) in mechanically ventilated patients with ALI. As a group, most patients were managed at PEEP settings ≥10 cm H_2O, yet the corresponding esophageal pressure exceeded PEEP in 50% of instances. This suggests that the lungs were compressed by the chest wall and not sufficiently recruited at end-expiration. (Used, with permission, from Talmor, et al. Esophageal and transpulmonary pressures in acute respiratory failure. *Crit Care Med.* 2006;34:1389.)

preliminary evidence that favors PEEP adjustments guided by esophageal manometry.[93] Notwithstanding uncertainty about "mediastinal artifacts" in recumbent patients with pleural effusions and "heavy lungs,"[94,95] the pressure in the mid to lower esophagus represents an estimate of local, if not global, lung surface (or pleural, Ppl) pressure. As such, when referenced to airway pressure (Pao, a surrogate of alveolar pressure in the absence of flow) the esophageal pressure (Pes) informs about lung stress (i.e., transpulmonary pressure, Ptp). Remarkably, several reports indicate that up to 50% of patients with injured lungs have a negative Ptp at end expiration (Pes >Pao) despite PEEP settings as high as 20 cm H_2O (Fig. 5-5).[82,93] It would be easy to dismiss these findings as artifact, were it not for a small prospective randomized clinical trial that hinted at a survival benefit in patients in whom PEEP therapy was targeted to an end-expiratory Ptp of +5 cm H_2O.[93] It suggests that in the recumbent posture the injured lung is mass loaded by the chest wall and resists emptying on account of interfascial forces from alveolar or airway fluid and foam.[56] It may also mean that the risks of overinflating nondependent lung units, which are undoubtedly stressed by the more aggressive PEEP approach, is not as great as generally thought.

For those who rely on acute changes in Pa_{O_2} as surrogate end points of PEEP management, certain caveats are in order. In critically ill patients with injured lungs, Pa_{O_2} is sensitive to changes in metabolic rate and cardiac output.[96,97] Because patients with injured lungs have $\dot{V}/\dot{Q}$ mismatch as well as shunt, changes in mixed venous oxygen tension, which result from changes in metabolic rate and cardiac output, must influence arterial P_{O_2}. Therefore, the P_{O_2} response to step changes in PEEP (and/or recruitment maneuvers) is determined by a net balance between positive and negative effects. Positive effects include (a) reductions in the number of lung units with low $\dot{V}/\dot{Q}$ and shunt as a result of their recruitment, (b) increases in cardiac output driven by the sympathomimetic effects of CO_2 retention (the latter invariably accompanies recruitment maneuvers), and (c) a fall in oxygen uptake associated with respiratory acidosis.[98,99] Negative effects include (a) increases in low $\dot{V}/\dot{Q}$ and shunt in patients who are PEEP-resistant and in whom the increased alveolar pressure diverts blood away from normal lung toward diseased lung,[100] (b) a fall in cardiac output resulting from volume- and pressure-mediated decreases in venous return,[101] (c) a fall in cardiac output resulting from volume-mediated and pressure-mediated increases in pulmonary artery pressure and right-ventricular afterload,[102] and (d) increases in systemic oxygen consumption as a behavioral response to increased lung expansion and CO_2 retention. The cardiovascular and metabolic confounders of the recruitment response may be deduced from pulse and blood-pressure responses. Alternatively, lung recruitment ought to result in a change in respiratory system mechanics. The clinician, however, should be under no illusion that such change will be large and easy to discern from peak and plateau pressure measurements.[79] This is so because comparisons between states require careful attention to muscle relaxation and the matching of volume and time histories.[103] Finally, because clinicians generally must rely on pulse oximetry as opposed to online P_{O_2} measurements, they must consider the time delays secondary to circulation time and signal processing when assessing the recruitment response.[104]

Choosing the Appropriate Tidal Volume

The choice of V_T is arguably the most important decision a care provider makes when initiating mechanical ventilation. For many years, physicians have chosen ventilator V_T between 10 and 15 mL/kg of actual body weight. This recommendation can be traced back to the early days of positive-pressure ventilation, when this therapy was reserved for patients with neuromuscular diseases, such as poliomyelitis. Patients with near-normal lungs feel more comfortable when they are ventilated with two to three times normal V_T. In patients with injured lungs, however, a V_T of as little as 10 mL/kg of actual body weight can have devastating effects on lung structure, function, and, ultimately, outcome.[33,34,50,105]

To fully appreciate the importance of V_T settings, it is useful to consider distinct physical lung-injury mechanisms: (a) regional overinflation, caused by the application of a local stress or pressure that forces cells and tissues to assume shapes and dimensions that exceed those experienced during even the most strenuous exercise,[106,107] (b) so-called low-volume injury associated with the repeated opening

and closure of unstable lung units,[57–59] (c) inactivation of surfactant, on account of large alveolar surface-area oscillations,[108,109] and (d) interdependence mechanisms that raise cell and tissue shear stress between neighboring structures with differing mechanical properties.[110]

The injured lung is particularly susceptible to physical damage because its inspiratory capacity is reduced and its dorsal units tend to get obstructed with liquid plugs.[111,112] As a result, the greater the V_T, the greater is the likelihood that the lung will be damaged by both high-volume and low-volume injury mechanisms. One approach that requires no judgment whatsoever is simply to adopt in all patients with injured lungs the settings of the low V_T arm of the ARDS Network clinical trial,[34] which established the efficacy of lung-protective mechanical ventilation. Patients randomized to the low V_T arm received a V_T of 6 mL/kg of predicted body weight. If their end-inflation pause pressure exceeded 30 cm H_2O, then V_T was reduced further to as little as 4 mL/kg of predicted body weight. In patients in whom 6 mL/kg of predicted body weight resulted in breath stacking, effectively doubling their V_T, and in whom stacking could not be abolished with sedation, V_T was increased up to 8 mL/kg of predicted body weight. This approach was associated with a 23% reduction in all-cause mortality compared with a high-V_T strategy.[34]

The uniform adoption of the ARDS Network recommendation to set V_T to 6 mL/kg predicted body weight in all patients with injured lungs has been challenged.[85,113] Epidemiologic studies have established height and gender as opposed to actual body weight as the best predictors of absolute lung volume, including total lung capacity (TLC).[114,115] The ARDS Network investigators predicted ideal body weight from an equation based on height and gender. A graphic comparison of the two predictive equations (Fig. 5-6) shows that 1 mL/kg of predicted body weight corresponds to 1% predicted TLC. Therefore, the recommendation to restrict V_T of patients with injured lungs to 6 mL/kg of predicted body weight amounts to restricting V_T during mechanical ventilation to no more than 6% of preinjury TLC. The right-hand side of the figure shows that there is no correlation between predicted TLC and actual body weight in a population of patients who were ventilated at the Mayo Clinic in 2001.[105] Although these observations underscore the fallacy of scaling V_T to actual body weight, one may reasonably argue that scaling V_T to predicted body weight also misses the mark. To the extent to which the treatment objective of lung-protective mechanical ventilation is to minimize lung stretch, one would want to scale V_T to the capacity of the injured lung and not that of the lung before it was injured. It is well established that the injured lung has fewer recruitable lung units than a normal lung, hence the analogy to "baby lung," a term coined by Gattinoni.[112] Given the variability in lung impairment and hence lung capacity between patients with ALI, it is not surprising that a seemingly uniform V_T setting of 6 mL/kg predicted body weight produces very different parenchymal deformations in a population with lung disease.[85,113]

Lung tissue deformation can be quantified as strain. A strain is a normalized measure of deformation representing the displacement between particles in the body relative to a reference length. A recent report suggests that in normal anesthetized and mechanically ventilated pigs, lung damage occurs only when a strain greater than 1.5 to 2.0 is reached or overcome, implying that normal lungs are quite resistant to ventilator-induced injury.[116] Strain was defined as the fractional volume change between functional residual capacity and the thoracic gas volume at end-inflation. Because none of the animals were ventilated with PEEP, strain equaled V_T/functional residual capacity. Although these data are reassuring for anesthesia practice, it is important to remember that the threshold for strain injury of 2.0 may not hold in instances in which the provider increases end-expiratory

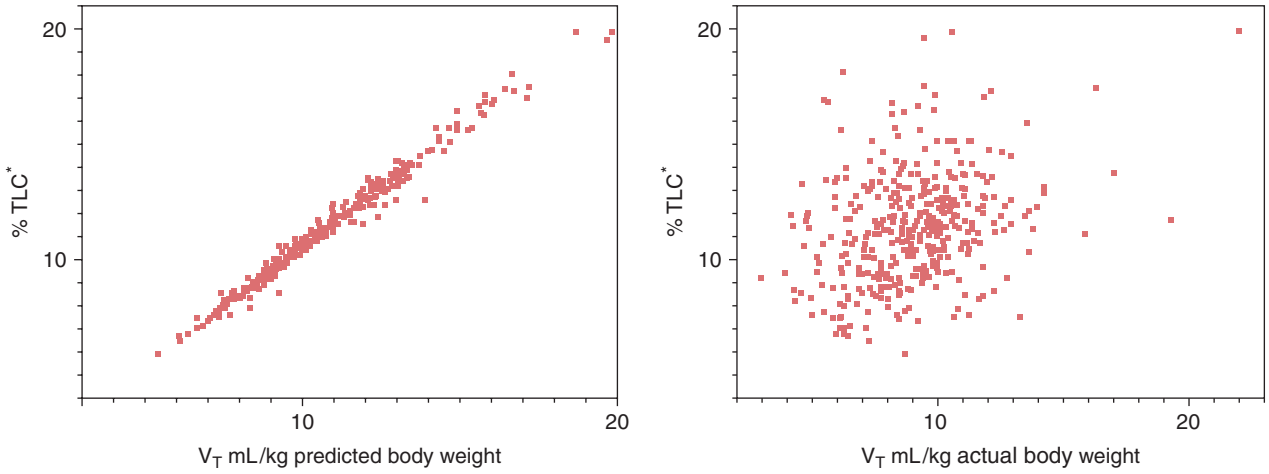

FIGURE 5-6 Predicted or ideal (*left panel*) and actual body weights (*right panel*) of 332 mechanically ventilated patients plotted against their predicted normal total lung capacity (%TLC). The predictive equations for ideal body weight and TLC are based on height and gender. Not surprisingly, the correlation between predicted body weight and predicted TLC is excellent. Note, however, that the correlation between actual body weight and percent TLC is extremely poor. The source data are from patients included in a report by Gajic et al.[105]

lung volume through the use of PEEP. Be this as it may, it must be understood that strain is critically dependent on the choice of reference volume.

Even though there is a powerful rationale for scaling V_T to the capacity of the injured lung, lung capacity or the number of recruitable lung units is rarely measured in current practice. The recommendation to limit airway inflation pressure to ≤30 cm H_2O reflects concerns about overstretching the lung,[117] but ignores the highly variable influence of the chest wall on lung volume and respiratory system mechanics in ALI.[118] Lung capacity, that is, the size of the "baby lung," can be inferred from measurements of thoracic gas volume at a defined airway pressure using either gas-dilution methods or computed tomography.[113,119] Alternatively, the inspiratory capacity can be inferred from the volume of gas that enters the lung during an inflation from 5 to 40 cm H_2O.[84] Although this approach is certainly feasible, there is currently no consensus as to what fraction of capacity V_T may safely occupy.

The results of the low-volume ventilation ARDS Network trial generated a heated debate as to whether outcome differences reflected the obsolete management of the high V_T group or improved management of the low V_T group.[120] Be this as it may, the debate produced some important questions: (a) Is the choice of V_T also important in patients who are ventilated with what generally are considered "safe" inflation pressures? (b) Are ventilator modes in which diaphragmatic activity is preserved superior to the low V_T approach used in the ARDS Network trial? (c) Should one care about V_T restrictions in patients with lung diseases other than ALI?

1. *Is the choice of V_T also important in patients who are ventilated with what generally are considered "safe" inflation pressures?* Inflating the lungs beyond TLC greatly increases the risk for barotrauma. Barotrauma is characterized by extraalveolar air and is an entity distinct from ventilator-induced lung injury.[50,51] In upright man, the transpulmonary and alveolar pressures at TLC approximate 25 and 35 cm H_2O, respectively.[121] The lungs of recumbent patients with ALI, however, are frequently not fully inflated at these pressures.[122] There is an ongoing debate as to whether mechanical ventilation with plateau pressures of less than 30 cm H_2O is safe irrespective of the choice of V_T. None of the available clinical and experimental studies is sufficiently convincing to base general management recommendations on. In the absence of convincing data, one should exercise extreme caution when departing from low V_T guidelines in patients with ALI. Indeed, circumstantial evidence and reasoning favor strict adherence to low V_T guidelines in patients with ALI because (a) spontaneous hyperventilation, which by definition never exceeds TLC, has been implicated as a cause of surfactant dysfunction and noncardiogenic pulmonary edema,[123] (b) repeated inflations of the respiratory system to pressures and volumes below TLC but above the upper inflection point of the inflation P-V curve are associated with lung injury,[81,116] and (c) a post hoc analysis of ARDS Network data suggested that patients in all plateau pressure quartiles derived benefit from V_T reductions.[124]
2. *Are ventilator modes in which diaphragmatic activity is preserved superior to the low V_T approach used in the ARDS Network trial?* Patient-assisted breathing modes, such as PSV, bilevel pressure ventilation, and APRV or NAVA, have been touted as modes of choice in the management of patients with ALI.[125,126] The evidence in support of this recommendation is not as strong as that in support of the low V_T strategy employed in the ARDS Network trial.[34] The rationale for partial support centers on the increased regional ventilation and reduced incidence of atelectasis in dorsal lung regions when diaphragmatic activity is preserved.[127,128] Whether this observation has bearing on patient survival, however, is currently unclear. It should be noted that, on general principles, V_T-related effects on lung structure and function, including injury mechanisms, are not specific to ventilator mode. Until proven otherwise it should be assumed that a V_T of 12 mL/kg predicted body weight is potentially injurious to the lungs regardless whether the patient breathes spontaneously, is mechanically ventilated in a low-pressure preset support mode, or is paralyzed and fully supported in a volume-controlled mode.
3. *Should V_T be restricted in patients with respiratory failure from conditions other than ALI?* To the extent to which lung strain and alveolar overdistension are the prevailing injury mechanisms, lungs with relatively preserved inspiratory capacity are much less susceptible to deformation injury.[116] To date, several prospective clinical trials in search of associations between intraoperative ventilator settings and biomarkers of lung stress have either uncovered no significant association or favor a low V_T strategy.[129,130] A retrospective cohort study, however, of patients who were mechanically ventilated for more than 48 hours and who did not have ALI from the outset, identified V_T as a major risk factor for the subsequent development of noncardiogenic pulmonary edema.[105] This association was recently confirmed in a prospective clinical trial.[131] Because there is no compelling reason why any patient with normal or near-normal lungs would benefit from or need a V_T of greater than 10 mL/kg of predicted body weight, V_T settings above this threshold should be used with caution.

Respiratory Rate

Having settled on a V_T and an end-expiratory volume, adjustments in the machine backup rate (f_M) should be made considering: (a) the patient's actual rate demand, (b) the patient's anticipated ventilatory requirement, and (c) the impact of the rate setting on breath timing (see Fig. 5-1). Virtually all patients with hypoxic respiratory failure are tachypneic and usually require f_M settings of between 20 and 30 breaths per minute. Unless the patient has been paralyzed

or has been so heavily sedated that spontaneous inspiratory triggering efforts are not sensed, f_M settings of 20 breaths per minute or lower are poorly tolerated because: (a) neurohumoral feedback from lung edema and inflammation induces rapid shallow breathing independent of chemoreceptive and mechanoreceptive effects on central pattern generation, (b) in the presence of a severe gas-exchange impairment, low rates and minute volumes would cause CO_2 retention, which, in turn, elicits its own disease state–independent effects on respiratory rate and drive, and (c) discrepancies between actual (triggered) and set machine (backup) rate promote breathing patterns with inverse inspiratory-to-expiratory timing ratios and double triggering. Inverse breathing-pattern ratios are not compatible with normal phase-switching mechanisms in the presence of respiratory distress. Conventional ventilator modes are not capable of varying T_I or inspiratory flow with the actual machine rate. For example, at an f_M setting of 10 breaths per minute, the T_{TOT} is 6 seconds. If the I:E ratio is set at 1:2, or if V_T and flow have been set to 0.5 and 0.25 L/s, respectively, then T_I is fixed at 2 seconds, and expiratory time (T_E) will be 4 seconds. If the patient actually triggers at 20 breaths per minute, then T_{TOT} declines to 3 seconds. T_I remains fixed at 2 seconds because it is determined by the preset machine (backup) rate, the I:E ratio, or the inspiratory-flow setting. T_E now must decrease from 4 seconds to 1 second, and the actual I:E ratio will increase from 1:2 to 2:1. At a rate of 30 breaths per minute (T_{TOT} = 2 seconds), T_E becomes 0, and "fighting the ventilator" must result. For these reasons, the f_M always should be set close to the patient's actual rate. If the actual rate is so high that effective ventilation cannot be achieved, then the patient needs additional sedation and possibly neuromuscular blockade. However, it should be emphasized that some patients, while ventilated in closed-loop modes, such as PAV or NAVA, chose rates in the high 30s and 40s, but maintain adequate gas exchange and sustainable workloads. Under these conditions, tachypnea need not imply discomfort or inadequate ventilator support!

Timing Variables

I:E RATIO

The setting of timing variables in conjunction with V_T and extrinsic PEEP determines the volume range over which lungs are cycled during ventilation. A long T_I, a high T_I/T_{TOT}, and a low mean inspiratory flow all promote ventilation with an inverse I:E ratio. Despite the considerable number of endorsements of inverse-ratio ventilation in ARDS, the beneficial effects of increasing I:E beyond 1:1 on pulmonary gas exchange tends to be marginal, provided that V_T and end-expiratory volumes are held constant.[132] All ventilators provide the option of maintaining lung volume at end inflation through the use of an inspiratory-hold time or pause time that usually is expressed as a percentage of the total cycle time (%T_{TOT}). For the purpose of defining the I:E ratio, the pause time is considered part of the inspiratory machine cycle. Long pause times favor the recruitment of previously collapsed or flooded alveoli and offer a means of shortening expiration independent of rate and mean inspiratory flow ($\dot{V}_I$). Although alveolar recruitment is a desired therapeutic end point in the treatment of patients with edematous lungs, one should at least consider that keeping the lungs expanded at high volumes (and pressures) for some time may damage relatively normal units and may cause adverse hemodynamic effects.

INSPIRATORY FLOW

Most ventilators require that mean $\dot{V}_I$ and its profile be specified. Mean $\dot{V}_I$ is equal to the ratio of V_T to T_I. Therefore, one cannot change flow without affecting at least one of the other timing variables (see Fig. 5-1). It is also important to consider that changing the flow profile from a square wave to a decelerating or sine-wave pattern prolongs T_I in ventilators that require a peak-flow setting. This is so because non–square-wave profiles have a higher peak-to-mean flow ratio; that is, it takes longer to deliver the predefined V_T than in square-wave flow delivery modes. Unless the patient is struggling, mean $\dot{V}_I$ usually is set to no more than 1 L/s during volume-preset ventilation. In patients in whom lung recruitment and oxygenation are the primary therapeutic end points, setting flow (and rate) so that the T_I/T_{TOT}) approximates 0.5 (I:E = 1) tends to achieve the goal. Increasing flow always will raise peak airway pressure, but this need not be of concern if most of the added pressure is dissipated across the endotracheal tube. On the other hand, there is experimental evidence that the rate of lung expansion is a V_T-independent risk factor for lung deformation injury. Although $\dot{V}_I$ is one of the factors that determine the regional distribution of inspired gas,[41] the lung volume–independent effects of flow on pulmonary gas exchange are too unpredictable to warrant general guidelines. Much more important is the realization that the combined effects of flow, volume, and time settings influence the functional residual capacity and the degree of dynamic hyperinflation.[40,133,134]

MEAN EXPIRATORY FLOW: THE HIDDEN VARIABLE

Mean expiratory flow is defined by the ratio of V_T to T_E. $T_E = T_{TOT} - T_I$. $T_{TOT} = 60/f$ (per minute). Because the f_M and the actual f may differ from each other in the assist-control mode (AC), the assumed and the actual T_{TOT} also may differ. Recall from the discussion on rate and timing that T_I is defined by both the set f_M and the set I:E ratio and that T_I remains constant irrespective of the actual rate. In contrast, T_E is affected by the actual breathing rate (f_A): $T_E = 60/f_A - T_I$. Therefore, the choice of volume and timing settings, together with the patient's trigger rate, determine mean expiratory flow. V_T/T_E is the principal ventilator setting-related determinant of dynamic hyperinflation. A patient with airway obstruction and a maximal forced expiratory flow (FEF) of

0.2 L/s in the mid–vital capacity range, and obviously cannot accommodate a V_T/T_E of 0.5 L/s without an increase in end-expiratory lung volume (see "Obstructive Lung Diseases" below).

Minute Ventilation

In general, minute ventilation ($\dot{V}_E$) is not a variable that is set directly by the operator, but it is the consequence of the V_T and rate settings. $\dot{V}_E$ is an important determinant of the body's CO_2 stores and consequently of the arterial CO_2 tension (Pa_{CO_2}):

$$Pa_{CO_2} = \frac{\dot{V}_{CO_2} \times k}{\dot{V}_E(1 - V_D/V_T)} \quad (8)$$

where $\dot{V}_{CO_2}$ = volume of CO_2 produced in liters per minute; V_D/V_T = dead-space-to-tidal-volume ratio, a variable with which the efficiency of the lung as a CO_2 eliminator can be approximated; and $k = 0.863$ and is a constant that scales $\dot{V}_{CO_2}$ and $\dot{V}_E$ to the same temperature and humidity.

If the main goal of mechanical ventilation were to normalize Pa_{CO_2}, then $\dot{V}_E$ would be the most important machine setting. Although a "normal" Pa_{CO_2} is one of the therapeutic end points of mechanical ventilation, at times, normocapnia can be achieved only with high lung inflation volumes and pressures. This is particularly true in patients with ALI because they are often hypermetabolic (high $\dot{V}_{CO_2}$) and in addition suffer from $\dot{V}/\dot{Q}$ mismatch (high V_D/V_T).[135] For these reasons, it is not unusual to encounter patients with ALI whose $\dot{V}_E$ requirements exceed 20 L. In the past, concerns about acid–base status dominated the choice of ventilator settings. In recent years, however, the focus on mechanical lung injury has resulted in a reappraisal of therapeutic priorities that now places the prevention of lung injury above the goal to normalize CO_2 tensions and acid–base status. The corresponding ventilation strategy has been termed *permissive hypercapnia*.[136,137] Permissive hypercapnia means that the physician accepts a Pa_{CO_2} outside the expected or "normal" range in order to minimize the potential for ventilator-induced lung injury. Because such a ventilation strategy runs contrary to the limits set by the chemoresponses of neural ventilatory control mechanisms, permissive hypercapnia usually requires heavy sedation, and sometimes paralysis of the patient. Until recently, most providers considered neuromuscular blockade as an intervention of last resort; several clinical trials, however, by the same team suggest a survival benefit associated with early, time-limited neuromuscular blockade in patients with severe ARDS.[138]

There is a great deal of interest in the consequences of hypercapnia on pulmonary vascular barrier function, signaling mediated by reactive oxygen and nitrogen species, innate immunity, and ultimately, patient survival.[2–7,139–141] The science is fascinating, but it is not sufficiently advanced to derive clinical management decisions. That said, most experts probably would agree that (a) there is no universal pH or P_{CO_2} threshold that mandates a corrective action, (b) the use of bicarbonate buffers to correct respiratory acidemia is unproven, and (c) tracheal gas insufflation generally is effective in reducing Pa_{CO_2} by 10 mm Hg or less.[142,143] Renewed interest in extracorporeal membrane oxygenation as an adjunct to lung-protective mechanical ventilation may well alter the current approach to permissive hypercapnia in years to come.[144] Except for several extracorporeal membrane oxygenation centers with high patient volumes, however, this intervention should be considered experimental at this point in time.[145]

OBSTRUCTIVE LUNG DISEASES

In patients with obstructive lung diseases, there is a reduced capacity for generating expiratory flow. When obstruction is severe enough to cause ventilatory failure, dynamic airway collapse is virtually always present during the expiratory phase of the ventilatory cycle.[10,146] This means that the passive elastic recoil forces of the relaxed respiratory system are large enough to produce maximal expiratory flows in the tidal breathing range. Such patients are prone to dynamic hyperinflation, which may adversely affect circulation,[147] may increase the risk of barotrauma,[148] and can place the diaphragm and inspiratory muscles at a mechanical disadvantage.[149–151] Consequently, the primary therapeutic goal of mechanical ventilation in obstructive lung disease is to minimize the thoracic volume about which the lungs are ventilated. Additional goals vary with the context in which airflow obstruction is observed. Patients with long-standing obstruction from emphysema or chronic bronchitis (unless they are "fighting the ventilator") usually are easy to ventilate and simply may need respiratory muscle rest and a resetting of the CO_2-response threshold to more normal values. These secondary therapeutic objectives are highly controversial. In contrast, patients with acute severe asthma often "fight the ventilator" and therefore often require sedation, neuromuscular blockade, and ventilation with permissive hypercapnia.[136,148] Such patients are prone to neuromuscular insults from glucocorticoids and paralytic agents and may require prolonged mechanical ventilation for weakness long after lung mechanics normalize.[152]

Minimizing Dynamic Hyperinflation

The ventilator management of patients who are prone to dynamic hyperinflation is best understood after a review of the expiratory mechanics of the relaxed respiratory system (see "The Mechanical Determinants of Patient–Ventilator Interactions" above). The key determinants of end-expiratory lung volume in a ventilated patient are the time constant of the respiratory system ($R \times C$) and the V_T/T_E that has been imposed by the ventilator settings.[40] Figure 5-6 underscores these concepts, which are fundamental to formulating a meaningful management plan. If it is assumed that a mechanical inflation of 1 L is initiated from Vrel at a rate of 20 breaths per minute and an I:E ratio of 1:2, the patient

has 2 seconds to exhale. In the example in Figure 5-6, the maximal mean passive expiratory flow that can be achieved in this volume range (between Vrel and Vrel + 1 L) is given by the expiratory flow-volume curve. In this example, the maximal mean flow is only 0.25 L/s. Hence, in the 2 seconds available for expiration, the patient can exhale only half the inspired volume (0.5 L) before the next inflation is initiated by the machine. Thus, the second breath is begun at a lung volume of Vrel + 0.5 L. Maximal mean expiratory flow over the new volume range (Vrel + 0.5 L and Vrel + 1.5 L) is 0.3 L/s. This flow is still insufficient for adequate lung emptying. A new steady state will be achieved only when the increase in lung volume results in a maximal mean expiratory flow of 0.5 L/s, which is equal to the obligatory mean expiratory flow imposed by the ventilator settings.

Dynamic hyperinflation is associated with an increase in alveolar pressure at end expiration. This pressure, also called *intrinsic positive end-expiratory pressure* (PEEPi), is the pressure of the respiratory system at end expiration plus any pressure generated by respiratory muscles.[10,153] In the absence of muscle activity, the degree of dynamic hyperinflation can be inferred from the end-expiratory airway occlusion pressure (PEEPi) and the elastance of the relaxed respiratory system (Ers):

$$\text{Vee} - \text{Vrel} = \text{Ers}/\text{PEEPi} \qquad (9)$$

where Vee is the volume of the lungs at end expiration.

In the presence of muscle activity from active expiration or inspiratory triggering efforts, PEEPi is a meaningless measurement. This limitation also applies to some extent to esophageal pressure-derived estimates of PEEPi. In some ventilators, PEEPi can be estimated at the "press of a button"—by pressing an end-expiratory hold button and waiting until airway opening pressure reaches a steady value. In ventilators in which the timing of end-expiratory occlusions is not automated, the measurement of PEEPi is considerably more difficult.

As illustrated in Figure 5-7, ventilator adjustments designed to minimize dynamic hyperinflation should be geared toward lowering mean expiratory flow (V_T/T_E). In a paralyzed patient with asthma, V_T can be reduced to as little as about 4 mL/kg of predicted body weight, whereas TE is prolonged through increases in mean inspiratory flow (1 to 1.5 L/s), adjustments in the I:E ratio (1:4 to 1:5), and reductions in f_M (approximately 10 breaths per minute). As discussed earlier, such a strategy is likely to produce hypercapnia, but even severe acidemia is usually well tolerated in paralyzed subjects.[154] High inspiratory-flow settings, which are required to prolong T_E, are bound to increase peak Paw and may raise concerns about barotrauma. It must be emphasized, however, that much of this added "resistive pressure" is dissipated along the endotracheal tube and proximal airways and that, on balance, increasing the rate of lung inflation seems less damaging than ventilating asthmatic lungs near TLC. Consistent with this hypothesis, the incidence of barotrauma can be reduced significantly in patients with status asthmaticus when ventilator settings are chosen to maintain peak lung volume within 1.4 L of Vrel.[148,155,156]

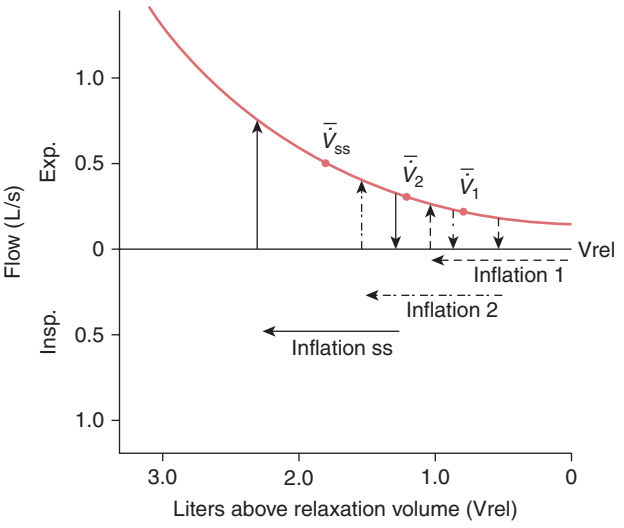

FIGURE 5-7 Diagrammatic demonstration of how insufficient expiratory flow produces dynamic hyperinflation. The *broken horizontal arrow* shows the first breath of 1 L initiated from relaxation volume (Vrel) at a rate of 20 breaths per minute and a T_I/T_{TOT}) of 0.33 (*inflation 1*). The *solid curved line* shows the maximal expiratory flow that can be produced during passive exhalation by the elastic recoil pressure of the system. In the 2 seconds available from expiration, the maximum mean expiratory flow of the first breath ($\dot{\bar{V}}_1$) is only 0.25 L/s. Therefore, only 0.5 L can be exhaled in the 2 seconds before the next inhalation of 1 L is initiated (*inflation 2*). According to the flow–volume relationship, a maximal mean expiratory flow of 0.3 L/s ($\dot{\bar{V}}_1$) can be achieved over this volume range. A steady state, during which inspiratory and expiratory volumes are matched, will be reached only when the maximal mean expiratory flow ($\dot{\bar{V}}_{ss}$) equals 0.5 L/s. (Used, with permission, from Hubmayr, et al. Physiologic approach to mechanical ventilation. *Crit Care Med.* 1990;18:103–113.)

Permissive hypercapnia and neuromuscular blockade are rarely required in patients with ventilatory failure from exacerbations of chronic obstructive lung diseases. Nevertheless, many such patients have respiratory rates in the high teens and low twenties, making it difficult to prolong T_E beyond approximately 2 seconds. This makes it virtually impossible to ventilate these patients near Vrel. Recall that patients with end-stage obstruction may have maximal expiratory flows of 0.2 L/s or less up to volumes near TLC.[146] In the nonparalyzed patient, hypercapnia sets limits to the reductions in V_T; consequently, attempts must be made to reduce the patient's respiratory rate. Sometimes the only way to minimize hyperinflation without having to resort to neuromuscular blockade is through the judicious use of sedatives with the intent of reducing inspiratory efforts until they fail to initiate a machine breath (see "Asynchrony Between the Patient's Effort and Machine-Delivered Breaths" below).

Use of Continuous Positive Airway Pressure

In patients with hypoxic respiratory failure, continuous positive airway pressure (CPAP) is used to raise lung volume to recruit closed and flooded alveoli and to improve oxygenation.

In contrast, the goal of CPAP therapy in patients with obstruction is to minimize inspiratory work.[157] Figure 5-8A shows the potential mechanisms of action of CPAP in obstructed patients schematically. The figure shows the pressure–volume relationships of the relaxed respiratory system and depicts the elastic work (Wel) needed to raise lung volume from end expiration to end inspiration (shaded area) in the presence of dynamic hyperinflation. Wel has two components: (a) work required to halt expiratory flow by counterbalancing respiratory system recoil at end expiration (W related to PEEPi) and (b) work expended during inflation of the lungs and thorax. In theory, the inspiratory work related to PEEPi (darker shaded area) can be provided externally with CPAP equal to PEEPi. As CPAP approaches PEEPi, however, additional hyperinflation may occur.[158] To guard against CPAP-induced worsening of hyperinflation, the physician can monitor peak or end-inflation hold pressure as an indicator of peak lung volume.

Figure 5-8B shows an alternative mechanism by which CPAP may reduce inspiratory Wel. CPAP may result in exhalation below the new Vrel through the recruitment of expiratory muscles.[153,159] Subsequent relaxation of the expiratory muscle inflates the lungs passively back to the new Vrel. Inspiratory muscles are unloaded because the expiratory muscles do part of the inspiratory work. This is depicted by the lighter-shaded area in Figure 5-7B. This mechanism is of limited value in patients with severe obstruction, however, because low maximal flows prevent significant reductions in lung volume below Vrel.

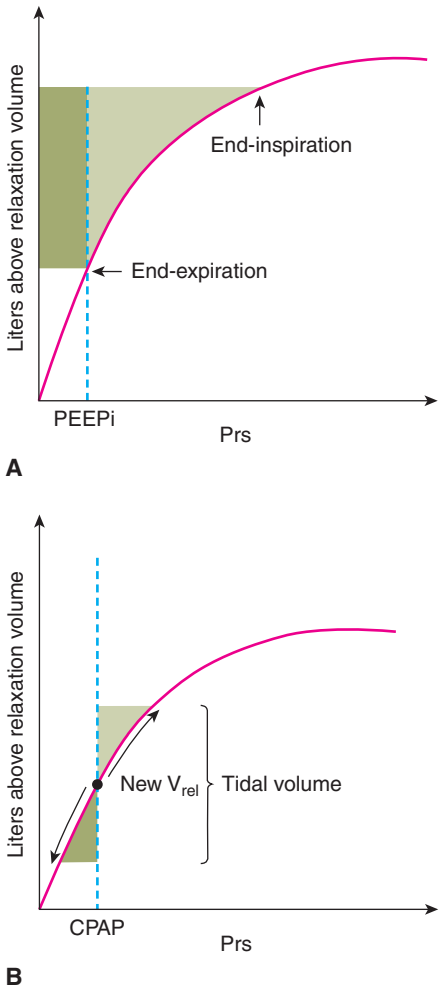

FIGURE 5-8 **A.** Effect of dynamic hyperinflation of elastic inspiratory work. The *solid curve* shows the relationship between the volume above Vrel and the recoil of the respiratory system (Prs). Dynamic hyperinflation exists. Inspiration is now initiated from a volume above Vrel. The increase in lung volume necessitates an increase in the elastic inspiratory work, which may be considered to have two components: work to halt expiratory flow (*darker-shaded area*) and work required to inflate the respiratory system (*lighter-shaded area*). **B.** Effect of CPAP on respiratory work. The *solid curve* is the pressure–volume curve of the respiratory system. With CPAP, a new Vrel is achieved. To conserve inspiratory elastic work, the patient recruits expiratory muscles and exhales below the new Vrel. The elastic work performed by the expiratory muscles is represented by the *darker-shaded area*. Relaxation of the expiratory muscles inflates the lungs back to the new Vrel without inspiratory effort. The inspiratory muscles then increase lung volume further, performing elastic inspiratory work *(lighter-shaded area)*. Hence CPAP reduced the work of the inspiratory muscles by letting the expiratory muscles do part of the inspiratory work. (Used, with permission, from Hubmayr, et al. Physiologic approach to mechanical ventilation. *Crit Care Med.* 1990;18:103–113.)

Ventilatory Pump Failure and Chronic CO_2 Retention

RESTING THE RESPIRATORY MUSCLES

In the 1970s and 1980s, much emphasis was placed on respiratory muscle fatigue as a common cause of ventilatory failure.[160] Experimental evidence that this truly occurs in a clinical setting remains elusive.[161] Without addressing all the pros and cons of minimizing the patient's contribution to inspiratory work, evidence is mounting that mechanical ventilation inhibits respiratory motor output primarily through mechanoreceptive pathways. Studies on volunteers and patients have shown that depending on state and ventilator settings, spontaneous respiratory muscle activity can be abolished, reduced, or entrained to the ventilator.[162–164] Two respiratory control aspects of patient–ventilator interactions deserve particular emphasis. First, volume-preset mechanical ventilation at settings that normalize blood-gas tensions provides no safeguard against excessive respiratory work.[44] This means that ventilating patients in a volume-preset assist-control mode offers no universal guarantee for sufficient respiratory muscle rest. Second, sleeping and obtunded patients are susceptible to PSV setting-induced central apneas.[26–29] This can lead to problems if a clinician feels compelled to increase ventilator support without a mandatory backup in order to reduce the work of breathing at night. If this is done through low IMV backup rates, then apneas may trigger ventilator alarms and cause arousal and sleep fragmentation.[25]

RESETTING THE CHEMOSTAT

It remains controversial whether patients with chronic hypercapnia and complicating acute ventilatory pump failure should be "mechanically" hyperventilated to normocapnia in an attempt to restore normal chemoresponsiveness. Proponents of such a ventilator strategy may argue that CO_2 has negative inotropic effects on respiratory muscles[165] and that experience with nocturnal ventilator assistance suggests that resetting CO_2 responsiveness is feasible in some instances.[166] Opponents argue that maintenance of normocapnia in the presence of lung disease requires a high minute volume, which could represent a fatiguing load on the respiratory muscles. As a general rule, at the time weaning is contemplated, sustainable CO_2 tensions should range between 40 and 50 mm Hg. Patients who are being weaned with CO_2 tensions in the sixties tend not to do well and are severely limited.

APPROACHES TO COMMON POTENTIALLY ADVERSE PATIENT–VENTILATOR INTERACTIONS

Respiratory Alkalosis

In spontaneously breathing normal subjects, $\dot{V}_E$ is closely coupled to Pa_{CO_2} and reflects both rate and V_T responses of the ventilatory control system. In mechanically ventilated subjects, V_T is often preset, thereby uncoupling ventilation from respiratory drive and confining the influence of neural control on the regulation of breathing to machine trigger rate. Consequently, ventilated patients with high intrinsic respiratory rates can have CO_2 tensions significantly below normal. Because associated alkalemia may contribute to arrhythmias and cardiovascular instability,[167] patients often are sedated, and the ventilator settings are adjusted with the goal of raising Pa_{CO_2}. In most instances of ventilator-induced hypocapnia, tachypnea is unrelated to hypoxemia or increased CO_2 drive per se. The causes of tachypnea may be behavioral in origin, as with pain and anxiety syndromes, or neurohumoral in origin, as with circulatory failure or in conjunction with lung and airway inflammation. Because tachypnea and increased ventilatory drive rarely are caused by CO_2 itself, any means of reducing ventilator-delivered volumes is effective in raising Pa_{CO_2}.

Asynchrony Between the Patient's Effort and Machine-Delivered Breaths

Asynchrony between vigorous spontaneous efforts and machine-delivered breaths is often referred to as "fighting the ventilator." Because inspiratory efforts often are followed by active expiration in patients with increased drive, discrepancies between machine and patient T_I cause peak Paw to exceed the alarm (safety) limit (usually set to 45 cm H_2O), resulting in premature termination of inspiratory flow and insufficient ventilation. Although the initial management should be to raise the f_M and increase inspiratory flow up to 1.5 L/s, many patients with asynchrony require sedation and, on rare occasions, neuromuscular blockade. It is of note that the mechanisms of action by which sedatives facilitate mechanical ventilation have not been fully detailed. When "fighting the ventilator" reflects pain and anxiety, their mode of action is easily understood. Not all manifestations of respiratory distress, however, are behavioral in origin. It is not known to what extent various sedatives reduce the magnitude of inspiratory efforts (drive), slow respiratory rate, or facilitate the entrainment of medullary inspiratory pattern generation to the ventilator.

Asynchrony between patient and machine breaths is very common. This is particularly true for patients with high intrinsic respiratory rates, for patients with reduced inspiratory pressure output from low drive or respiratory muscle weakness, for patients with airways obstruction, and when ventilator support results in greater than normal V_T.[13,14,16,153] For example, Figure 5-9 shows pressure and flow tracings of a patient with airways obstruction and hypercapnic ventilatory failure during PSV of 10 and 5 cm H_2O. Arterial O_2 and CO_2 tensions were normal at both settings, and the patient did not appear to be in distress. The small deflections in expiratory flow marked by arrows represent inspiratory efforts (I) during the expiratory phase of the machine cycle. In the presence of dynamic hyperinflation, Pmus must counterbalance the expiratory recoil forces (Pel) before a new machine breath can be triggered. If ΔPmus is less than Pel minus the machine trigger sensitivity, then the inspiratory effort is wasted and does not result in a machine breath. At the PSV setting of 10 cm H_2O in this example, only every third inspiratory effort results in a machine breath (3:1 coupling). The low ΔPmus, the persistence of machine inflation after the cessation of inspiratory effort, and the presence of airways obstruction, with its propensity for dynamic hyperinflation, all contribute to machine trigger failure. Note that the reduction in PSV from 10 cm H_2O to 5 cm H_2O and the lower peak volume account for the reduced number of wasted inspiratory efforts. An awareness of this problem is important because the physician otherwise may attribute an increase in machine rate following reductions in PSV to impending failure or a fatiguing load response.

Because asynchrony between the patient and machine is common, its diagnostic and prognostic significance remains uncertain. When asynchrony impairs ventilator assistance or causes patient discomfort, treatment is required in the form of sedation and adjustments in CPAP, rate, flow, or trigger mode. When "wasted" inspiratory efforts are not perceived as uncomfortable, however, it is not clear that adjustments in ventilator settings are warranted. After all, increases in machine rate to match the rate of patient efforts may cause worsening dynamic hyperinflation and may compromise circulation. Alternatively, the use of large amounts of

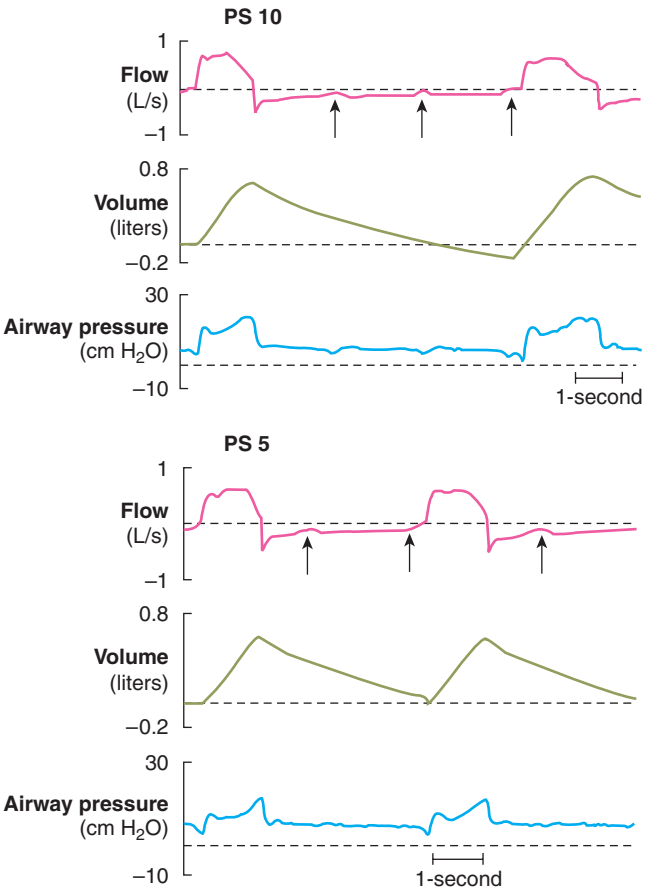

FIGURE 5-9 Flow, volume, and pressure tracings of a patient recorded during PSV with 10 cm H_2O (*upper panel*) and 5 cm H_2O (*lower panel*). Each *arrow* indicates an inspiratory effort. See the text for a further explanation. (Used, with permission, from Hubmayr RD. Coordinación de la musculatura respiratoria durante la desconexión de la ventilación mecánica en pacientes con enfermedades neurológicas (Respiratory muscle coordination during the weaning of patients with neurological diseases). In: Net A, Mancebo J, Benito S, eds. Retirada de la ventilación mecánica. Barcelona: Springer-Verlag Ibérica; 1995:164–181. With kind permission of Springer Science and Business Media.)

sedatives to assure synchrony cannot be considered harmless.[168] Patients who have been heavily sedated, but whose lung function is beginning to recover, can be particularly challenging insofar as their spontaneous tidal volumes often exceed "safe" levels. Consequently, imposing lung-protective V_T settings is commonly met with "double triggering," in effect raising machine delivered V_T to 12 mL/kg predicted body weight. Because delirium and impaired airway protective reflexes often preclude extubation, the provider is faced with the difficult decision, whether to deepen sedation, institute neuromuscular blockade, reduce flow (i.e., prolong machine T_I) at the cost of flow-starving the patient and thereby increase the patient's work of breathing, or to ignore the high tidal volumes as a transient sedation/narcotics side effect. Although each of these options is defensible on theoretical grounds, most providers will slow deep breaths if liberation from endotracheal intubation is judged imminent.

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ASSIST-CONTROL VENTILATION

6

Jordi Mancebo

Volume assist-control ventilation (ACV) is a ventilator mode in which the machine delivers the same tidal volume during every inspiration, whether initiated by the ventilator or by the patient. This occurs regardless of the mechanical load on the respiratory system and no matter how strenuous or feeble the inspiratory muscle effort. Current data indicate that ACV is still the most frequently used mode in intensive care units (ICUs).[1] Nowadays, the main reason for patients being admitted to an ICU is the need for mechanical ventilation,[2] and the most common reason to initiate mechanical ventilation is acute respiratory failure.[1,3,4] Approximately 60% of intubated, ventilated patients receive ACV.[5] This percentage is similar for patients ventilated for decompensated chronic obstructive pulmonary disease (COPD),[5] and even higher for those ventilated for acute respiratory distress syndrome (ARDS).[6]

BASIC PRINCIPLES

In ACV, mechanical breaths can be triggered by the ventilator or the patient. With the former, triggering occurs when a certain time has elapsed after the previous inspiration if the patient fails to make a new inspiratory muscle effort (Fig. 6-1). The frequency at which time triggering takes place is determined by the backup rate set on the ventilator. When patients trigger a mechanical breath, their spontaneous inspiratory effort is sensed by the machine, usually as a change in airway pressure or airflow. When such a change crosses the trigger-sensitivity threshold, the ventilator delivers the preset tidal volume. Chapter 3 provides a detailed explanation regarding the working principles of ventilators.

Mechanical breaths have precise mechanisms for being initiated (trigger variable), sustained (limit variable), and stopped (cycle variable). These are known as phase *variables*.[7] In ACV, the mechanical breaths are limited by volume and/or flow and cycled by volume or time. The inspiratory flow-shape delivery is usually a square (constant) during ACV, although some ventilators also permit sinusoidal and/or ramp (ascending or descending) gas flows.

PHYSIOLOGIC EFFECTS

Mechanical ventilation is a lifesaving supportive treatment that improves gas exchange and decreases the mechanical workload of the respiratory muscles while buying time for the patient to recover. The way mechanical ventilation is used is central to its short-term and long-term effects. Ventilator settings are a major determinant of the

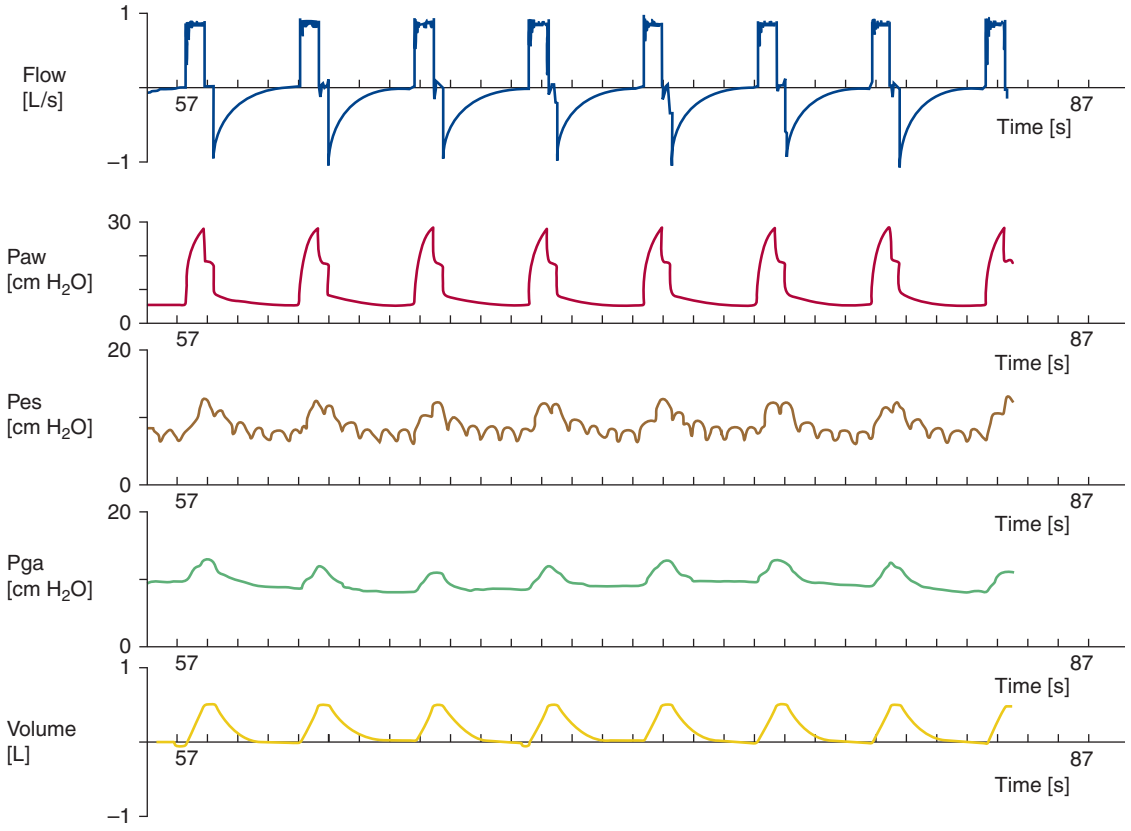

FIGURE 6-1 (*From top to bottom*) Tracings of airflow (*FLOW*), airway pressure (*Paw*), esophageal pressure (*Pes*), gastric pressure (*Pga*), and tidal volume (*VOLUME*). Each mark on the time axis denotes 1 second. These recordings were obtained in a passively ventilated patient. Each breath is time-triggered.

physiologic and clinical effects of ACV. Chapters 36 and 37 address the physiologic effects of ACV on gas exchange and cardiovascular function.

In every assisted mode, the ventilator responds to a patient's inspiratory effort. Both pressure-triggering and flow-triggering systems of modern ventilators offer high performance, and the differences are small in terms of the added work of breathing. A bench study comparing the performance of new-generation ventilators versus old-generation ventilators revealed that triggering function, pressurization capacity, and expiratory resistance are globally similar, thus suggesting that a technological ceiling has been reached.[8]

Inspiratory Muscle Effort

Marini et al[9] reported that decreases in trigger sensitivity increased the work of breathing. Although decreasing the inspiratory flow rate from 100 to 80 L/min did not affect the effort to breathe at a moderate minute ventilation (12 L/min), it increased the work expenditure significantly when the minute ventilation was doubled.[9] When inspiratory flow was reduced to 40 L/min and thus did not match the subject's demand, the work of breathing increased by 50%. Marini et al[10] later analyzed the inspiratory work at two inspiratory flow settings, 60 and 100 L/min, in twenty patients. Tidal volume was unchanged. The patients' work per liter of ventilation at both ACV inspiratory flow settings represented approximately 60% of the work dissipated during spontaneous breathing. Dead space was added in half the patients and led to marked increases in muscle effort. Patients' work of breathing did not correlate with minute ventilation, although it was highly correlated with respiratory drive and muscle strength. A decrease in inspiratory flow to 40 L/min (in five patients) led not only to an increase in effort but also to premature expiratory efforts, encroaching on the ventilator's inspiratory time. In total, these data demonstrated that inspiratory muscle effort persists throughout the inflation and that a substantial amount of muscle work is dissipated during ACV.

Ward et al[11] analyzed the inspiratory muscle effort at several inspiratory flow rates between 25 and 65 L/min and confirmed the findings by Marini et al. Cinella et al[12] compared ACV and assist pressure-controlled ventilation (PCV) and used two tidal volume settings (12 and 8 mL/kg) with an inspiratory time of 1 second and no end-inspiratory pause. At high tidal volumes, no differences were observed between the two modes in terms of breathing pattern or

indices of inspiratory muscle effort. When a tidal volume of 8 mL/kg was used (and thus inspiratory flow decreased with ACV), differences arose. Respiratory rate and occlusion pressure (a measure of respiratory motor output) tended to be higher with ACV, and indexes of inspiratory muscle effort showed a marked increase as compared with PCV. In the second part of this study,[12] the authors compared the effects of ACV and assist PCV using a fixed tidal volume (8 mL/kg) and two different settings for inspiratory time: 1 second and 0.6 second with no pause. With the longer inspiratory time, the differences were the same as stated previously. When inspiratory time was reduced and thus inspiratory flow increased during ACV, the differences between the modes virtually vanished. The study showed that both modes unloaded the respiratory muscles equally, provided that the inspiratory flow rate was set appropriately during ACV. These data confirm the importance of maintaining an inspiratory flow rate high enough to satisfactorily unload the respiratory muscles and also point out that moderate to low tidal-volume ventilation using high flow rates results in a short inspiratory time, which may not be optimal for some patients. The duration of diaphragmatic contraction was unaffected by the ventilator settings and always was shorter than 1 second.[12] Thus, it appears that the effects of high airflow settings on muscle unloading are mainly exerted at the very beginning of inspiratory efforts. Similar results were obtained by McIntyre et al[13] when comparing ACV with a pressure-limited volume-guaranteed dual mode. These authors, however, suggested that the pressure-limited breaths could reduce patient–ventilator flow dyssynchrony. These physiologic effects were confirmed in a subsequent study performed by the same group.[14]

Inspiratory Flow Settings and Breathing Pattern

A number of investigators have shown that patients[12,15–17] and healthy individuals[18,19] react to an increase in inspiratory flow with an increase in respiratory rate when tidal volume is kept constant. In these circumstances, the imposed ventilator inspiratory time shortens as flow increases. This leads to a decrease in neural inspiratory time. When tidal volume is increased by lengthening the duration of inspiratory flow, neural expiratory time increases, and respiratory rate tends to decrease. These changes have opposite effects on respiratory rate. The mechanisms explaining these responses are complex and include the Hering-Breuer reflex (inhibits inspiration and prolongs expiration), reflexes mediated by vagal mechanoreceptors, and perhaps consciousness-mediated reflexes.[20–22]

Airflow-induced changes in breathing pattern carry important clinical implications, especially in patients with dynamic hyperinflation. Because inspiratory time is made up of the time of flow delivery and inspiratory pause, Laghi et al[17] hypothesized that a decrease in ventilator inflation time would cause an increase in rate. In ten noninvasively ventilated stable patients with an obstructive airway disease, the investigators increased flow at constant tidal volume and decreased the inspiratory pause, keeping inspiratory flow and tidal volume constant. When inspiratory time was decreased (by increasing flow from 30 to 90 L/min), respiratory rate and expiratory time increased significantly. Intrinsic positive end-expiratory pressure (PEEP) diminished significantly despite the increase in respiratory rate. When inspiratory time was decreased by shortening the inspiratory pause, both respiratory frequency and expiratory time increased significantly. Again, intrinsic PEEP decreased significantly. Additionally, the higher inspiratory flow rates also decreased respiratory drive and inspiratory effort. These results suggest that imposed ventilator inspiratory time duration determines the respiratory rate and that the strategies that reduce ventilator inspiratory time, although accompanied by an increase in respiratory rate, also prolong the time for exhalation, thus decreasing intrinsic PEEP.

Respiratory Muscles

Mechanical ventilation per se can induce respiratory muscle damage,[23–25] and patients appear to exhibit diaphragmatic weakness after a period of mechanical ventilation.[26] The term *ventilator-induced diaphragm dysfunction* was coined to express the decrease in the force-generating capacity of the diaphragm that results after a period of passive controlled mechanical ventilation.[27] Le Bourdellès et al[28] showed that anesthetized, passively ventilated rats had lower diaphragmatic weight and a reduction in their force-generating capacity in comparison with spontaneously breathing control animals. Anzueto et al[29] studied sedated, paralyzed baboons under ACV for 11 days. Endurance time decreased over this period, and transdiaphragmatic pressure diminished by 25%, suggesting that the duration of passive ACV is also a relevant factor.

Sassoon et al[30] showed that 3 days of passive ventilation in rabbits led to a progressive decrease in the force-generating capacity of the diaphragm in comparison with control animals who received the same total amounts of sedatives but were breathing spontaneously. They also showed that significant diaphragmatic myofibril damage had occurred. Other authors have reported similar data.[31,32] Several investigators[33–36] have begun to elucidate the complex cellular, molecular, and gene expression mechanisms underlying passive ventilation-induced respiratory muscle damage. Such mechanisms include, among others, decreased protein synthesis, increased proteolysis, oxidative stress, and alterations in cytosol calcium metabolism.[27]

Subsequent findings by Sassoon et al[37] carry important clinical implications. The authors found that ACV, as compared with passive ACV, can attenuate markedly the decrease in diaphragmatic force induced by total inactivity in rabbits. Another investigation with clinical ramifications has shown that passive ACV improves diaphragmatic force production in rats challenged with intravascular endotoxin

as compared with equally challenged spontaneously breathing animals.[38]

An interesting issue is the combined effects of certain drugs (e.g., corticosteroids) on diaphragmatic function during passive ventilation. Maes et al[39] studied the effects of corticosteroid administration in rats (a single injection of 80 mg methylprednisolone/kg) on diaphragm function. The animals were ventilated with passive ACV for 24 hours. The main finding of this investigation was that a very high dose of corticosteroids protected the diaphragm against the deleterious effects of passive ACV. The diaphragm of treated animals maintained force, fiber dimension, and myogenin protein levels, whereas the diaphragm of nontreated animals exhibited a reduction in force, fiber atrophy, and reduced myogenin expression. The mechanism of this protective effect is the avoidance of muscle proteolysis, probably mediated by calpain. In a similar study with rabbits, Sassoon et al[40] showed that very high doses of methylprednisolone (60 mg/kg/day for 2 days) have no additive effects on diaphragmatic dysfunction induced by passive ACV. The same doses administered during ACV, however, produced a significant decrease in the maximal tetanic force elicited by the diaphragm.[40] Thus, the effects of high-dose methylprednisolone on diaphragmatic function depend on the mode of ventilation: if the muscle contracts, the effects are injurious, whereas if the muscle is passive, the effects are protective or neutral.

Important data have appeared in the last few years regarding the effects of ACV in human subjects. Levine et al[41] showed that complete diaphragmatic inactivity for 18 to 69 hours (mean: 34 hours) in brain-dead subjects resulted in marked atrophy of slow and fast-twitch fibers of the diaphragm as compared to matched controls (individuals who were ventilated for a scheduled surgery for 2 to 3 hours). The major mechanism explaining the diaphragmatic atrophy was increased muscle proteolysis. Peripheral skeletal muscles (pectoralis major) did not show histologic findings of atrophy. A subsequent study by Hussain et al,[42] conducted in humans and using a similar design, extended the findings and provided data suggesting that both protein synthesis and breakdown are involved in the diaphragmatic dysfunction.

Jaber et al[43] have investigated the time course of the decrease in diaphragm contractility in humans under passive ACV. The authors observed a progressive loss in diaphragmatic force, as reflected by measurements of tracheal pressure. The tracheal twitch pressure significantly decreased over time: mean reduction was 32% after 6 days of passive ventilation. The degree of muscle injury as detected by electron microscopy was significantly correlated with the duration of passive ACV. Again, upregulation of proteolytic systems played a major role in the ventilator-induced diaphragmatic injury induced by mechanical ventilation.

If passive ventilation is one extreme, the other is a fatiguing loading. Both extremes are harmful to the respiratory muscles. Normal subjects submitted to inspiratory-resistive loading up to a fatiguing threshold showed a decrease in diaphragmatic contractility lasting for at least 24 hours.[44] Jiang et al[45] showed diaphragmatic injury and inflammation at 3 days after a 90-minute period of acute moderate and high inspiratory-resistive loading in rabbits. The same group[46] subsequently reported a marked decrease in the force production of the diaphragm at 3 days after high inspiratory-resistive loading over the same time. Such stress also induces selective upregulation of a number of cytokines in the diaphragmatic fibers, and eventually may lead to systemic effects.[47,48] Toumpanakis et al[49] have further analyzed the effects of inspiratory resistive breathing in rat lungs. The animals received 100% oxygen during the experiments. The authors showed that after 3 to 6 hours of stressful breathing, the alveolar–capillary membrane permeability increased, the static lung compliance decreased, and significant lung inflammation developed, as manifested by changes in histology (appearance of interstitial and intraalveolar neutrophils) and cytokine expression (increase in tumor necrosis factor and interleukin levels in lung tissue).

Sleep

Research studies conducted in patients admitted to an ICU reveal that patients experience major sleep disturbances in terms of quantity and quality.[50–52] The acuity of illness, the use of medications (such as sedatives or opioids), caregiver interventions, and environmental elements are contributing factors.[50] Gabor et al[53] indicated that only 30% of sleep disruption in ventilated patients was attributable to elements of the ICU environment.

Parthasarathy and Tobin[54] sought to determine if sleep quality was influenced by the mode of ventilation. They hypothesized that sleep is more fragmented during pressure-support ventilation (PSV) as compared to ACV because of the development of central apneas. Eleven patients were ventilated with ACV at tidal volumes of 8 mL/kg, inspiratory flow rate 1 L/s, and a backup rate of four breaths below the total assisted rate. PSV was set to deliver the same tidal volume. Patients also received PSV with 100 mL of added dead space. During wakefulness, respiratory rate was similar with the two modes. During sleep, minute ventilation fell more during PSV than during ACV. Sleep fragmentation, measured as the number of arousals and awakenings, was significantly greater during PSV than during ACV (seventy-nine versus fifty-four events per hour). Six patients had apneas while receiving PSV, whereas none had apneas while receiving ACV. The percentage of patients who had congestive heart failure was significantly higher among patients exhibiting apneas than among patients free of apneas (83% vs. 20%). Minute ventilation during sleep was greater in patients who did not develop apneas, suggesting that increased drive protects against the development of apneas. The addition of dead space reduced the number

of apneas markedly: from fifty-four to four apneas per hour. These data suggest that settings that generate overassistance promote the occurrence of apneas during assisted ventilation.

Cabello et al[55] conducted a study in fifteen ventilator-dependent patients and compared three modes: ACV, PSV, and automatically adjusted PSV. The hypothesis was that PSV settings adjusted to patient ventilatory needs could improve sleep quality as compared to ACV. During ACV, settings were adjusted to provide a tidal volume of 8 mL/kg with a constant inspiratory flow of 1 L/s (and backup rate at 10 breaths/min). In the second arm, PSV was adjusted by clinicians to obtain a tidal volume of 6 to 8 mL/kg and a respiratory rate below 35 breaths/min. In the third arm, PSV was automatically regulated in a way that continuously adjusted the level of support so as to keep the patients within a comfort zone.[56] PEEP was kept constant at 5 cm H_2O, and patients were free of sedative drugs. The median tidal volumes (390 to 500 mL), respiratory rates (20 to 21 breaths/min), and minute ventilation did not differ between the three modes. Nine patients exhibited sleep apneas, and ten displayed ineffective efforts. The number of ineffective efforts per hour of sleep did not differ among the modes (mean: six to sixteen ineffective efforts per hour). The number of apneas was similar between the two PSV modalities (five to seven apneas per hour of sleep). Sleep fragmentation (arousals and awakenings per hour), sleep architecture, and sleep quantity did not differ among the modes. One explanation for the difference with the findings in the study by Parthasarathy and Tobin is that tidal volumes and minute ventilation were similar for all modes in the study of Cabello et al. The relative infrequency of ineffective efforts and apneas in this study suggests that patients were not overassisted. Together these data indicate that excessive ventilator support is central in the development of sleep fragmentation.

The clinical consequences of these sleep abnormalities are not known. Researchers have noted that sleep deprivation may generate immune suppression, loss of circadian hormonal secretion (melatonin and cortisol), profoundly alter respiratory muscles endurance and neurocognitive function, and modify the normal physiologic responses to hypoxia and hypercapnia.[51,52] Whether the sleep disturbances are a marker of brain dysfunction related to critical illness or represent a specific syndrome with an independent effect on outcomes is not known.

RATIONALE, ADVANTAGES, AND LIMITATIONS

The main reasons for using ACV are to unload the inspiratory muscles and to improve gas exchange. ACV permits complete respiratory muscle rest, which is usually the case when patients do not trigger the machine, and a variable degree of respiratory muscle work. ACV commonly achieves an improvement in gas exchange, and only a minority of ventilated patients die because of refractory hypoxemia.

During passive ventilation with ACV at a constant inspiratory flow, fundamental variables related to respiratory system mechanics, such as tidal volume, inspiratory flow, peak airway pressure, end-inspiratory plateau airway pressure, and total PEEP (the sum of external PEEP and intrinsic PEEP, if any), are measured easily (Fig. 6-2). These variables allow calculation of resistance, compliance, and the time constant of the respiratory system.

If airway pressure tracings are obtained during passive ACV as well as during patient-triggered ACV at the same settings, we can estimate a patient's work of breathing simply by superimposing the two tracings (Fig. 6-3). When patients are triggering the breaths, the end-inspiratory plateau pressure also can be influenced by the amount and duration of inspiratory muscle effort (Fig. 6-4). When mechanical breaths are triggered by the patient, the scooping on the airway pressure profile allows indirect evaluation of patient–ventilator interaction (Fig. 6-5). Such capabilities are unique to ACV. These capabilities represent a major advantage because they enable one to properly understand respiratory system mechanics and patient–ventilator interactions.

A major limitation of ACV is that it imposes a number of constraints on the variability of the patient's breathing pattern: inspiratory flow, inspiratory time, and backup rate. Adjusting ACV settings may be more complex than with pressure-limited modes. One reason is that manufacturers employ different algorithms for implementing the delivery of a tidal breath. The other reason is that during ACV it is difficult to pinpoint the inspiratory flow rate and tidal volume settings that are optimal for an individual patient. Some settings are almost impossible to achieve with ACV. For instance, the simultaneous adjustment of a moderate tidal volume at a high inspiratory flow rate will produce a short machine inspiratory time, which, under certain circumstances, may not match the patient's neural inspiratory time properly. In addition, the patient's varying ventilatory needs and the change in the mechanical properties of the respiratory system over the course of ventilation imply that periods of underassist are likely to be interspersed with periods of overassist (Fig. 6-6). These problems, however, are common to most ventilator modes.

INDICATIONS AND CONTRAINDICATIONS

ACV is indicated when a life-threatening physiologic derangement in gas exchange or cardiovascular dynamics has not been corrected by other means. Clinical manifestations of severely increased work of breathing or impending respiratory arrest are indications for instituting ACV.[57] Although there appear to be no absolute contraindications

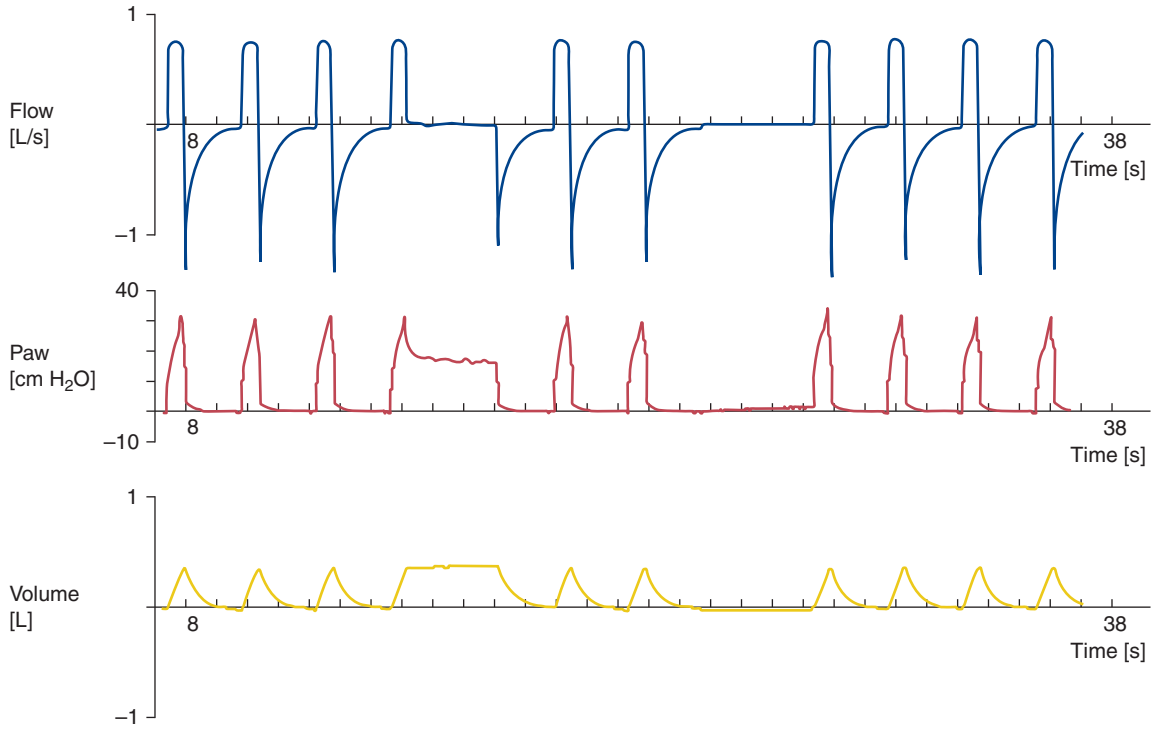

FIGURE 6-2 (*From top to bottom*) Tracings of airflow (*FLOW*), airway pressure (*Paw*), and tidal volume (*VOLUME*). Each mark on the time axis denotes 1 second. Note that expiratory flow is interrupted by the beginning of each breath, thus heralding dynamic hyperinflation. A prolonged end-inspiratory occlusion (fourth breath from the left) enables measurement of the static recoil pressure of the respiratory system. A prolonged end-expiratory occlusion (sixth breath from the left) illustrates the presence of intrinsic PEEP (3 cm H_2O). These values, together with peak airway pressure, inspiratory flow rate, and tidal volume, enable the calculation of resistance, compliance, and respiratory system time constant in passively ventilated patients.

to ACV, some of its shortcomings may prompt physicians to use other modes.

COMPARISON WITH OTHER MODES

Pressure-Controlled Ventilation, Airway Pressure Release, and Adaptive Support Ventilation in Acute Respiratory Failure Patients

During PCV, the ventilator functions as a pressure controller, and operates in a pressure-limited and time-cycled mode. With PCV, delivery of airflow and tidal volume changes according to the mechanical impedance of the respiratory system and patient inspiratory muscle effort. This mechanism implies that every increase in transpulmonary pressure is accompanied by an increase in tidal volume. Numerous studies[58–68] have compared the effects of PCV and ACV. In general, these studies included a limited number of patients and different adjustments were used. Taken together, no major differences in terms of gas exchange and major outcomes emerge between ACV and PCV.

Two studies[69,70] have analyzed outcomes between ACV and airway pressure release ventilation (APRV). APRV is similar to PCV except that it allows spontaneous breathing (in the form of continuous positive airway pressure) at any part of the ventilatory cycle. The study by Maxwell et al[70] was carried out in trauma patients: thirty-two received ACV and thirty-one were ventilated with APRV. Tidal volumes did not differ between the modes and, although patients ventilated with APRV had higher mean airway pressures, the Pa_{O_2}/FI_{O_2} ratios were similar. Days of mechanical ventilation, ICU length of stay, incidence of pneumothoraces, need for tracheostomy, and ventilator-associated pneumonia rates did not differ between the two modes. Sedative doses were similar between the modes and mortality was almost identical (approximately 6.4% in each group).

González et al[69] compared outcomes of assorted patients receiving ACV ($n = 234$) and APRV ($n = 234$) as a primary mode. The data were obtained from an observational multicenter cohort study, and a case-matched analysis on propensity score was performed. No differences in relevant clinical outcomes were detected between the modes: days of mechanical ventilation, ICU and hospital length of stay, reintubation rates, and hospital mortality. Surprisingly, the tracheostomy rate was significantly higher in the patients

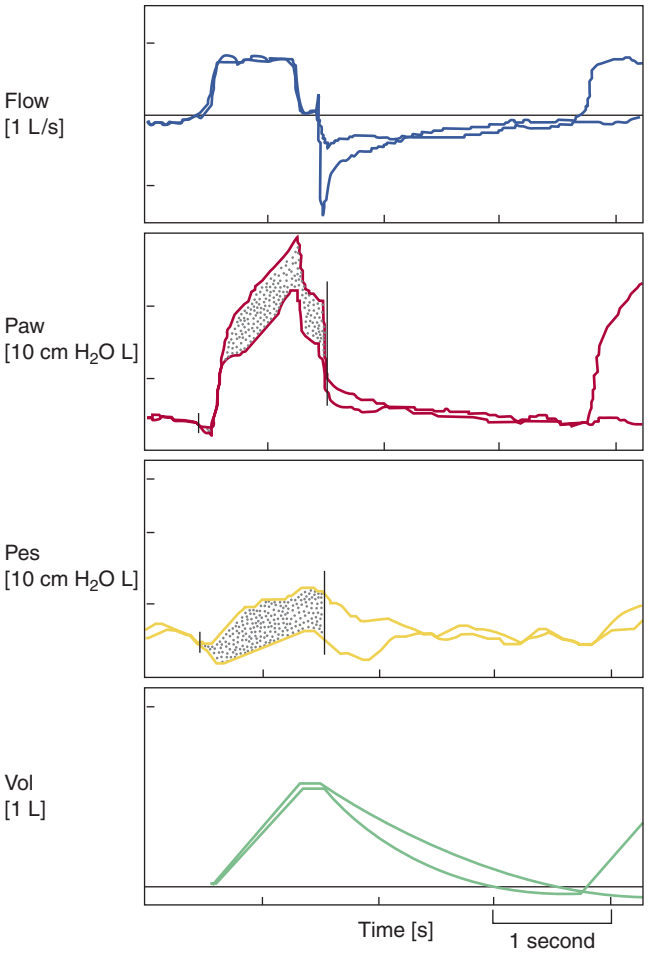

FIGURE 6-3 (*From top to bottom*) Tracings of airflow (*FLOW*), airway pressure (*Paw*), esophageal pressure (*Pes*), and tidal volume (*VOL*). Each mark on the time axis denotes 1 second. The tracings in each panel were obtained from the same individual at two different times. They were then superimposed. Ventilator settings were identical. The vertical line on the airflow, airway pressure, and esophageal pressure tracings indicates the end of ventilator's total inspiratory time. The *dotted areas* within the airway pressure and esophageal pressure tracings are identical. The *dotted areas* denote the amount of inspiratory muscle effort that the patient made during the assisted breath.

who were ventilated with APRV (20%) versus ACV (11%). Tidal volumes were similar (approximately 9 mL/kg) in both groups. The partial pressure of arterial oxygen (Pa_{O_2})-to-fractional inspired oxygen concentration (FI_{O_2}) ratio was significantly higher with APRV than with ACV (263 vs. 232 mm Hg), probably because expiratory pressure was lower with ACV (3 vs. 7 cm H_2O). The dominant factor associated with the use of this mode was geography: 196 of 234 patients receiving APRV were located in German ICUs.

Chung et al[71] compared high-frequency percussive ventilation and ACV in patients with acute respiratory failure secondary to severe burns. High-frequency percussion is pressure-limited and time-cycled at high frequency (above 300 breaths/min) and is superimposed on a biphasic inspiratory and expiratory pressure cycle set at a normal rate (approximately 10 to 15 cycles/min). A total of sixty-two patients were randomized—thirty-one to ACV and thirty-one to percussive ventilation. Patients treated with ACV received fixed tidal volumes (6 mL/kg) and PEEP levels were set according to an algorithm. Mean airway pressure was virtually identical with the two modes and a significantly better Pa_{O_2}-to-FI_{O_2} ratio was observed in the percussive ventilation group over the first 3 days. Sedation requirements and ventilator-free days did not differ between the groups. Although rescue ventilator therapy (29% vs. 6%) and barotrauma (13% vs. 0%) were more frequent during ACV as compared to percussive ventilation, no differences in mortality rates were observed between the two groups (19% each).

Adaptive-support ventilation is a closed-loop mode that selects a target ventilatory pattern based on patient weight, minimum minute volume, and a pressure limit. The ventilatory pattern is selected to minimize the total work of inspiration. Two studies have compared adaptive support ventilation with ACV. Sulemanji et al[72] conducted a bench test with different experimental scenarios of lung mechanics, PEEP levels and body weights. Target volume during ACV was 6 mL/kg and inspiratory time was 0.8 second. Adaptive-support ventilation was able to maintain a lower plateau pressure compared to ACV in settings of low compliance, high PEEP, and high minute volume. This resulted from the expected decrease in tidal volume during adaptive-support ventilation when facing a condition of high impedance, especially low compliance. During adaptive support ventilation, the plateau pressure was exceeded by approximately 2 cm H_2O, whereas in ACV the plateau pressure was exceeded by up to 10 cm H_2O.

This behavior of adaptive-support ventilation has been also reproduced in passively ventilated patients.[73,74] In the study of Iotti et al,[74] ACV (as set by the attending clinician) was compared to adaptive support ventilation (set to obtain the same minute ventilation). A total of eighty-eight patients were studied: twenty-two with no obvious lung disease, thirty-six with a restrictive disease, and thirty with obstructive disease. Adaptive support ventilation achieved a lower respiratory rate (17 vs. 19 breaths/min) and larger tidal volume than during ACV (9.4 vs. 8.4 mL/kg). Compared to ACV, adaptive support ventilation achieved a slight decrease in partial pressure of arterial carbon dioxide (Pa_{CO_2}) (from 41.6 to 40 mm Hg) and lower machine work (from 17.7 Joules/L to 14.6 Joules/L) when Pa_{CO_2} was kept constant. Compared to ACV, the obstructed patients received larger tidal volumes at lower respiratory rates. In restrictive patients, adaptive-support ventilation selected the lowest tidal volume (4.8 mL/kg) in patients with the shortest time constant (low compliance) and the highest tidal volume (10 mL/kg) in patients with normal time constant (near-normal compliance). These data suggest that adaptive support ventilation in passively ventilated patients is at least as efficient as ACV in terms of alveolar ventilation and work of breathing, and it is able to provide

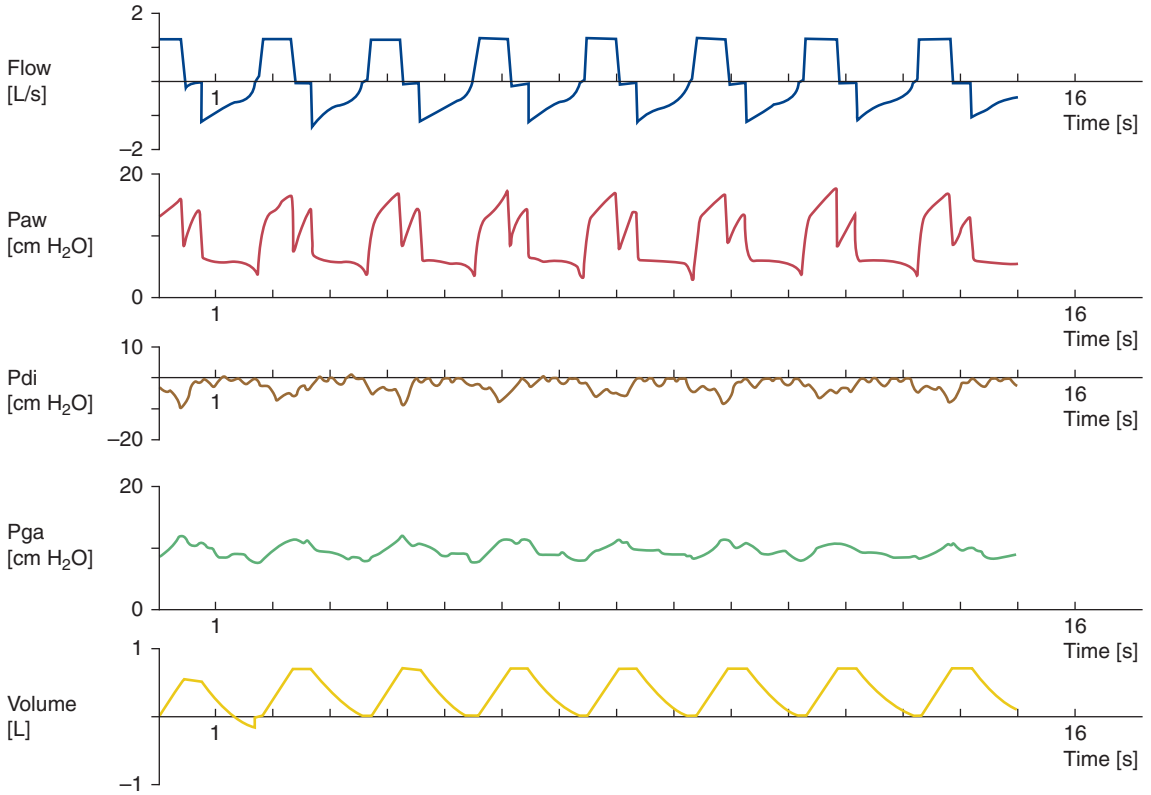

FIGURE 6-4 (*From top to bottom*) Tracings of airflow (*FLOW*), airway pressure (*Paw*), transdiaphragmatic pressure (*Pdi*), gastric pressure (*Pga*), and tidal volume (*VOLUME*). Each mark on the time axis denotes 1 second. The time of inspiratory flow is shorter than the duration of diaphragmatic contraction. This patient did not exhibit expiratory muscle recruitment, as indicated by the gastric pressure recording. Inspiratory muscles relax at the end of the inspiratory pause time, thus explaining the "M" wave shape on the airway pressure recording.

a breathing pattern tailored to the individual respiratory system mechanics.

Intermittent Mandatory Ventilation

Marini et al[75] compared ACV with intermittent mandatory ventilation (IMV) to provide 80%, 60%, 40%, 20%, and 0% of the ventilation observed during ACV (100% IMV). Tidal volume and flow settings during ACV were 10 mL/kg and 1 L/s, respectively, and average respiratory rate was 23 breaths/min. The total breathing frequency and spontaneous tidal volume increased as far as IMV assistance was decreased. Duration of inspiratory effort during assisted breaths was similar across the different IMV levels. At all levels of support, patients performed a substantial effort during the machine-assisted breaths that increased progressively as IMV assistance was withdrawn.

These data emphasize several points. Machine assistance does not suppress patient effort. There is a poor adaptation to ventilator assistance on a breath-by-breath basis, suggesting that the intensity of muscle effort is fixed before cycle initiation. Off-switching of inspiratory muscle contraction is independent of volume and flow ventilator settings. Viale et al[76] showed a rapid and gradual downregulation of inspiratory muscle effort and respiratory drive in ventilator-dependent patients with COPD, when they were switched from spontaneous unassisted breathing to PSV. This downregulation needed 6 to 8 breaths to achieve total stability, and the authors speculated that possible mechanisms explaining the gradual response were changes in Pa_{CO_2} and vagal stimulation.[76]

Leung et al[77] compared ACV, IMV (80%, 60%, 40%, and 20% levels of assist), PSV (100%, 80%, 60%, 40%, and 20% levels of assist), and a combination of IMV with PSV of 10 cm H_2O. No PEEP was used. Average tidal volume and respiratory rate during ACV were 600 mL and 17 breaths/min, respectively. The observed rate during ACV was considered equivalent to IMV 100%. PSV 100% (average: 17 cm H_2O) was the level of assistance that resulted in the same tidal volume as during ACV; this led to a respiratory rate of 16 breaths/min. Nontriggering attempts occurred with every mode and were most numerous at the highest levels of assistance. At 100% levels of assistance, the inspiratory effort and dyspnea sensation were similar among the modes, and both increased progressively when assistance was decreased. When the total inspiratory effort was partitioned between its triggering and posttriggering

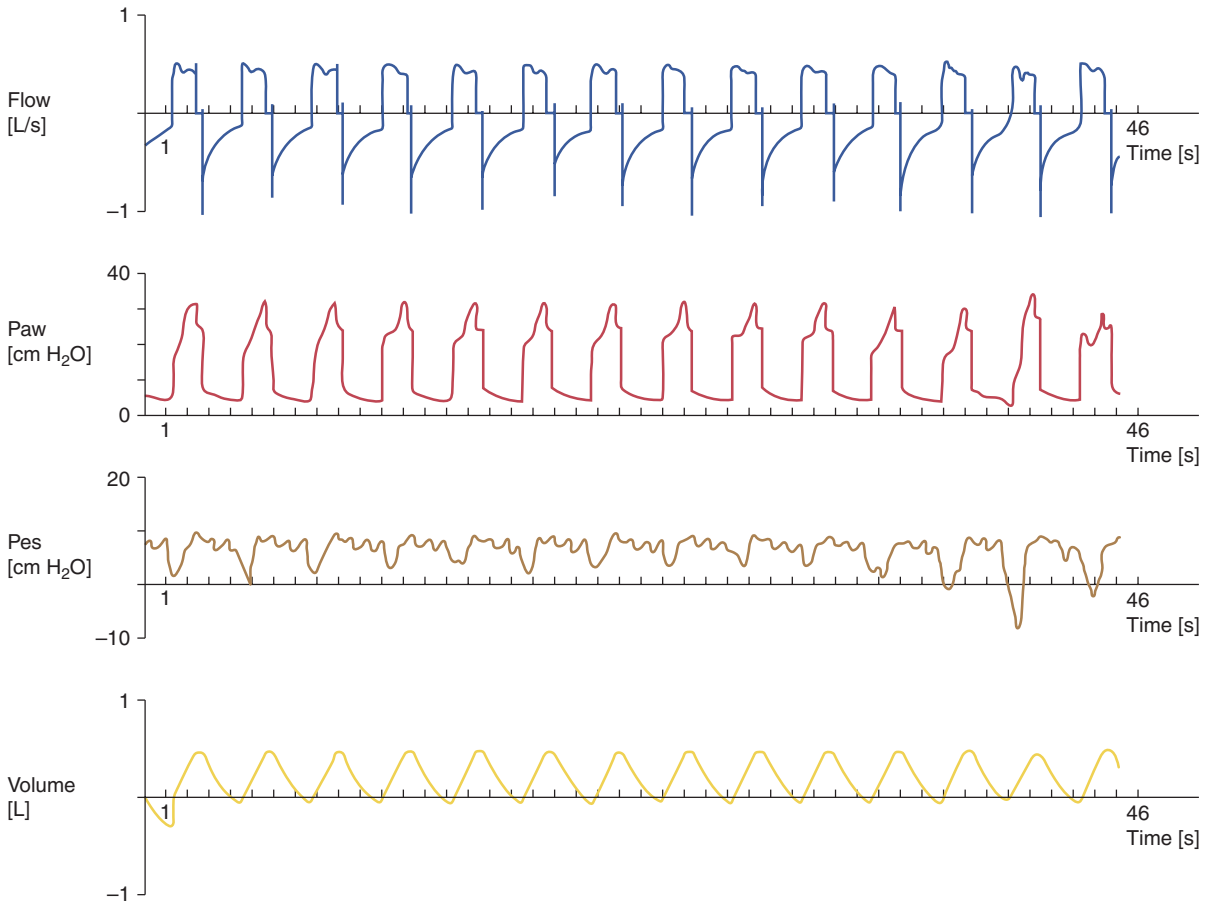

FIGURE 6-5 (*From top to bottom*) Tracings of airflow (*FLOW*), airway pressure (*Paw*), esophageal pressure (*Pes*), and tidal volume (*VOLUME*). Each mark on the time axis denotes 1 second. As seen easily on the esophageal pressure tracing, there is a highly variable inspiratory muscle effort over time, thus inducing permanent scooping on the airway pressure recording.

components, the former was unchanged despite varying levels of ventilator assistance. The posttriggering effort, however, was highly correlated with the respiratory drive at the beginning of the breath.

Outcomes in patients receiving synchronized IMV with PSV (n = 350) and patients receiving ACV (n = 1228) as primary ventilator support modes have been compared.[78] Physicians were more likely to select synchronized IMV with PSV in less-sick patients, and ACV was mostly used in severely ill patients. After adjusting for a propensity score, no differences between the modes were detected in the duration of weaning, rates of reintubation, tracheostomy, or mortality. The clinical relevance of these data is not straightforward, as the propensity score only had a moderate level of discrimination.

Pressure-Support Ventilation

Tokioka et al[79] compared ACV with PSV set to achieve the same value of peak airway pressure as during ACV. This resulted in PSV levels of 27 cm H_2O above a PEEP of 12 cm H_2O. With these settings, tidal volume was significantly higher and machine respiratory rate significantly lower during PSV. These data indicate that peak airway pressure during ACV is an inappropriate surrogate variable to adjust PSV to get similar levels of assistance. Tejeda et al[80] compared ACV with PSV in patients with respiratory failure of assorted etiologies. PSV was adjusted to deliver the same tidal volume as with ACV, although it actually resulted in significantly higher tidal volumes. The authors found a slightly better partial pressure of arterial oxygen (Pa_{O_2}) only in a subgroup of patients with restrictive disorders. Surprisingly, the calculated shunt in these patients (18% to 20%) was lower than in patients with COPD (26% to 29%). A significantly higher dead-space-to-tidal-volume ratio also was observed during PSV (24%) than during ACV (18%). These are extremely low values for patients with respiratory failure. For these reasons, the overall clinical significance of these findings is difficult to judge.

Kreit et al[81] analyzed work of breathing during ACV and PSV in eleven patients. During ACV, tidal volume was 10 to 12 mL/kg, and inspiratory flow was 75 to 80 L/min.

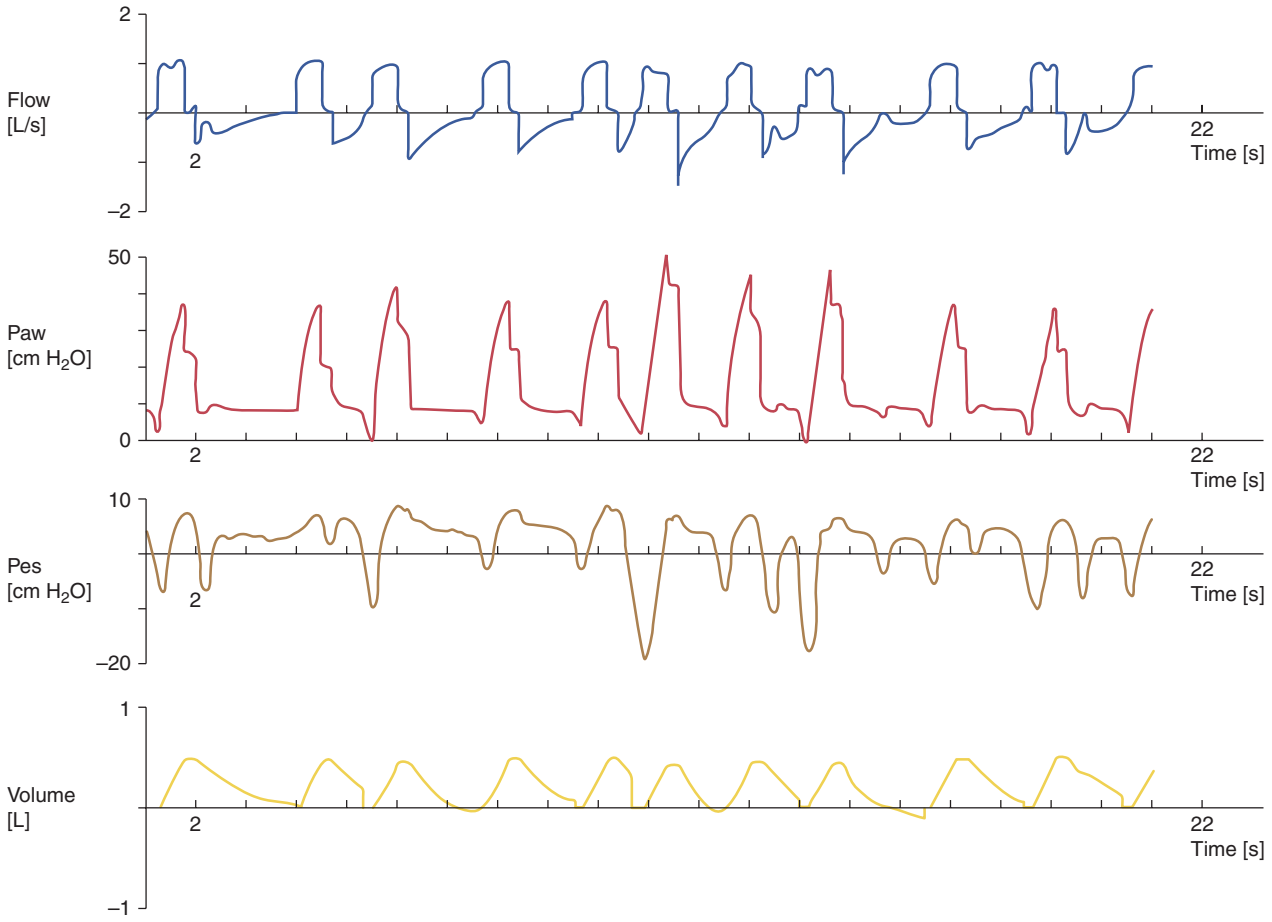

FIGURE 6-6 (*From top to bottom*) Tracings of airflow (*FLOW*), airway pressure (*Paw*), esophageal pressure (*Pes*), and tidal volume (*VOLUME*). Each mark on the time axis denotes 1 second. Note the marked breath-by-breath variability in inspiratory muscle effort (esophageal pressure swings) and airway pressure profile. There is profound patient–ventilator dyssynchrony, and numerous inspiratory attempts fail to trigger the ventilator. It is also remarkable how difficult it can be to estimate the end-inspiratory plateau airway pressure in such circumstances.

PSV was increased progressively to reach the same tidal volume as during ACV. This strategy resulted in an average pressure support of about 19 cm H_2O. The authors confirmed previous studies indicating that both work of breathing and respiratory rate vary inversely with the PSV level. With such adjustments, the patient work of breathing and minute ventilation were almost identical between the modes.

In a study not specifically designed to compare ACV with PSV, Aslanian et al[82] used the average tidal volume measured during clinician-titrated PSV for later adjustments of ACV. PSV levels were set at a target respiratory rate of between 15 and 30 breaths/min, which resulted in an average PSV of 16 cm H_2O and an average tidal volume of 500 mL. Settings during ACV were tidal volume 500 mL with an inspiratory flow rate at 50 L/min. With such adjustments, respiratory rate, minute ventilation, breathing pattern, and several indexes of inspiratory muscle effort were similar between the modes.

Chiumello et al[83] compared the effects of PSV at 5, 15, and 25 cm H_2O with assist PCV at the same levels of pressure and inspiratory time as during PSV and ACV. ACV was delivered with a square and decelerating flow pattern, both matched for the same tidal volume and peak inspiratory flow as during PSV. No differences among the modes were observed. The authors also compared clinician-titrated PSV (average 10 cm H_2O) with two ACV modes (square and decelerating flow), both at two flow settings (high and low). Tidal volume was always the same. The peak inspiratory flow obtained during PSV (0.78 L/s) was the high-flow setting for both ACV types. When high-flow settings were used, no differences were observed. The low-flow setting, approximately 0.64 L/s, induced a significant increase in work of breathing without differences in respiratory rate or gas exchange.

In a selected population of patients with acute lung injury, Cereda et al[84] studied the physiologic changes that appeared during the 48 hours after the transition from ACV to PSV. Hemodynamics and oxygenation were similar. An increase in minute ventilation and a lower Pa_{CO_2} were observed during PSV. Of forty-eight patients, ten did not tolerate PSV. These patients had a lower static

compliance and a higher dead-space-to-tidal-volume ratio when compared with patients who succeeded. These data suggest that PSV might be an alternative to ACV in carefully selected patients with acute lung injury.

Biologically Variable Ventilation

Tidal volume during ACV is, by design, delivered in a monotonous manner. To re-create the spontaneous variability of physiologic rhythms, mechanical ventilation using computer-generated biologic variability in respiratory rate and tidal volume has been used. The goal of this approach is to improve gas exchange and respiratory system mechanics, and to minimize ventilator-induced lung injury. Data comparing ACV with ventilation achieved with randomly variable tidal volumes and respiratory rates have been obtained in several experimental models of acute lung injury.[85–91] Models include different animal species (e.g., rodents, pigs, and dogs), different type of insults (e.g., chemical, mechanical, and biologic), and different ventilator settings (e.g., PEEP or no PEEP). In these short-term experiments, variable ventilation was matched to ACV in terms of minute ventilation.

All studies, except the study by Nam et al,[90] reported benefits of variable ventilation over ACV in terms of arterial oxygenation, lung mechanics, redistribution of pulmonary blood flow, degree of lung edema, proinflammatory cytokine production, histologic damage, or combinations of these. Variable ventilation may induce a better distribution of tidal volume—thereby matching ventilation to perfusion—better recruitment, and increased surfactant production. Whether these putative benefits are attributable directly to the ventilator mode per se, the type of injury, the animal species, the ventilator settings (degree of variability, PEEP levels), or the respiratory system mechanical characteristics is unclear. The physiologic effects of this new mode in patients with acute lung injury are still unknown.

VARIATION IN DELIVERY AMONG VENTILATOR BRANDS AND TROUBLESHOOTING

This section does not pretend to explain exhaustively the working principles of the dozens of different mechanical ventilators available on the market. The decision to stick with one style or another depends solely on the manufacturer. Some machines are user-configurable, but in different ways (inspiratory flow rate, inspiration-to-expiration ratio, and so on).

The fundamental settings during ACV are respiratory rate, tidal volume, and inspiratory flow rate. The backup respiratory rate determines the total breath duration, and both tidal volume and inspiratory flow rate determine the duration of mechanical inflation within a breath. The inspiratory pause, if used, appears immediately after the machine's flow delivery has ceased and thus increases the inspiratory time. The expiratory time is the only part of the breathing cycle that is allowed to vary when a patient triggers an ACV breath. For this reason, we consider machines that require inspiratory-to-expiratory ratio adjustment during ACV to be totally counterintuitive.

Some ventilators allow direct setting of respiratory rate, tidal volume, inspiratory flow rate, and inspiratory pause time. In my opinion, this is the most comprehensive approach, because the time for flow delivery depends on the tidal volume and inspiratory flow rate. Mechanical ventilators are lifesaving machines when used properly. Inappropriate use can be life-threatening. Because manufacturers follow different principles and strategies to build their machines, it is fundamental to get acquainted with the specifics of each ventilator and read the instruction manual carefully.

Recent bench studies[8,92] evaluating the performance of multiple ventilators, have shown that triggering delay, pressurization capacity during PSV, tidal volume delivery during ACV, and expiratory resistance significantly differ across a wide range of new-generation ventilators. It is interesting to note that new turbine-based ventilators perform better (on average) in terms of trigger function and pressurization quality when compared to conventional servo-valve ventilators and perform as well as the best compressed-gas ICU ventilators.

Comparisons between target tidal volume and actually delivered tidal volume during ACV at different impedance conditions, and taking into account the differences in gas temperature and humidity between inspiration and expiration, showed marked differences across various new-generation ICU ventilators.[92] Tidal volumes of 300, 500, and 800 mL were selected. Differences between targeted and delivered tidal volume ranged between −13% and +32%. Interestingly, ventilators that use compensation algorithms (which account for volume compensation when gas is compressed) delivered significantly larger tidal volumes (although less than 10% on average) than preset tidal volumes under body temperature and pressure-saturated conditions.[92] The clinical relevance of these differences needs to be carefully evaluated.

Solving problems related to mechanical equipment requires special skills and intuition. Some troubles are intrinsically related to machines and their own working principles/algorithms but can be minimized if manufacturers' recommendations are followed. It should be unnecessary to emphasize that thorough reading of the operator's manual is mandatory. Overall, the reported frequency of ventilator malfunctions seems to be very low.[93]

ADJUSTMENTS AT THE BEDSIDE

Settings to be adjusted in ACV are inspired oxygen concentration, trigger sensitivity (to be set above the threshold of autotriggering), backup rate, tidal volume, inspiratory

flow rate (or inspiratory time), end-inspiratory pause, and external PEEP, if any. When ACV is instituted after tracheal intubation, patients usually are sedated and passively ventilated. Proper measurement of end-inspiratory plateau airway pressure and calculations of compliance and airflow resistance may help in adjusting the ventilator's backup breathing pattern. The time constant of the respiratory system determines the rate of passive lung emptying. The product of three time constants is the time needed to passively exhale 95% of the inspired volume.[94,95] If expiratory time is insufficient to allow for passive emptying, this will generate hyperinflation.

During ACV, when a patient triggers a mechanical breath, the expiratory time is no longer constant. Consequently, exhaled volume might change on a cycle-to-cycle basis and modify the degree of dynamic hyperinflation. This may alter patient–ventilator synchrony and cause subsequent wasted inspiratory efforts, as is seen in patients with low inspiratory drive (i.e., patients who are sedated) and those with prolonged time constants (Fig. 6-7). One study showed that sedation level is a predictor of ineffective triggering[96] and at least two studies showed that patient–ventilator asynchrony (mainly ineffective triggering) is associated with worse outcomes: increased duration of mechanical ventilation, more tracheostomies, and lower likelihood of being discharged home.[97,98] Importantly, ineffective triggering is associated not only with sedatives and the presence of an obstructive disease, but also with excessive levels of support and excessive tidal volumes.[97–99]

Chapters 29 to 31 discuss mechanical ventilation in specific scenarios. Some general principles, however, are worth recalling. The goals of mechanical ventilation, in particular during ACV, have changed profoundly in the last years. Nowadays, moderate tidal volumes are customary, and achieving normocapnia is no longer required per se. This is the case for virtually all ventilated patients. One exception, however, is the patient with brain injury and relatively normal lungs, in whom a tight Pa_{CO_2} control is required to avoid undesirable episodes of brain ischemia or hyperemia.

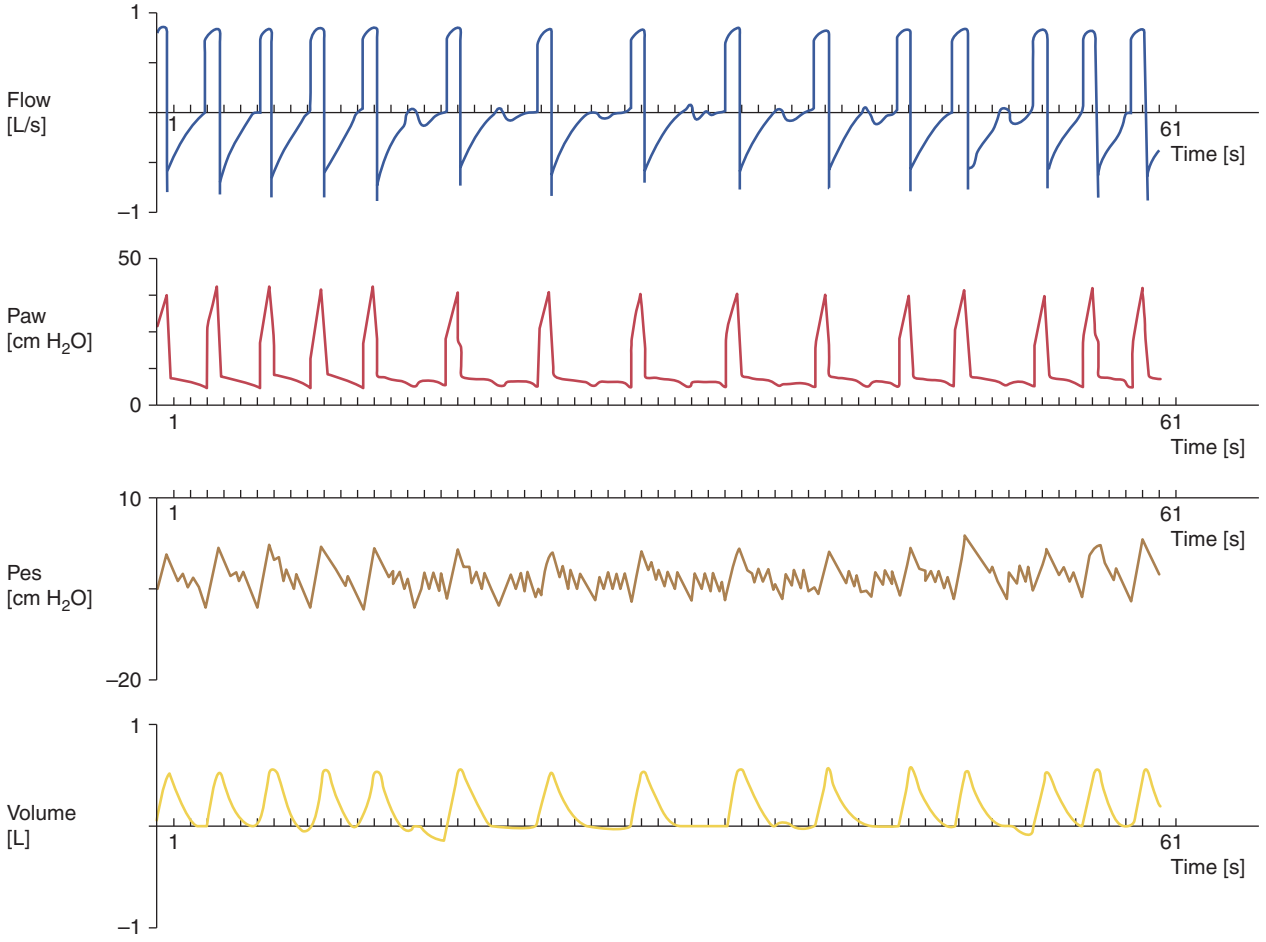

FIGURE 6-7 (*From top to bottom*) Tracings of airflow (*FLOW*), airway pressure (*Paw*), esophageal pressure (*Pes*), and tidal volume (*VOLUME*). Each mark on the time axis denotes 1 second. As can be seen from the esophageal pressure recordings, this patient was markedly unloaded and exhibited a feeble respiratory drive. As a result, multiple wasted inspiratory efforts are interspersed between the patient-triggered breaths.

In patients with COPD, data indicate that the quotient between tidal volume and expiratory time—mean expiratory flow—is the principal ventilator setting influencing the degree of dynamic hyperinflation.[94,100] An arterial oxygen saturation of approximately 90% is sufficient and is usually achieved with moderate oxygen concentrations. A respiratory rate of 12 breaths/min, tidal volume of approximately 8 mL/kg or lower, and a constant inspiratory flow rate of between 60 and 90 L/min are usually acceptable initial settings. These settings need to be readjusted, as needed, once basic respiratory system mechanics and arterial blood gases have been measured. In these patients, the goal is to keep a balance between minimizing dynamic hyperinflation and providing sufficient alveolar ventilation to maintain arterial pH near the low-normal limit, not a normal Pa_{CO_2}. When patients are receiving ACV and mechanical breaths are triggered by the patient, external PEEP counterbalances the elastic mechanical load induced by intrinsic PEEP secondary to expiratory flow limitation and decreases the breathing workload markedly.[101]

The ventilator strategy in acute asthma favors moderate tidal volumes, high inspiratory flow rates, and a long expiratory time.[102–108] These settings avoid large end-inspiratory lung volumes, thus decreasing the risks of barotrauma and hypotension. The main goal in asthma is to avoid these complications rather than to achieve normocapnia. A reasonable recommendation from physiologic and clinical viewpoints when initiating ACV is to provide an inspiratory flow of 80 to 100 L/min and a tidal volume of approximately 8 mL/kg, and to avoid end-inspiratory plateau airway pressures higher than 30 cm H_2O. The respiratory rate should be adjusted to relatively low frequencies (approximately 10 to 12 cycles/min) so as to minimize hyperinflation. These settings are accompanied most often by hypercapnia and respiratory acidosis and require adequate sedation, even neuromuscular blockade in some patients. Ventilator settings should be readjusted in accordance with the time course of changes in gas exchange and respiratory system mechanics.

Most patients with ARDS require mechanical ventilation during their illness. In this setting, mechanical ventilation is harmful when delivering high tidal volumes.[99,100] There is general agreement that end-inspiratory plateau airway pressure should be kept at values no higher than 30 cm H_2O. End-inspiratory plateau airway pressure, however, is a function of tidal volume, total PEEP level, and elastance of both the lung and chest wall. Importantly, patients with ARDS have small lungs with different mechanical characteristics of the lungs and chest wall,[101,102] and recommending a single combination of tidal volume and PEEP for all patients is not sound. Patients with more compliant lungs possibly can receive somewhat higher tidal volumes and PEEP levels than those delivered to patients with poorly compliant lungs. As in any other disease state, individual titration of tidal volume and PEEP according to underlying physiologic abnormalities and to the time course of the disease seems the most reasonable.[109] Besides, such an approach serves as a control for comparison purposes.

IMPORTANT UNKNOWNS AND THE FUTURE

Mechanical ventilation is instituted mainly to improve gas exchange and to decrease respiratory muscle workload. The clinical response to this lifesaving treatment in terms of gas exchange is usually evaluated by means of intermittent arterial blood-gas measurements, continuous pulse oximetry monitoring, and, less often, monitoring end-tidal CO_2. These measurements provide an objective way to titrate therapy. Although gas exchange is the main function of the lungs, the respiratory system also has a muscular pump that is central to its main purposes. The way we evaluate the function of the respiratory muscles clinically during the course of ACV and patient–ventilator interactions is rudimentary. Knowing how much effort a particular patient is making and how much unloading is to be provided is very difficult to ascertain on clinical grounds. Too much or too low respiratory muscle effort may induce muscle dysfunction, and this eventually could delay ventilator withdrawal.

When ACV is first initiated, the ventilator usually overcomes the total breathing workload. How long the period of respiratory muscle inactivity is to be maintained is unknown. When ACV is triggered by the patient, multiple factors interplay between the patient and the ventilator. Although high levels of assistance decrease the sensation of dyspnea, they also increase the likelihood of wasted inspiratory efforts (see Fig. 6-7). How ACV is adjusted, in particular concerning inspiratory flow rate and tidal volume settings, is a major determinant of its physiologic effects. If the settings are selected inappropriately, these may lead the physician to erroneously interpret that the problem lies with the patient and perhaps administer a sedative agent when, in reality, the patient is simply reacting against improper adjustment of the machine.

When patients are receiving ACV, they are at risk of undergoing periods of underassistance alternating with periods of overassistance. This is so because of the varying ventilatory demands (see Fig. 6-5) and because the mechanical characteristics of the respiratory system also change over time. The frequency of such phenomena and their clinical consequences are unknown. The effects of permanent monotonous tidal volume delivery, as well as whether or not sighs are to be used in this setting, also remain to be elucidated.

The only way to interpret clinically whether the patient is doing well or not during ACV is to evaluate respiratory rate and the airflow and airway pressure trajectories over time. During patient-triggered ACV, muscle effort can be estimated by superimposing the current and the passive airway pressure trajectories. Airway occlusion pressure is an important component of the airway pressure trajectory during patient-triggered breaths. This variable is a good

estimate of the central respiratory drive and is highly correlated with the inspiratory muscle effort. Such measurements would allow clinicians to analyze trends and estimate patient–ventilator interactions objectively. It is surprising that such sound noninvasive monitoring possibilities have yet to be widely implemented, and it is ironic to realize how many new ventilator modes are introduced without having passed rigorous physiologic and clinical evaluations.

SUMMARY AND CONCLUSION

The most widely used ventilator mode in mechanically ventilated patients continues to be ACV. Many of its physiologic effects are well characterized, and it is conceivable that, in the main, its purposes are met. ACV is also very versatile because it offers ventilator support throughout the entire period of mechanical ventilation. As with any other mode, the effects depend on the way ACV is implemented. The necessity to impose a number of fixed settings, in essence, tidal volume and inspiratory flow rate, implies that the respiratory pump may be unloaded suboptimally and contraction of the respiratory muscles may asynchronous with the ventilator. The clinical consequences of these phenomena are not negligible.

Since its introduction, ACV implementation has undergone considerable changes, and it is presently applied less aggressively than in the past. Thanks to an enormous amount of physiologic and clinically oriented research, we have learned that ACV can be harmful to patients, injuring both the lungs and the respiratory muscles. Future research should help us to deliver ACV in such a manner that a patient's clinical needs are served more optimally.

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INTERMITTENT MANDATORY VENTILATION

Catherine S. Sassoon

Intermittent mandatory ventilation (IMV) allows the patient to breathe spontaneously between machine-cycled or mandatory breaths. This concept originated in 1955 with an unnamed ventilator designed by Engstrom.[1,2] In the early 1970s, Kirby et al[3,4] introduced IMV as a means of ventilator support of infants with respiratory distress syndrome. In 1973, Downs et al[5] were the first to propose IMV as a method to facilitate discontinuation from mechanical ventilation in adults. Those investigators[6,7] also pioneered IMV use as a primary means of ventilator support during acute respiratory failure. Subsequently, breath-delivery design has been modified. Mandatory breaths initially delivered regardless of respiratory timing are synchronized with the patient's inspiratory effort.[8,9] This mode of ventilation has been termed *intermittent demand ventilation,*[8] *intermittent assisted ventilation,*[9] and *synchronous intermittent mandatory ventilation* (SIMV). SIMV is an established partial mechanical ventilation mode in critically ill patients, both adult[10] and neonate, worldwide.[11] Currently, however, SIMV application in adults has declined except in North America[12] and Australia–New Zealand,[13] whereas in neonates, SIMV application remains prevalent.[14] This chapter uses the terms *IMV* and *SIMV* interchangeably unless specifically indicated for clarification.

BASIC PRINCIPLES

Description

IMV is a means of ventilator support in which a preset number of positive-pressure (mandatory) breaths are delivered while the patient breathes spontaneously between the mandatory breaths. The mandatory breaths can be in the form of a preset volume (flow-limited, volume-cycled), pressure (pressure-limited, time-cycled),[15] or a combination of pressure and volume (dual control).[16] In principle, IMV is similar to controlled mechanical ventilation (CMV), in which the patient receives a predetermined number of mandatory machine-triggered breaths independent of spontaneous breathing effort. Likewise, SIMV is similar to assist-control ventilation (ACV), in which mandatory breaths are triggered by the patient. In contrast to CMV and ACV, however, in both IMV and SIMV the patient is allowed to breathe spontaneously between the mandatory breaths. In addition, with IMV and SIMV, the clinician can vary the ventilator support level according to the set IMV rate. At a high IMV rate, in which the patient's spontaneous effort is suppressed, IMV provides full ventilator support. At a zero IMV rate, it provides no support, and all breaths are spontaneous. Between these extremes, IMV provides partial ventilator support.

System Design

Three types of IMV systems are described: continuous-flow IMV and pressure-triggered and flow-triggered SIMV systems.

CONTINUOUS-FLOW IMV

The original IMV design uses a continuous-flow system.[3] Two parallel circuits—one for the patient's spontaneous breaths and the other for the mechanical breaths—are connected through a sidearm and a one-way valve, and share a common oxygen and air source. The continuous-flow IMV setup can be either an open or a closed system.[17] The open system employs a reservoir tube that has a capacity of at least 1.5 times the patient's tidal volume (V_T) and is open to the atmosphere (Fig. 7-1). For this reason, continuous positive airway pressure (CPAP) cannot be applied during the spontaneous breathing cycles. To reduce inspiratory resistance, the side port of the spontaneous breathing circuit is placed between the patient Y and the humidifier. The continuous flow of fresh gas is humidified using a venturi nebulizer. The reservoir tubing's considerable length and the inability to maintain a CPAP level make this open system cumbersome.

The closed system employs a reservoir bag (Fig. 7-2) that minimizes airway pressure fluctuations because the inspired gas flow rate may be limited by the maximum flow generated by the hospital's compressed air and oxygen source. In addition, constant positive airway pressure can be maintained during both the mandatory (i.e., positive end-expiratory airway pressure [PEEP]) and spontaneous breaths (i.e., CPAP). During spontaneous breathing, the patient breathes from the reservoir bag via the one-way valve. When the ventilator cycles, the one-way valve closes, and a positive-pressure breath is delivered to the patient. During the mechanical breath, excess gas in the reservoir bag is vented through a relief valve. Exhalation occurs through the ventilator's exhalation circuit, which is supplied with a PEEP valve.

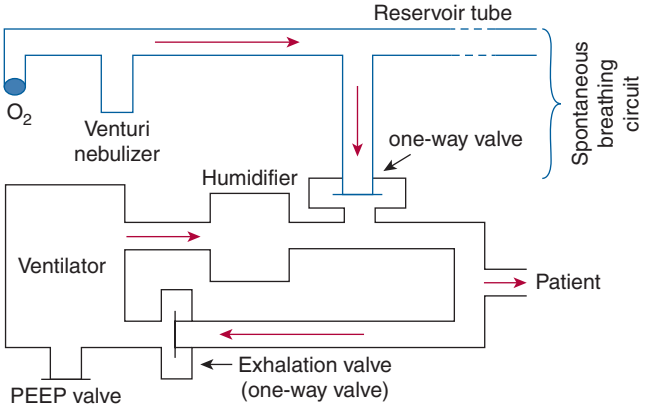

FIGURE 7-1 Continuous-flow intermittent mandatory ventilation setup with a reservoir tube. The sidearm of the spontaneous breathing circuit is connected through a one-way valve to the inspiratory limb of the ventilator circuit. The sidearm is placed between the humidifier and the patient Y. See text for further explanation. *PEEP*, positive end-expiratory pressure.

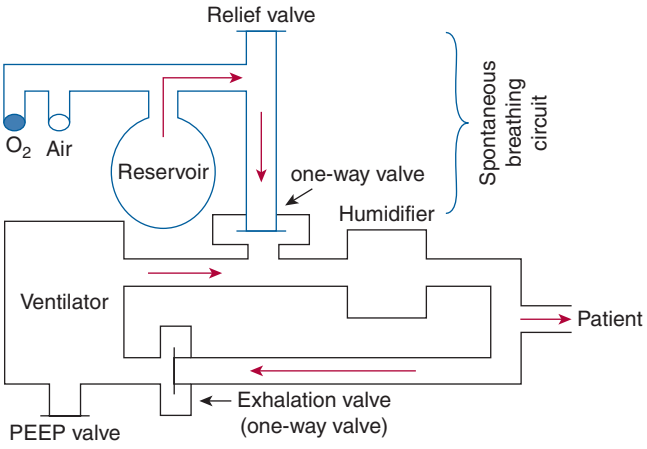

FIGURE 7-2 Continuous-flow intermittent mandatory ventilation setup with a reservoir bag. The sidearm for the spontaneous breathing circuit is connected through a one-way valve to the inspiratory limb of the ventilator circuit. The sidearm is placed proximal to the humidifier. See text for further explanation. *PEEP*, positive end-expiratory pressure.

In a continuous-flow IMV system, the inspired gas flow rate within the spontaneous breathing circuit must exceed the patient's peak inspiratory flow rate to minimize airway pressure fluctuations and hence the patient's inspiratory work. When set appropriately, spontaneous breathing in continuous-flow IMV should resemble breathing from the atmosphere.

Continuous-flow IMV has several disadvantages.[18–23] In addition to gas wastage, inaccurate V_T measurement and extra circuitry requirement, patient–ventilator asynchrony potentially can occur because mandatory breaths are not delivered in concert with the patient's inspiratory effort (Fig. 7-3A). Whereas asynchrony has no significant effect in adults,[24] in neonates, particularly preterm infants,[25] asynchrony associated with continuous-flow IMV resulted in large fluctuations of V_T[26] and lower partial pressure of arterial oxygen (Pa_{O_2})[27,28] than with SIMV. The effect of IMV on Pa_{O_2} was confirmed in a large randomized multicenter trial.[29] The degree and duration of hypoxia appear to result from active exhalation,[30] while muscle relaxant improves oxygenation.[31,32] Furthermore, the application of SIMV is superior to IMV in terms of reduced duration of mechanical ventilation, requirement for reintubation, incidence of intraventricular hemorrhage, and bronchopulmonary dysplasia.[33] In term infants and children (ages 1 month to 4 years), however, IMV or SIMV plus pressure support has similar effects on duration of mechanical ventilation, weaning, and intensive care unit length of stay.[34]

A technologically advanced continuous-flow IMV or CPAP is the flow-regulated IMV or CPAP.[35] Flow within the circuit is polled, for example, every 20 minutes and used as a feedback signal to increase the basal flow to match the patient's ventilatory demand during inspiration and subtract it during exhalation. Flow-regulated IMV or CPAP eliminates airway fluctuations and decreases imposed work during both

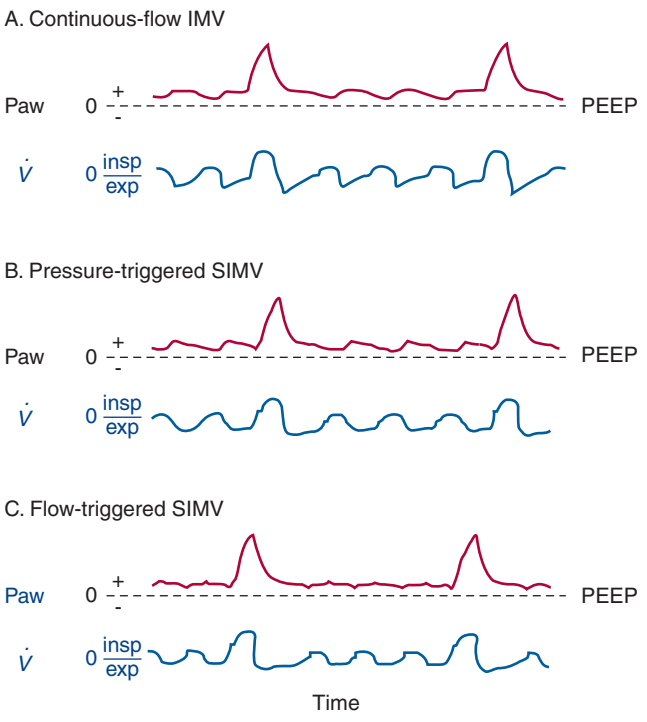

FIGURE 7-3 A. Continuous-flow intermittent mandatory ventilation (IMV). Airway pressure (*Paw*) and flow tracings ($\dot{V}$). The vertical *dashed line* indicates the onset of inspiratory flow. Minimal fluctuations of Paw are a result of circuit resistance. Large fluctuations of Paw occur when inspiratory flow rates are insufficient and a reservoir bag is not used. *exp*, Expiration; *insp*, inspiration; *PEEP*, positive end-expiratory airway pressure. **B.** Pressure-triggered synchronous intermittent mandatory ventilation (SIMV). A period of zero flow before the onset of flow (indicated by the vertical *dashed line*) can be detected on the flow tracing. Zero flow coincides with patient triggering to open the proportional valve. During the unassisted breathing after flow onset, Paw continues to drop during inspiration because of inadequate flow delivery. **C.** Flow-triggered synchronous intermittent mandatory ventilation (SIMV). Triggering phase is significantly shorter than with pressure-triggered SIMV. During the unassisted breathing following patient triggering, Paw is maintained at or slightly above the PEEP level, suggesting adequate flow delivery during inspiration.

inspiration and exhalation. Using a mechanical lung model with flow-regulated CPAP of 5 cm H_2O, the total imposed work was 3.4 mJ/breath versus 43.5 mJ/breath with a continuous-flow CPAP device and an added 20-L reservoir bag.[35]

DiBlasi et al[36] described a modified continuous-flow IMV, a combination of continuous-flow IMV and low-to-moderate frequency oscillatory ventilation. It is also called Bubble IMV (B-IMV), intended as an inexpensive means of ventilator support in infants. The device is equipped with a microprocessor-controlled rate, inspiratory timing, and pinch valve. The pinch valve regulates the path of gas exiting the system into a water-seal chamber (Fig. 7-4). The inhalation path controls the peak inspiratory pressure level of the mandatory breaths, and the exhalation path allows spontaneous breaths (i.e., CPAP), and control PEEP level. The exhalation path outlet is connected to an adjustable bubbler with three configurations: a bubbler angle of 0 degrees, 90 degrees, and 135 degrees. The bubbler angle determines the oscillation amplitudes in airway pressure (Paw). Only the bubbler angle of 135 degrees is associated with the largest pressure oscillations at a frequency of 2 to 5 Hz, and, hence, the largest change in volume (Fig. 7-5A).[37] In paralyzed juvenile rabbits with saline lavage-induced lung injury, B-IMV provided comparable peak inspiratory and mean Paw, PEEP, and Pa_{O_2} as with CMV, irrespective of the bubbler angle (Fig. 7-5B).[36] B-IMV_{135}, however, was associated with consistently low mean partial pressure of arterial carbon dioxide (Pa_{CO_2}; 35 mm Hg). Mean Pa_{CO_2} with B-IMV_{90}, B-IMV_0, and CMV was 45, 45, and 55 mm Hg, respectively. The low Pa_{CO_2} with B-IMV_{135} is caused by additional volume produced by the oscillatory pressures (DiBlasi, personal communication) (Fig. 7-5A). At this time, B-IMV is an experimental ventilator, its potential application in preterm infants with respiratory distress syndrome and its efficacy when compared with SIMV remains to be determined.

PRESSURE-TRIGGERED AND FLOW-TRIGGERED SIMV

SIMV is currently the standard for clinical use.[10,11] SIMV incorporates a demand valve that is triggered by the patient with each spontaneous breath and delivers a mandatory breath in concert with the patient's inspiratory effort. If the patient ceases to trigger the ventilator, mandatory breaths will be triggered by the machine and delivered according to the preset rate. The demand valve can be triggered by either a fall in pressure (pressure-triggered) or a change in flow (flow-triggered). In pressure-triggered SIMV, a preset pressure sensitivity must be achieved before the ventilator delivers fresh gas into the inspiratory circuit.[38,39] A noticeable delay in opening the demand valve occurs between onset of inspiratory effort and flow delivery (see Fig. 7-3B). Flow-triggered SIMV uses a preset flow sensitivity as the trigger mechanism.[38,39]

The pressure-triggering and flow-triggering characteristics of the spontaneous breaths (CPAP) are an important component of the imposed work of a SIMV system (see Chapter 3).[40,41] This situation arises because there is little adaptation to the mandatory breaths' ventilatory assistance unless the system is set at a substantial assistance level.[42] Fortunately, most modern microprocessor-based ventilators employ a remarkably responsive proportional solenoid valve such that the work imposed during the trigger phase (the interval from onset of patient effort to valve opening or flow delivery) is a small percentage of the total inspiratory work of breathing (<10% with pressure-triggered SIMV).[43] Nevertheless, flow triggering has become the preferred triggering method not only for SIMV but also for various other ventilation modes because of its faster response time and therefore shorter triggering phase compared with pressure triggering (see Fig. 7-3C).[44] In the posttrigger phase (the interval from onset of flow delivery to the end of inspiration), flow delivery with pressure triggering may not be adequate during the spontaneous breaths.[38] The feedback signal for flow delivery is the gradient between a manufacturer-determined target pressure and circuit pressure. As

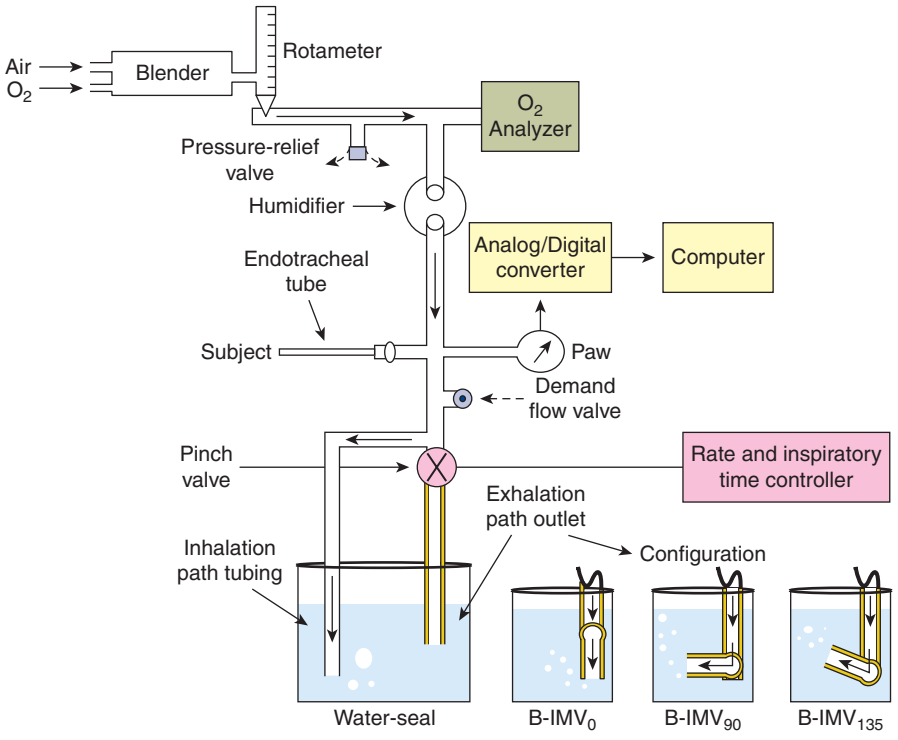

FIGURE 7-4 Bubble-intermittent mandatory ventilation (B-IMV). A modified continuous-flow IMV is equipped with a rotameter to control bias flows of air and oxygen. In line of patient's circuit are a high-pressure relief valve set to a limit of 40 cm H_2O, oxygen analyzer, humidifier, airway pressure monitor, a demand flow valve that allows room air to enter the circuit if the bias flow does not meet the patient's flow demand, and a pinch valve with a rate and inspiratory time controller. The pinch valve controls the path of gas exiting the system, either through the inhalation path with the tube placed deep in the water-seal chamber to control peak inspiratory pressure level of the mandatory breaths, or through the exhalation path to allow spontaneous breaths (continuous positive airway pressure [CPAP]) and control positive end-expiratory airway pressure (PEEP) level. The exhalation path outlet is connected to a bubbler with the angles adjustable to 0 degrees, 90 degrees, and 135 degrees (B-IMV$_0$, B-IMV$_{90}$ and B-IMV$_{135}$, respectively). (Adapted, with permission, from DiBlasi RM, Zignego JC, Smith CV, et al. Effective gas exchange in paralyzed juvenile rabbits using simple, inexpensive respiratory support devices. *Pediatr Res.* 2010;68:526–530.)

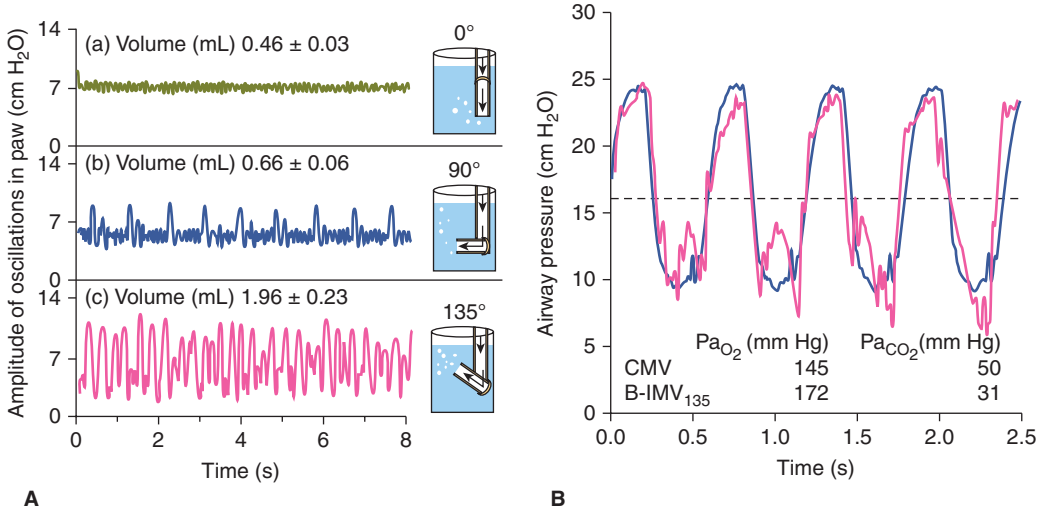

FIGURE 7-5 **A.** Effects of bubbler angle configuration on airway pressure (*Paw*) oscillations. Bubble-continuous positive airway pressure connected to a test lung with a bias flow set at 8 L/min. Bubbler angle of 135 degrees produces the largest airway pressure oscillations at a frequency of 2 to 5 Hz, and largest change in volume. **B.** Superimposed airway pressure waveform during CMV (*solid black*) and bubble-intermittent mandatory ventilation with bubble angle of 135 degrees (*B-IMV$_{135}$*) (*double gray line*) in an animal with lung injury. *Horizontal dashed line* represents mean airway pressure. (Adapted, with permission, from DiBlasi RM, Zignego JC, Tang DM, et al. Noninvasive respiratory support of juvenile rabbits by high-amplitude bubble continuous positive airway pressure. *Pediatr Res.* 2010;67:624–629.)

the pressure gradient increases, flow delivery increases. This pressure gradient can be enhanced by adding pressure support or sensing the circuit pressure at the distal end of the endotracheal tube.[45,46] From a practical standpoint, adding pressure support is preferable. Alternatively, flow delivery during the spontaneous breaths may be augmented by using changes in flow instead of pressure as a feedback signal for adding and subtracting flow from the base flow during inspiration and exhalation, respectively.[35]

The mandatory breaths can be in the form of volume-limited or pressure-limited. In preterm infants, pressure-targeted ventilation is prevalent,[14] with similar efficacy as with volume-targeted ventilation in maintaining oxygenation.[47] Augmenting flow delivery during the mandatory breaths can be accomplished by setting the pressure-attack rate sufficiently high when pressure-limited mandatory breaths are employed.[48,49] To maintain a constant V_T with pressure-limited mandatory breaths, both pressure-limited and volume-limited breaths can be combined in the form of dual control within breaths[50] or breath-to-breath ventilation (see Chapter 15).[51] Several microprocessor-based ventilators are equipped with dual-control breath-to-breath ventilation that can be applied in the SIMV mode.[52] In essence, this form of mandatory breath is a pressure-limited, time-cycled breath that uses V_T as feedback control for continuously adjusting the pressure limit to attain the set V_T. The volume signal used as feedback to the ventilator controller is the volume exiting the ventilator and not the exhaled V_T. This step prevents runaway of airway pressure that could occur if a leak in the circuit caused inaccurate measurement of exhaled volume. As an additional safety feature, if the volume exiting the ventilator exceeds 150% of the set V_T, then the ventilator exhalation valve opens, ending the mechanical inspiration. With SIMV, most microprocessor-based ventilators are able to apply pressure support and dual-control breathing to the spontaneous and mandatory breaths, respectively, to improve flow delivery and maintain a set V_T during pressure-limited mandatory breaths. In preterm infants, because changes in respiratory system mechanics occur frequently, the set V_T of the mandatory dual-control breaths not only provides a guaranteed volume when respiratory system compliance decreases but also prevents overinflation when compliance improves.[53,54] In fact, a recent report demonstrates a decrease in mortality and chronic lung disease with volume-targeted compared with pressure-targeted ventilation.[55]

PHYSIOLOGIC EFFECTS

The physiologic effects of IMV not listed in this section are discussed in comparison with other ventilation modes.

Control of Breathing and Breathing Patterns

In early IMV development, it was thought that inspiratory muscle activity is downregulated during the mandatory breaths and that IMV allows a combination of unassisted breathing with respiratory muscle rest to promote weaning.[5,56] By adjusting mandatory breath frequency, inspiratory effort could be modified until the patient resumed complete control of spontaneous breathing. Several studies, however, disproved this hypothesis.[42,57–60] Imsand et al[57] studied the neuromuscular output of patients recovering from acute exacerbation of chronic obstructive pulmonary disease who were receiving pressure-triggered SIMV. The mandatory-breath V_T was set at 10 to 12 mL/kg. Neuromuscular output was estimated from the amplitude of the integrated diaphragmatic electrical activity (Edi), measured using bipolar esophageal electrodes. Sternocleidomastoid muscle electrical activity was recorded using surface electrodes. Neuromuscular output, occlusion esophageal pressure ($Pes_{0.1}$, another index of neuromuscular output), and neural inspiratory time (T_I) were measured at three ventilator support levels: >60%, 50% to 20%, and 0% of total support. Total support was defined as the support at which Edi was suppressed completely. Only at the highest machine assistance rate did Edi decrease significantly, whereas sternocleidomastoid muscle electrical activity did not (Fig. 7-6). Moreover,

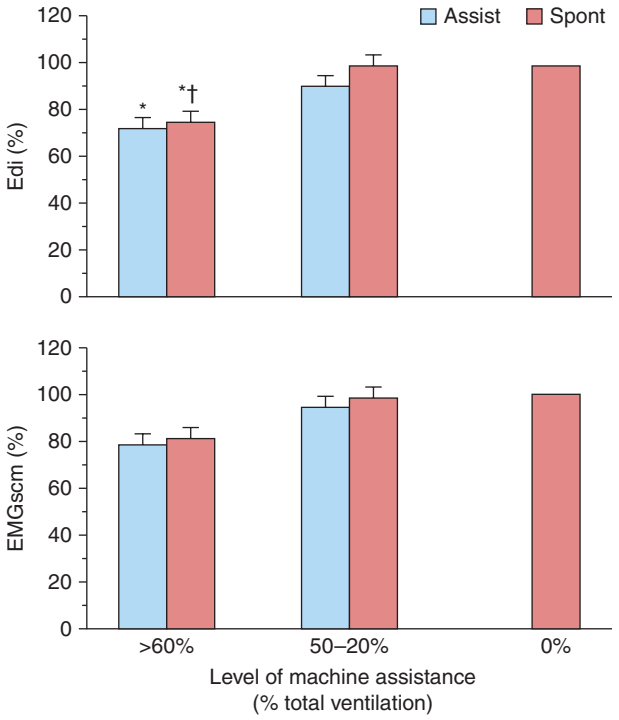

FIGURE 7-6 Peak inspiratory amplitude of integrated electrical activity of the diaphragm (*Edi*) and sternocleidomastoid muscles (*EMGscm*) at three levels of machine assistance during SIMV, expressed as a percentage of mean value of 0% of or minimal (4 breaths/min) machine assistance. Values are mean ± standard error. *$P < 0.01$ compared with 0% of machine assistance. †$P < 0.05$ compared with spontaneous cycles at 50% to 20% of assistance. *Assist*, Machine-assisted breaths; *spont*, intervening spontaneous breaths. (Adapted, with permission, from Imsand C, Feihl F, Perret C, et al. Regulation of inspiratory neuromuscular output during synchronized intermittent mechanical ventilation. *Anesthesiology.* 1994;80:13–22.)

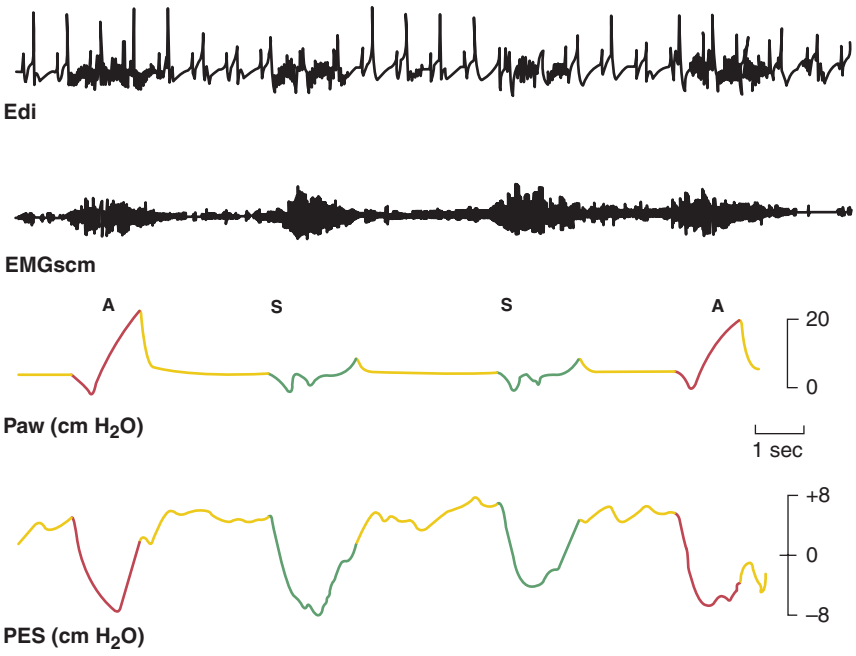

FIGURE 7-7 Electrical activity of the diaphragm (*Edi*) and sternocleidomastoid muscles (*EMGscm*) in a patient receiving SIMV. Intensity and duration of electrical activity in successive assisted (*A*) and intervening spontaneous (*S*) breaths are similar. The regular spikes in the Edi tracing are the QRS complex of the electrocardiogram signal. *Paw*, Airway pressure; *Pes*, esophageal pressure; *red lines* and *green lines*, inspiratory phase of the assisted and spontaneous breaths, respectively; *yellow lines*, expiratory phase. (Adapted, with permission, from Imsand C, Feihl F, Perret C, et al. Regulation of inspiratory neuromuscular output during synchronized intermittent mechanical ventilation. *Anesthesiology.* 1994;80:13–22.)

across all levels of ventilator support, both Edi (Fig. 7-7) and $Pes_{0\cdot1}$ of the unassisted and machine breaths were similar. $Pes_{0\cdot1}$, however, tended to increase with decreasing machine assistance. Likewise, neural T_I, defined as the interval from onset to peak Edi, was equivalent for unassisted and machine breaths.

In another study, Uchiyama et al[58] applied continuous-flow IMV to anesthetized rabbits and measured Edi with implanted electrodes into the diaphragm. The IMV rate was set at 0, 5, 10, 15, and 20 breaths/min, at which Edi was suppressed completely. Edi was expressed as percent of Edi at zero IMV rate per minute. Compared with spontaneous breathing, Edi decreased significantly only at an IMV rate of 15 breaths/min (75% of total support). In contrast with the study of Imsand et al,[57] at an IMV rate of 10 and 15 breaths/min, Edi of the mandatory breaths was absent. The difference in neuromuscular output response during mandatory breaths in the study of Uchiyama et al[58] may be related to the effect of anesthesia and the large V_T applied (15 mL/kg), causing vagally mediated inspiratory inhibition.[59] It appears that in anesthetized animals at ventilator support of 50% or greater, breath-by-breath adaptation to ventilator assistance occurred, but it was not observed in conscious humans.

In unsedated preterm infants with acute respiratory failure receiving flow-triggered SIMV, Beck et al[60] measured Edi and neural timing of mandatory breaths and the unassisted breaths immediately preceding and following the mandatory breaths using miniaturized electrodes mounted on a feeding tube. The set SIMV rate ranged from 5 to 25 breaths/min. Both Edi and neural T_I amplitude were similar for the mandatory and unassisted breaths (Fig. 7-8). In contrast to improved triggering in adults,[57] during the mandatory breaths, a substantial delay was observed from onset of Edi to flow delivery, an average of 95 milliseconds (range: 5 to 110 milliseconds). Because most of the infants had bronchiolitis and likely were hyperinflated, the authors attributed the trigger delay or inspiratory asynchrony to neuroventilatory uncoupling (a delay from onset of diaphragmatic activation to flow generation)[61] rather than to the ventilator triggering system. Neural expiratory time (T_E) of the mandatory breath, defined as the interval from peak to Edi onset of the subsequent breath, was prolonged. The relative increase in neural T_E during the mandatory breaths was related to the time the ventilator continued to inflate beyond the end of neural T_I ($R^2 = 0.66$; $P = 0.01$). This extended time was consistent with a vagally mediated reflex when pulse inflation was delivered into early expiration.[62,63] Both inspiratory asynchrony and expiratory asynchrony were present during every mandatory breath and constituted, on average, 53% of the total breath duration (Fig. 7-9). Expiratory asynchrony may result in increased peak airway pressure as the subject attempts to terminate inspiration by recruiting the expiratory muscles.[64] It also may result in increased work of breathing and discomfort and manifest as a patient "fighting the ventilator,"[65] potentially dictating sedation.

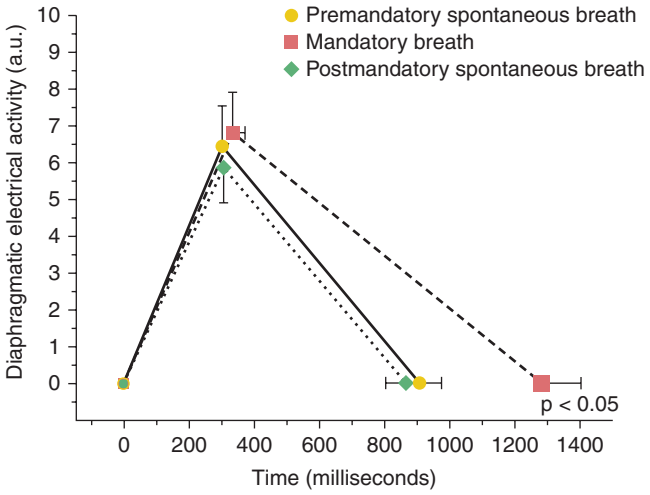

FIGURE 7-8 Diaphragmatic electrical activity (Edi) time profile for group mean data. No significant difference exists between peak Edi amplitude and neural timing on inspiration for the premandatory spontaneous breaths (*solid line*), mandatory breaths (*dashed line*), or after mandatory spontaneous breaths (*dotted line*). Neural expiratory time was prolonged significantly for the mandatory breaths (*dashed line*). The plot does not represent the shape of the Edi recruitment pattern but simply represents three points: the onset of Edi, peak of Edi, and onset of Edi of subsequent breath. Values are mean ± standard error. (Adapted, with permission, from Beck J, Tucci M, Emeriaud G, et al. Prolonged neural expiratory time induced by mechanical ventilation in infants. *Pediatr Res.* 2004;55:747–754.)

Using airway occlusion pressure ($P_{0.1}$) and mean inspiratory flow rate (V_T/T_I) as indices of neuromuscular output, Weiss et al[66] examined the effect of IMV on respiratory drive in stable ventilator-dependent patients who received mechanical ventilation for 12 to 24 hours each day. The IMV rate was initially set at 10 breaths/min and reduced gradually to 6, 3, 2, and 1 breath/min, and each level was maintained

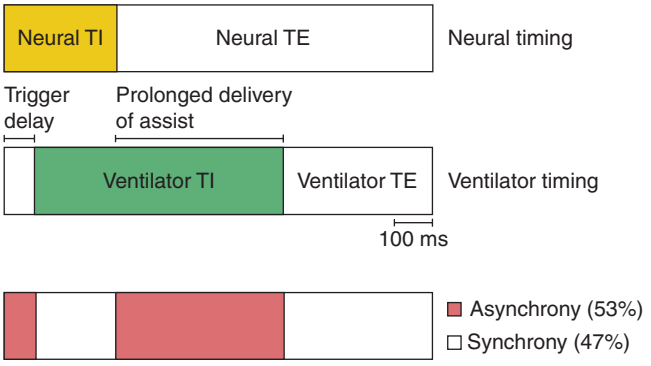

FIGURE 7-9 Inspiratory and expiratory asynchrony during mandatory breaths. Schematic of patient neural timing (*upper bar*) and ventilator timing (*middle bar*) during mandatory breaths. Upper bar shows the neural inspiratory time (T_I) (*yellow area*) and neural expiratory time (T_E) (*white area*). Middle bar shows periods of ventilator timing, including trigger delay, ventilator T_I (*green area*), and ventilator T_E. Bottom bar shows periods of infant–ventilator synchrony (*white area*) and asynchrony (*red area*). (Adapted, with permission, from Beck J, Tucci M, Emeriaud G, et al. Prolonged neural expiratory time induced by mechanical ventilation in infants. *Pediatr Res.* 2004;55:747–754.)

for 10 minutes. The V_T of the mandatory breaths was set at 8 to 12 mL/kg. End-tidal partial pressure of carbon dioxide (P_{CO_2}) and arterial oxygen saturation did not change as the IMV rate was reduced. In the presence of stable chemical input, $P_{0.1}$ and V_T/T_I measured during spontaneous breathing varied inversely with IMV rate. Increases in V_T/T_I with IMV rate reduction primarily were the result of progressive V_T augmentation because inspiratory time (T_I) and the duty cycle (T_I/T_{TOT}) remained unchanged at all IMV support levels. This V_T response probably was related to changes in CO_2 production that stimulated chemoreceptors. In acutely ill patients,[42] the effect of IMV on $P_{0.1}$, measured during spontaneous breathing, is similar to that in stable patients.[66] Using another index of neuromuscular output, dP/dt (change in pressure over change in time) of esophageal pressure at the onset of ventilator triggering, Leung et al[43] also demonstrated an inverse relationship between dP/dt and machine-assistance level.

As with neuromuscular output, IMV's effects on breathing patterns are determined by assistance level. Both V_T and unassisted breath frequency increase progressively with a decreasing IMV rate.[42,43,57,67] Because V_T of the unassisted breaths is relatively small compared with the mandatory breaths, dead-space-to-tidal-volume ratio inevitably increases. Consequently, spontaneous breathing frequency increases to maintain constant alveolar ventilation. Indeed, Pa_{CO_2} remained constant at all machine-assistance levels.[67]

The sensation of dyspnea during SIMV depends on the assistance level when applied without pressure-support ventilation (PSV) but was independent of assistance level when 10 cm H_2O of pressure support was added to the unassisted breaths.[43] During low assistance levels, dyspnea probably is secondary to increased inspiratory effort, whereas the high rate of nontriggering efforts may be responsible for the dyspnea at higher assistance levels. Knebel et al[68] also demonstrated that during the weaning trial on SIMV, the sensation of dyspnea and patient anxiety were independent of support level. In that study,[68] a PEEP of 5 cm H_2O was maintained, which might have offset the increased inspiratory muscle work with a decreasing IMV rate.[69,70]

In summary, with IMV, the neuromuscular output of both the mandatory and unassisted breaths is downregulated only at high machine-assistance levels (approximately 75% to 80% of total machine assistance).[57,58] Breath-by-breath adaptation to machine assistance does not occur. The fact that Edi was the same during assisted and preceding unassisted breathing suggests that neuromuscular output during the mandatory breaths must be determined at least in part by factors operating during the previous breath. This could be accounted for by the central neural feedback mechanism in the manner of a "memory" phenomenon as described by Eldridge[71] (see below). Neuromuscular output increases inversely with the set IMV rate. Whereas V_T and frequency increase when IMV rate decreases, neural inspiratory timing of the mandatory and unassisted breaths is of the same duration across all levels of machine assistance. Neural expiratory timing of the mandatory breaths is prolonged secondary to

mechanical T_I encroaching into neural T_E, causing expiratory asynchrony. Respiratory timing asynchrony, however, can be substantially mitigated by using inspiratory and expiratory neural triggering with a neurally adjusted ventilatory assist.[61,72,73]

Work of Breathing and Inspiratory Effort

The effect of IMV on inspiratory muscle work and inspiratory effort is, as expected, determined by the level of machine assistance, and the response is similar in adults[42,43,57] and neonates.[67] A higher number of mandatory breaths reduces total workload and inspiratory effort in patients during acute respiratory failure[42] or recovery.[43,74,75] Marini et al[42] measured work of breathing per liter of ventilation (joules per liter) and pressure-time product per breath during ACV and at SIMV support levels of 80%, 60%, 40%, 20%, and 0% of the ACV rate. When the SIMV support level was less than 80% of the ACV rate, the patient's total workload increased markedly compared with that during ACV. Moreover, at all SIMV levels, the patient expended a similar effort during both the mandatory and spontaneous breaths, as gauged by pressure-time product per breath, which reflects the energy consumed by contracting respiratory muscles (patient effort). The patient does not vary effort on a breath-by-breath basis in response to machine unloading, as confirmed by others on the basis of Edi recording.[57,60] It appears that during SIMV the heightened respiratory activity during the spontaneous breath is carried over to the subsequent mandatory breath in the manner of an "after discharge" or "memory" phenomenon.[71] In fact, when 10 cm H_2O of pressure support was applied during the intervening spontaneous breaths, inspiratory muscle effort decreased not only during the intervening breaths but also during the mandatory breaths (Fig. 7-10).[43] This afterdischarge phenomenon is central in origin and unrelated to chemoreceptor or mechanoreceptor feedback or the state of sleep or wakefulness.[71,76]

The patient workload during IMV is determined not only by machine-assistance level, but also by the IMV system employed.[74,75] Patient workload or inspiratory effort during spontaneous breathing cycles with flow-triggered SIMV was significantly less than with a pressure-triggered SIMV system,[74,75] particularly at a relatively low SIMV rate.[75] The effect, however, of the triggering system on patient mandatory breath workload is conflicting. Sassoon et al[75] demonstrated that the triggering system had no effect on patient mandatory-breath workload. In contrast, Giuliani et al[74] found that patient mandatory-breath workload was significantly less with flow-triggered than with pressure-triggered SIMV irrespective of the mandatory-breath type (whether SIMV was flow-limited or pressure-limited). Moreover, patient workload with combined flow-triggered and pressure-limited mandatory breaths was lower than the other combinations of triggering and mandatory-breath types (flow-triggered flow limit and pressure-triggered flow and pressure limit).[74] The decrease was so substantial that the pressure-time product per breath of the mandatory breath was significantly less than that of the intervening spontaneous breaths. It is not clear as to why the data of Giuliani et al[74] differed from the data of others[42,43,57,60] who demonstrated the lack of breath-by-breath adaptation to machine unloading.

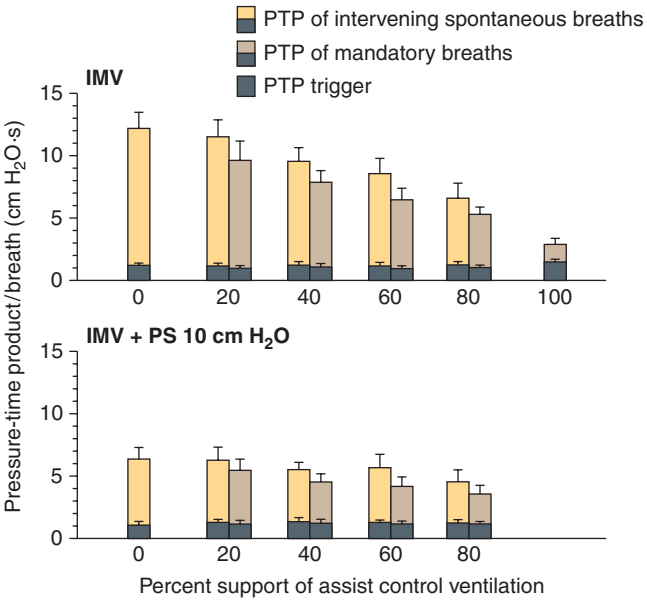

FIGURE 7-10 Pressure-time product (PTP) per breath during synchronous intermittent mandatory ventilation (IMV) in the presence and absence of pressure support (PS). The addition of 10 cm H_2O PS to the intervening spontaneous breaths decreased the overall PTP per breath. PTP per breath, however, did not differ between the mandatory and intervening spontaneous IMV breaths at each level of machine assistance, irrespective of whether PS was present or absent. (Adapted, with permission, from Leung, et al. *Am J Respir Crit Care Med.* 1997;155:1940–1948. Reprinted with permission of the American Thoracic Society. Copyright © American Thoracic Society.)

In summary, during acute respiratory failure or recovery, patient workload during SIMV remains substantial unless the SIMV support is equivalent to or greater than 80% of the support during ACV.[42,43] IMV often allows adequate gas exchange at lower support levels[77] (see the section Intermittent Mandatory Ventilation and Assist-Control Ventilation) but at the expense of increased patient workload.[42,43,57]

RATIONALE, ADVANTAGES, AND LIMITATIONS

IMV was developed as an alternative to CMV and ACV. The rationale for developing IMV was based on the premise that by maintaining spontaneous breathing amid the mechanical breaths, (a) machine breaths can be titrated to adjust alveolar ventilation, thereby decreasing the incidence of respiratory alkalemia,[78] (b) distribution of inspired gas and ventilation-perfusion to the lung base improves, and physiologic dead space decreases,[79] (c) mean airway pressure and pulmonary vascular resistance decrease, allowing PEEP titration

and therefore more effective treatment of hypoxemia,[80] and (d) pleural pressure decreases, resulting in better venous return and cardiac output.[79] Unfortunately, subsequent clinical trials did not support some of the rationales (see the section Intermittent Mandatory Ventilation and Controlled Mechanical Ventilation).

IMV's flexibility in providing a range of support levels makes it advantageous for use as a primary means of ventilator support[81] and as a method for discontinuing mechanical ventilation.[5] An inherent limitation of IMV is the fixed rate of machine breaths. When set at a very high rate, IMV functions as CMV that has been shown to rapidly lead to diaphragmatic muscle atrophy in both experimental animals[82,83] and humans.[84,85] During weaning from mechanical ventilation, the pace of decreasing the IMV rate potentially can prolong weaning when it is inappropriately slow.

INDICATIONS AND CONTRAINDICATIONS

IMV has been used as a primary means of ventilator support in postoperative patients[86] and during acute respiratory failure of various etiologies.[6,7,87–91] For treatment of acute respiratory failure in adults, North Americans apply SIMV with pressure support more frequently than ACV (49% vs. 27%, respectively).[12] A similar trend is observed in Australia and New Zealand, 41% versus 17% with other mandatory pressure-limited modes of ventilation.[13] In preterm neonates, the frequency of SIMV application in acute respiratory failure is higher than in adults, 60% versus 31% with ACV.[14] However, it needs to be emphasized that in preterm infants in addition to the ventilatory strategy used, early treatment with surfactant is essential.[92] The level of machine assistance must be tailored to the patient's ventilatory requirement. The optimal mandatory-breath settings are similar in principle to those for ACV.[93–95] A low IMV setting is contraindicated when the patient's ventilatory demand is high; likewise, the setting should not be left high after the patient's ventilatory requirement has decreased. A gradual decrease in the IMV rate is unwarranted when discontinuation from mechanical ventilation is imminent.

COMPARISON WITH OTHER MODES

Intermittent Mandatory Ventilation as a Primary Means of Ventilator Support

INTERMITTENT MANDATORY VENTILATION AND CONTROLLED MECHANICAL VENTILATION

Unlike IMV, CMV imposes a fixed breathing pattern. Hence, to some extent, a comparison favors IMV, which has been claimed to be superior to CMV for the following reasons: (a) it prevents the patient from "fighting the ventilator," reducing the need for sedation and paralysis; (b) it prevents respiratory alkalosis; (c) it improves intrapulmonary gas distribution; (d) it lowers mean airway pressure, benefiting cardiac output and preventing barotrauma; (e) it decreases oxygen consumption ($\dot{V}_{O_2}$); (f) it prevents muscle atrophy and discoordination; and (g) it improves renal function.

1. *IMV prevents the patient from "fighting the ventilator," reducing the need for sedation and paralysis.* Because the patient has no autonomy to alter breathing pattern with CMV, the patient will increase inspiratory effort, which is manifested as "fighting the ventilator" when ventilatory demand rises.[78] No studies, however, have compared the respective sedative doses used during CMV and IMV.
2. *IMV prevents respiratory alkalosis.* In a prospective study comparing IMV and CMV in patients with acute respiratory failure, CMV resulted in a mean pH of 7.49 and a Pa_{CO_2} of 32.3 mm Hg, whereas IMV resulted in a mean pH of 7.44 and a Pa_{CO_2} of 39.9 mm Hg.[7] The CMV rate, however, was set to suppress spontaneous respiratory effort, whereas, during IMV, the rate was adjusted downward continuously as long as pH remained greater than 7.30. Hence the result in favor of IMV is to be expected. When a normal pH is achieved at a low IMV rate, subsequent data suggested that it was at the expense of increased work of breathing.[42,74] Moreover, some patients on mechanical ventilation who are allowed to set their own Pa_{CO_2} do not always choose a normal level (e.g., patients with brain injury). These patients will have persistent respiratory alkalosis regardless of ventilation mode.[77,96]
3. *IMV improves intrapulmonary gas distribution.* This hypothesis is based on the premise that in the supine position, spontaneous breathing causes inspired gas to be distributed preferentially to dependent lung regions because the dependent diaphragm, which is displaced cephalad, operates at an improved mechanical advantage.[97] Conversely, during mechanical ventilation, ventilation is distributed preferentially to nondependent lung regions because the diaphragm is not used, and the nondependent lung and chest wall are more compliant.[98] Therefore, IMV's combination of spontaneous and mechanical breaths theoretically should result in a better matching of ventilation and perfusion.[99] A comparison study evaluating IMV and CMV ventilation–perfusion distribution with the inert-gas elimination technique[100] was performed in stable patients recovering from major abdominal aortic surgery.[101] During CMV, V_T was set at 14 to 16 mL/kg with a set rate of 8 to 10 breaths/min. During SIMV, the rate was set at 50% of the CMV rate (4 to 5 breaths/min); a pressure support of 5 to 8 cm H_2O was added to the intervening spontaneous breaths to overcome the ventilator circuit and endotracheal tube resistance.[102] Each ventilator mode was maintained for 45 minutes. Compared with CMV, physiologic dead space increased with SIMV (22.0% vs. 26.8%, respectively; $p < 0.05$) and was associated with a significant increase in $\dot{V}_E$, resulting in a similar Pa_{CO_2}. The SIMV perfusion distributions remained unaltered. This study, using the inert-gas elimination technique, shows that IMV does not improve ventilation–perfusion distributions.

4. *IMV lowers mean airway pressure, benefiting cardiac output and preventing barotrauma.* Because IMV intersperses spontaneous breaths between mechanical breaths, mean airway pressure averaged over time is lower than with CMV. The lower mean airway pressure results in maintenance of cardiac output. Several studies have shown a higher cardiac output with IMV than with CMV.[90,91,103] The interactions between intrathoracic pressure associated with mechanical ventilation and cardiac performance, however, are quite complex.[104] Right-ventricular and left-ventricular interaction, direct pressure on the heart, and changes in systemic and pulmonary venous return all play a role. The net effect of this interaction depends on left-ventricular filling pressure and reserve. Mathru et al[105] compared the effect of CMV, IMV with 5 cm H_2O PEEP (IMV–5PEEP), and IMV with 0 cm H_2O PEEP (IMV–0PEEP) in two groups of patients following aortocoronary bypass surgery. V_T and ventilator rate were adjusted to achieve a Pa_{CO_2} of between 35 and 40 mm Hg. One group had normal left-ventricular function. The second group had decreased left-ventricular reserve: left-ventricular diastolic pressure of greater than 16 mm Hg and ejection fraction of less than 0.6. In the first group, IMV–0PEEP resulted in an increase in cardiac output of 27% compared with CMV. In the second group, however, IMV resulted in a significant decrease in cardiac output (19%) compared with CMV. IMV–5PEEP affected cardiac output similarly to CMV. These data indicate that when compared with CMV, IMV improves cardiac output in patients with normal left-ventricular function or hypovolemia, but it may be harmful in patients with poor left-ventricular reserve.

   The frequency of barotrauma with IMV and CMV was compared in a retrospective study of 292 postoperative and nonsurgical patients who received mechanical ventilation for 24 hours or more.[106] The ventilator V_T was set at 12 to 15 mL/kg. The IMV rate was set at 6 breaths/min or lower, provided that normocapnia was maintained. If hypercapnia developed, it was treated by increasing V_T to 15 mL/kg and, if necessary, by increasing the IMV rate to 8 breaths/min. No sedation or muscle relaxants were used. In the CMV group, the rate was set at 12 breaths/min. Hypercapnia was corrected by increasing V_T. The patients were sedated and paralyzed. Compared with the CMV group, patients receiving IMV had a significantly higher peak airway pressure (34 vs. 51 cm H_2O, respectively) and PEEP/CPAP (15 vs. 27 cm H_2O, respectively). Yet the barotrauma was 22% in the CMV group compared with 7% in the IMV group. The authors speculated that the less frequent barotrauma with IMV was related to the smaller number of mechanical breaths with large V_T. Mean transpulmonary pressure, which may be responsible for the barotrauma, was not measured in either group.
5. *IMV decreases oxygen consumption*. Downs et al[7] found that $\dot{V}_{O_2}$ was lower both during mechanical ventilation and 15 minutes after its discontinuation in patients ventilated with IMV versus CMV. The authors speculated that the higher $\dot{V}_{O_2}$ on CMV could be ascribed to respiratory alkalosis[107,108] and abrupt withdrawal from mechanical ventilation rather than reflecting metabolic work of breathing. In contrast, Wolff et al[103] showed that CO_2 production ($\dot{V}_{O_2}$) tended to be lower with CMV than with IMV. Because the respiratory quotient was similar with both ventilation modes, it is reasonable to assume that $\dot{V}_{O_2}$ during CMV was lower than that during IMV. In this study, Pa_{CO_2} was 39 and 44 mm Hg on CMV and IMV, respectively, suggesting that pH was within the normal range.[103] This observation suggests that, in the absence of alkalemia, $\dot{V}_{O_2}$ is lower on CMV than on IMV.
6. *IMV prevents muscle atrophy and discoordination*. Maintaining spontaneous breathing activity during IMV has been proposed to achieve respiratory muscle conditioning and preserve respiratory muscle function.[5] The periodic hyperinflation also may reinforce coordinated breathing.[5,109] During CMV, muscle atrophy[84,85,110,111] and myofibrillar damage,[82,112,113] which account for ventilator-induced diaphragmatic dysfunction, have been demonstrated in both experimental animals and humans.[84,85] Like in experimental animals, in the human diaphragm the atrophic protein kinase B–forkhead Box-O (AKT-FOXO) signaling plays an important role in activating the ubiquitin-proteasome pathway.[114] Overexpressions of the atrophic genes, atrogin-1 and muscle ring finger-1 (MuRF-1) of the ubiquitin-proteasome pathway, are responsible for myofibril degradation and atrophy with CMV-induced diaphragm muscle inactivity.[114] Conversely, maintaining diaphragmatic activation with ACV attenuates expression of atrogin-1 (muscle atrophy F-box [MAF-box]; see Chapter 43).[83] With IMV, diaphragmatic electrical activity of both mandatory and spontaneous breaths persists. Thus, it is possible that IMV prevents respiratory muscle atrophy. This hypothesis remains to be tested.

   Respiratory muscle discoordination with IMV and CMV has not been compared. IMV's efficacy in counteracting respiratory muscle discoordination was demonstrated by Andersen et al[109] in a study of twenty-eight patients during discontinuation of mechanical ventilation. The mandatory breaths were increased gradually to 75% of the patient's $\dot{V}_E$. In contrast, Gibbons et al[115] failed to show similar results when IMV was applied to six patients receiving prolonged mechanical ventilation. The lowest spontaneous breathing rate was 29 breaths/min at the lowest IMV rate of 10 breaths/min. Gas exchange was adequate. Five of the six patients manifested breathing discoordination in the form of either ribcage or abdominal paradox. In the patients whose diaphragmatic electrical activity was measured, an electromyographic fatigue pattern also was observed. In this study, IMV was insufficient to reduce respiratory muscle workload, as reflected by the relatively high spontaneous breathing rate. IMV's efficacy in counteracting respiratory muscle discoordination appears to depend primarily on the extent of respiratory muscle unloading.

7. *IMV improves renal function*. Steinhoff et al[116] studied the effect of CMV and IMV on renal function in patients with acute respiratory failure. With CMV, the ventilator rate was set to suppress inspiratory efforts, which averaged 10 to 16 breaths/min. IMV was set at 4 to 10 breaths/min. PEEP was maintained constant during both CMV and IMV. With CMV, urinary flow and creatinine and osmolal clearance decreased, with a net effect of water retention, in comparison with IMV. Impaired renal function during CMV was attributed to the increased intrathoracic pressure, which caused stimulation of atrial stretch receptors and release of antidiuretic hormone. A more important factor may be that increased intrathoracic pressure during CMV decreases venous return, and the consequent decrease in cardiac output produces a decrease in renal plasma flow. Hence the effects of CMV and IMV on renal function are related directly to their respective effects on cardiac function.

INTERMITTENT MANDATORY VENTILATION AND ASSIST-CONTROL VENTILATION

Comparison of IMV with ACV is more appropriate than comparison of IMV with CMV because both IMV and ACV provide partial ventilator support. Few studies have compared IMV with ACV. As discussed below, these studies primarily concern effects on cardiac output,[117,118] $\dot{V}_{O_2}$,[117–119] and respiratory alkalosis.[77,117,120] (Because IMV's effects on work of breathing were discussed extensively earlier, comparison of IMV with ACV is limited to its application in the neonate.[121,122])

1. *Effect on cardiac output*. Groeger et al[117] studied the effect of SIMV and ACV in forty patients with acute respiratory failure of various etiologies other than chronic obstructive pulmonary disease. SIMV, at a set V_T of 10 to 15 mL/kg, was the initial ventilation mode in all patients, and the mandatory rate was adjusted to the minimum required to maintain a normal pH and Pa_{CO_2}. When the combined mandatory and spontaneous breathing rates were greater than 35 breaths/min, the IMV rate was increased to ensure patient comfort. The ventilator mode was then switched to ACV, and V_T, PEEP, inspiratory flow rate, and inspired oxygen fraction (FI_{O_2}) were held constant. After 30 minutes on SIMV or ACV, hemodynamic variables were measured. At this point, mean IMV rate was 7 breaths/min, with a total rate of 34 breaths/min, whereas the ACV rate was 15 breaths/min. Cardiac output, measured by thermodilution, was 6% higher with SIMV than with ACV. Likewise, studying twelve patients recovering from acute respiratory failure of various etiologies, Sternberg and Sahebjami[118] demonstrated that cardiac index was significantly higher with SIMV than with ACV (3.6 vs. 3.3 L/min/m^2). (The investigators also compared SIMV with PSV, which is discussed in the section Intermittent Mandatory Ventilation and Pressure-Support Ventilation.) The average V_T with ACV was 715 mL, whereas with SIMV it was 491 mL. The SIMV mandatory breaths were set at 75% of the ACV rate. Although the cardiac output with SIMV was significantly higher than with ACV, the changes fall within the variability of the thermodilution technique.[123] Despite the limited differences in cardiac output with IMV and ACV, IMV may be helpful in patients who demonstrate significant hemodynamic deterioration during ACV. In the original description of intrinsic PEEP (PEEPi),[124] two patients with chronic obstructive pulmonary disease developed hemodynamic compromise secondary to significant PEEPi while receiving ACV. The institution of IMV and fluid repletion produced an improvement, although cardiac output was not measured directly during either IMV or ACV. The conflicting data concerning the effects of ACV and IMV on cardiac output underscore the complex interaction between intrathoracic pressure and cardiac function.
2. *Effect on oxygen consumption*. In the above-mentioned study by Groeger et al,[117] $\dot{V}_{O_2}$ was comparable for both pressure-triggered SIMV and ACV. When the patients were grouped according to the ratio between $\dot{V}_E$ achieved by the mandatory breaths and total $\dot{V}_E$, however, the mean $\dot{V}_{O_2}$ for patients with a ratio of less than 0.5 was significantly higher during SIMV than during ACV (320 vs. 296 mL/min/m^2, respectively; $p \leq 0.05$). Conversely, in the study of Sternberg and Sebahjami,[118] when the mandatory breaths during SIMV were set at 75% of the ACV rate, $\dot{V}_{O_2}$ was unaltered during SIMV despite total frequency being higher with SIMV than with ACV (20 breaths/min vs. 12 breaths/min). In healthy subjects breathing via a mouthpiece on SIMV or ACV, $\dot{V}_{O_2}$ (measured with a metabolic cart) also was similar with the two modes.[119] With SIMV, both the V_T and mandatory-breath rate were equivalent to those of the ACV. These studies[117–119] demonstrate that compared with ACV, the degree of machine assistance during IMV determines $\dot{V}_{O_2}$.
3. *Effect on respiratory alkalosis*. Three prospective studies[77,117,120] comparing IMV and ACV showed a significantly lower pH and higher Pa_{CO_2} during IMV than during ACV (Table 7-1). Groeger et al[117] suggested that the higher Pa_{CO_2} during IMV was related to an increased dead-space-to-tidal-volume ratio, because $\dot{V}_{CO_2}$ and $\dot{V}_E$ were similar for both IMV and ACV. Conversely, Hudson et al[77] showed that the higher Pa_{CO_2} during IMV came at the expense of a high patient workload given elevated CO_2 and an unchanged alveolar ventilation level. Regardless of the mechanisms of the elevated Pa_{CO_2} during IMV, all three groups of investigators concluded that the decrease in pH and increase in Pa_{CO_2} were minimal and of questionable clinical significance. Furthermore, in studies where IMV was compared with ACV in a subgroup of patients with preexisting respiratory alkalosis, respiratory alkalosis persisted during IMV.[77,120]
4. *Effects on work of breathing in the neonate.* Kapasi et al[122] undertook a comparison of the effects of pressure-limited ACV, SIMV, and IMV on work of breathing and inspiratory effort of clinically stable neonates with respiratory distress syndrome. The mandatory breath

TABLE 7-1: EFFECT OF IMV VERSUS ACV ON pH AND Pa_{CO_2}

Reference No.	pH		Pa_{CO_2} (mm Hg)		Rate (Breaths Per Minute)		
	IMV	ACV	IMV	ACV	IMV	ACV	*n*
63	7.41 ± 0.06[a]	7.45 ± 0.06	43.0 ± 6.3[a]	38.0 ± 6.3	7.1 (33.6)	15.1	40
102	7.48 ± 0.05[b]	7.51 ± 0.04	29.7 ± 6.1	28.6 ± 4.9	1/2 ACV rate	NA	26
105	7.42 ± 0.08[a]	7.45 ± 0.04	40.7 ± 7.6[a]	37.9 ± 6.7	4 (21)	15.0	18
Patients with Preexisting Respiratory Alkalosis							
63	7.49 ± 0.03	7.49 ± 0.03	27.4 ± 6.3	29.1 ± 4.7			17
105	7.46 ± 0.07[b]	7.49 ± 0.03	37.8 ± 7.4	35.7 ± 6.7			12

[a] $p < 0.01$.

[b] $p < 0.05$.

Note: Values are mean ± SD; only mean rate is shown. Number in parenthesis denotes total mandatory and spontaneous breath rates. Tidal volume was maintained the same for the mandatory breath with both IMV and ACV.

Abbreviations: IMV, intermittent mandatory ventilation; *ACV*, assist-control ventilation; *NA*, not available.

Sources: Adapted, with permission, from Hudson et al,[77] Groeger et al,[117] and Culpepper et al.[120]

rate with both SIMV and IMV was set the same as that of the ACV (range: 14 to 25 breaths/min). Average total respiratory rate was not significantly different among the modes (IMV, 56.3 breaths/min; SIMV, 58.3 breaths/min; ACV, 58.8 breaths/min). The work of breathing was estimated using the esophageal pressure, calculated using the Campbell diagram.[125,126] Both work of breathing and inspiratory effort were least with ACV and highest with IMV; SIMV had values between ACV and IMV. Patient–ventilator asynchrony occurred only with IMV. Jarreau et al[121] reported a similar result when comparing IMV, ACV with inspiratory pressure set at 10 to 15 cm H_2O, and spontaneous breathing on CPAP. Work of breathing with IMV was similar to that with CPAP: 0.81 versus 0.90 J/L. Work of breathing fell significantly only during ACV to 0.48 to 0.47 J/L at inspiratory pressures of 10 and 15 cm H_2O, respectively. Thus, in neonates, patient-triggered ACV provides better patient–ventilator synchrony and unloading of workload than does continuous-flow IMV.

In summary, the limited number of studies suggests minimal differences between the effects of high levels of IMV and ACV on cardiac output, $\dot{V}_{O_2}$, and respiratory alkalosis. Because of lower mean airway and intrapleural pressures, IMV should help to improve cardiovascular function in patients who exhibit hemodynamic compromise during ACV. In neonates, ACV is more effective in unloading the work of breathing and providing synchrony than IMV.

INTERMITTENT MANDATORY VENTILATION AND PRESSURE-SUPPORT VENTILATION

As with IMV, PSV provides the patient with some autonomy to alter breathing patterns in response to ventilatory demand. PSV is a form of ventilatory support in which the patient's inspiratory effort is assisted by the ventilator up to a preset inspiratory pressure level and remains at that level until a fixed[127,128] or operator-adjustable[129] ventilator cycle-off algorithm is activated. Unlike IMV, in which the number of mandatory breaths is fixed, PSV assists every breath, and the ventilator contribution to total workload is variable. Because the set inspiratory pressure is fixed with PSV, when patient ventilatory demand increases, inspiratory effort may exceed the ventilator contribution to total workload (see Chapter 8).[130,131] PSV can be added to IMV to unload inspiratory muscle work during the spontaneous breathing cycles. The addition of a small amount of PSV (5 cm H_2O) to pressure-triggered SIMV is adequate to overcome the lack of flow delivery observed with some pressure-triggered SIMV systems.[41] Higher levels of PSV not only help in overcoming the ventilator circuit and endotracheal tube resistance[132,133] but also augment V_T and unload the elastic work of the spontaneous breaths.[134,135] In one study of a small number of patients with acute respiratory failure,[136] PSV application at levels of up to 30 cm H_2O during SIMV (IMV rate of 6 to 10 breaths/min) and PEEP of 3 to 13 cm H_2O did not result in cardiovascular compromise. In clinically stable preterm infants, application of pressure support to the intervening spontaneous breaths to deliver V_T of 5 to 8 mL/kg stabilized breathing pattern,[137] and prevented an increase in inspiratory effort when SIMV rate was reduced.[138] Comparison between IMV and PSV is discussed pertaining to cardiac output,[118] ventilation–perfusion distribution,[139] and unloading of patient effort.[84]

1. *Effects on cardiac output.* Hemodynamics during SIMV and PSV were studied in critically ill patients by initially applying ACV to the patients.[118] The V_T of the mandatory breaths with SIMV then was set the same as that of ACV, at a rate of 75% of the ACV rate. With PSV, the inspiratory pressure was set to produce a V_T similar to that of ACV (average pressure of 21 cm H_2O). Cardiac output

(measured by thermodilution), oxygen transport, and $\dot{V}_{O_2}$ were the same for both ventilation modes. As a primary means of ventilatory support, both SIMV and PSV have comparable effects on hemodynamics.

2. *Effects on ventilation–perfusion*. Valentine et al[139] studied the effect of SIMV, PSV, and airway pressure-release ventilation (see in the section Intermittent Mandatory Ventilation and Airway Pressure-Release Ventilation) on ventilation–perfusion distribution in post–cardiac surgery patients who were ready to be weaned; this section discusses only the comparison between SIMV and PSV. SIMV was the initial ventilatory support mode. The IMV rate was adjusted to maintain a pH of greater than 7.35. With PSV, pressure was titrated to achieve a mean end-tidal P_{CO_2} of 40 mm Hg. Ventilation–perfusion distribution was assessed using the inert-gas elimination technique.[100] The dispersion of ventilation–perfusion ratios, calculated as the logarithmic standard deviation of perfusion (log SD$\dot{Q}$) and ventilation (log SD$\dot{V}$), was similar for SIMV and PSV. Right-to-left intrapulmonary shunt and fractional dead-space ventilation did not differ significantly. Table 7-2 shows the effects on arterial blood gases, respiratory mechanics, and $\dot{V}_{O_2}$. Differences in arterial blood gases were of questionable clinical significance. Peak airway pressure was significantly higher with SIMV, but mean transpulmonary pressure was comparable. As sole ventilator support, SIMV and PSV provide comparable and adequate gas exchange in postoperative patients who were ready to be weaned. No study has yet compared the efficacy of IMV and PSV as a primary means of ventilator support during acute respiratory failure.

3. *Effects on patient effort*. Leung et al[43] carried out a head-to-head comparison of the efficacy of SIMV and PSV in unloading inspiratory effort at various levels of assistance. The rate of change in inspiratory effort with increasing assistance levels, estimated as pressure-time product per minute, did not differ between the two modes. Unloading efficacy, however, differed according to the level of assistance. From 0% to 60% of maximum, the decrease in pressure-time product per minute was greater with PSV than with SIMV. At a higher assistance level, the converse was observed (Fig. 7-11). Frequency decreased linearly with increase in PSV. With SIMV, frequency changed little until a high assistance level was provided (Fig. 7-11).[140] Thus, when a high assistance level is needed, both SIMV and PSV provide comparable assistance. At low to medium assistance levels, however, a greater decrease in patient effort with PSV makes it more useful clinically than SIMV. Leung et al[43] also assessed the patient's wasted efforts or nontriggered attempts during both SIMV and PSV. The number of nontriggered attempts is proportional to the assistance level and highest at 100% of machine assistance (29% with SIMV and 26% with PSV). The breaths preceding the nontriggered attempts had a shorter total duration and expiratory time, higher V_T, and higher dynamic PEEPi than did the breaths preceding triggered breaths. This observation suggests that nontriggered attempts resulted from an inspiratory effort that was insufficient to overcome the elevated recoil pressure associated with dynamic hyperinflation. Thus, increasing the ventilator assistance level decreases inspiratory muscle effort but also increases ineffective triggering.[43,141] Ineffective

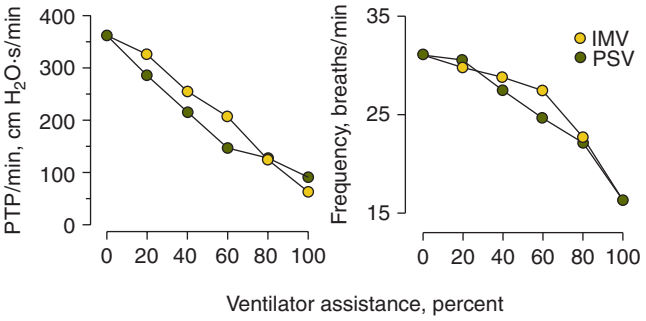

FIGURE 7-11 Changes in PTP per minute (*left panel*) and frequency (*right panel*) as intermittent mandatory ventilation (IMV) and pressure-support ventilation (PSV) were increased progressively. PSV of 100% represents the level necessary to achieve a V_T equivalent to that during ACV (10 mL/kg); IMV 100% is the same ventilator rate and V_T as during ACV. (Adapted, with permission, from Leung P, Jubran A, Tobin MJ. Comparison of assisted ventilator modes on triggering, patient effort, and dyspnea. *Am J Respir Crit Care Med*. 1997;155:1940–1948; and Tobin MJ, Jubran A, Laghi F. Patient-ventilator interaction. *Am J Respir Crit Care Med*. 2001;163:1059–1063.)

TABLE 7-2: GAS EXCHANGE, MECHANICS, AND OXYGEN CONSUMPTION DURING SIMV AND PSV

	SIMV	PSV
FI_{O_2}	0.44 ± 0.11	0.44 ± 0.11
pH	7.41 ± 0.02	7.36 ± 0.02[a]
Pa_{CO_2}, mm Hg	33.0 ± 2.0	39.0 ± 2.0[a]
Pa_{CO_2}, mm Hg	102.0 ± 7.0	98.0 ± 8.0
Peak Paw, cm H_2O	32.8 ± 1.3	19.4. ±. 2.1[a]
Mean Paw, cm H_2O	9.6 ± 1.1	8.4 ± 1.0
Ppl, cm H_2O	3.8 ± 1.0	3.8 ± 1.1
Ptp, cm H_2O	5.8 ± 0.6	4.6. ± 0.5
$\dot{V}_E$, liters/min	9.4 ± 0.6	9.0 ± 0.5
fS, breaths per minute	3.4 ± 1.8	
fM, breaths per minute	8.4 ± 0.4	15.8 ± 0.9[a]
V_TS, liters	0.08 ± 0.07	
V_TM, liters	1.03 ± 0.03	0.58 ± 0.03[a]
$\dot{V}_{O_2}$, ml/min	269 ± 13	268 ± 14

[a] $p < 0.05$.

Note: Values are mean ± SE; $n = 9$.

Abbreviations: SIMV, synchronous intermittent mandatory ventilation; PSV, pressure-support ventilation; FI_{O_2}, inspired oxygen fraction. Paw, airway pressure; Ppl, pleural pressure; Ptp, transpulmonary pressure; $\dot{V}_E$, total minute ventilation; fS, frequency of spontaneous breaths during SIMV; fM, frequency of mandatory breaths or pressure support assisted breaths; V_TS, tidal volume of spontaneous breath during SIMV; V_TM, tidal volume of mandatory breath or presssure-support assisted breath; $\dot{V}_{O_2}$, oxygen consumption.

Sources: Adapted, with permission, from Valentine el al.[139]

triggering is associated with prolonged duration of mechanical ventilation.[142]

INTERMITTENT MANDATORY VENTILATION AND AIRWAY PRESSURE-RELEASE VENTILATION

Airway pressure release ventilation (APRV) consists essentially of two CPAP levels with a transient decrease or "release" of airway pressure from a higher CPAP to a lower CPAP for a set release time. Spontaneous breathing is allowed to occur between airway pressure releases.[128,143–145] The pressure gradient between the two CPAP levels and the frequency of releases determine the level of ventilator support (see Chapter 11). The original version of APRV used a short release time, and in the absence of spontaneous breathing, APRV resembled pressure-controlled inverse-ratio ventilation.[143] The modified version, in which the inspiration-to-expiration (I:E) ratio is adjustable, is termed *biphasic intermittent positive airway pressure*.[145] The primary indication for APRV is the provision of ventilation during an oxygenation crisis.[143] Although the indications and operating principles of IMV and APRV differ significantly, both modes allow the patient to breathe spontaneously between machine-cycled breaths.[143,144] Comparison of IMV with APRV is discussed with regard to its efficacy as a primary means of ventilator support in patients with acute respiratory distress syndrome (ARDS)[146] in relation to gas exchange,[139,146–149] hemodynamics,[146,148,150] lung recruitment,[151] breathing comfort,[148,152] intubation duration, and sedative use.[146,153]

Varpula et al[146] undertook a randomized, controlled comparison of pressure-limited SIMV (with 10 cm H_2O of pressure support added to the unassisted breaths) and APRV in patients with ARDS. The primary end point was the number of ventilator-free days from the time of randomization to day 28. The secondary end points were the effect on gas exchange, hemodynamics, and sedative use. PEEP was set slightly above the lower inflection point on the pressure-volume curve obtained during paralysis (or if not detected, at 10 cm H_2O). The upper inflection point was never exceeded (or if not detected, the inspiratory pressure was set at less than 35 cm H_2O). The pressure-release frequency with APRV and the machine assistance rate with SIMV were similar at 12 breaths/min. The I:E ratio with APRV was set at 4:1; with SIMV, it was set at 1:2 and adjusted to 2:1. Ventilator-free days, gas exchange, hemodynamics, and sedative dosage were comparable with the two modes, although average inspiratory pressure was significantly lower with APRV than with SIMV (25.9 vs. 28.6 cm H_2O). Moderate hypercapnia developed during the first study day in both groups but returned toward normal after 4 days. The effects of SIMV and APRV on gas exchange and hemodynamics appear comparable in patients with lung injury[147,148] or after cardiac surgery.[139] In contrast to earlier studies, recently, one trial in patients with ARDS demonstrated the superiority of APRV over SIMV in terms of gas exchange and mortality.[149] Mortality was 31% with APRV compared to 59% with SIMV. Unfortunately, this study was a retrospective trial conducted over 6 years with SIMV applied in the first 3 years followed thereafter with APRV; consequently, ventilator settings were not well matched.[149] Application of short-term APRV also proved superior to SIMV in patients who underwent coronary artery bypass surgery.[150] Intubation duration was approximately 4 hours shorter with APRV than with SIMV (mean: 10.1 vs. 14.7 hours). Analgesic and sedative dosage also was less with APRV than with SIMV. This study, however, was a nonrandomized, open clinical trial.

In a recent, prospective, randomized trial in acute lung injury using similar ventilator settings as above,[146] Varpula et al[151] compared the effects APRV ($n = 13$) and SIMV plus PSV ($n = 10$) in recruiting nonaerated lungs. The investigators hypothesized that a strategy employing spontaneous breathing with active diaphragmatic contractions, as with APRV, is associated with better aeration of the dependent lung region.[98] The degree of lung recruitment was estimated using computer-assisted tomographic densitometry technique at the beginning of randomization, and after 7 days of the assigned ventilator mode. On day 7, the median peak Paw was significantly lower with APRV than with SIMV: 24.0 versus 30.4 cm H_2O. The computer-assisted tomographic number (in Hounsfield units) was similar with both APRV and SIMV at both the carinal and dependent diaphragmatic level. Thus, APRV did not appear to improve aeration of the consolidated lung parenchyma.

Breathing comfort during SIMV and APRV were evaluated in inexperienced healthy subjects breathing via a mouthpiece and compared with PSV. SIMV was set at 8 breaths/min, V_T at 5 mL/kg, and PEEP at 5 cm H_2O. The low and high PEEP levels with APRV were set at 5 and 10 cm H_2O, the release rate was 8 breaths/min, and the I:E ratio was 1:2. PSV was set at 10 cm H_2O with PEEP of 5 cm H_2O. Breathing comfort was measured with a visual analog scale (0 to 10 cm). PSV achieved the greatest comfort, SIMV the worst, and APRV fell between PSV and SIMV (2.03, 5.38, and 4.12 cm, respectively). Unfortunately, flow-limited SIMV was employed rather than pressure-limited SIMV (both APRV and PSV are pressure-limited ventilation modes).

INTERMITTENT MANDATORY VENTILATION AND PROPORTIONAL-ASSIST VENTILATION, ADAPTIVE-SUPPORT VENTILATION, PRESSURE-REGULATED VOLUME CONTROL VENTILATION, AND VOLUME SUPPORT VENTILATION

Proportional-Assist Ventilation. Proportional-assist ventilation (PAV) is a mode in which the ventilator instantaneously generates pressure in proportion to the patient's effort (see Chapter 12).[154] The ventilator amplifies the patient's inspiratory effort without any preselected target volume or pressure. A randomized crossover comparison of continuous-flow IMV versus PAV was conducted in

thirty-six preterm infants.[155] The inspiratory pressure with IMV was set to deliver a V_T of 4 to 6 mL/kg. The IMV rate was not reported. With PAV, the volume-assist gain was adjusted to decrease lung elastance to its normal value, whereas the flow-assist gain was set at −20 cm H_2O/L/s. Each mode was applied for 45 minutes. With PAV, peak and mean airway pressures and transpulmonary pressure were significantly lower, frequency was higher, and V_T was comparable to that with IMV, resulting in a higher $\dot{V}_E$. Pa_{CO_2}, however, remained the same as with IMV, and Pa_{O_2} was higher. There were no significant differences in the number of apneic or hypoxemic episodes. The lower transpulmonary pressure with PAV might help to prevent lung injury during prolonged mechanical ventilation. The results in preterm infants were similar to those in an earlier short-term trial in a few adult patients.[156]

Adaptive-Support Ventilation. Adaptive-support ventilation (ASV) is based on the work by Otis et al[157] and Mead et al,[158] who demonstrated that any given level of alveolar ventilation has an optimal respiratory frequency that is least costly in terms of respiratory work: the frequency at which the respiratory muscles develop the least-average force or tension.[158] ASV is a mode that can alternate between pressure control and pressure support, relying on closed-loop regulation of ventilator settings that respond to changes in respiratory system mechanics and spontaneous breathing efforts (see Chapter 15). ASV adjusts inspiratory pressure, I:E ratio, and mandatory rate to maintain the target minute ventilation and respiratory rate within a frame designed to avoid both rapid, shallow breathing and excessive inflation volumes.[159] Tassaux et al[160] compared the short-term effects of ASV versus SIMV plus pressure support on patient–ventilator interaction in patients ready to be weaned from mechanical ventilation. ASV achieved a $\dot{V}_E$ similar to that of SIMV. Central neural drive, however, estimated as $P_{0.1}$, and sternocleidomastoid electrical activity, measured with surface electrodes, were reduced markedly. Thus, ASV provided comparable total $\dot{V}_E$ but with a significantly decreased inspiratory load than did SIMV plus pressure support.

Pressure-Regulated Volume-Controlled Ventilation. Pressure-regulated volume-controlled ventilation (PRVCV) is a dual-control, breath-to-breath mode. PRVCV has both the benefits of pressure-controlled ventilation, with a constant V_T, and automatic weaning from pressure limit as patient compliance improves and/or patient effort increases (see Chapter 15). Four prospective, randomized trials have compared the efficacy of PRVCV and IMV with different primary goals in preterm infants.[161–164] Two trials were short-term in stable preterm infants during the weaning phase,[161,162] and two trials during acute respiratory failure.[163,164] In the stable infants, SIMV was compared with PRVCV on the effects of respiratory mechanics and gas exchange.[161,162] The SIMV mandatory breaths consisted of volume guarantee or pressure-regulated volume-controlled breaths. Abubakar and Keszler[161] concluded that SIMV resulted in higher work of breathing than PRVCV on the basis of a high respiratory rate, although work of breathing was not directly measured. Scopesi et al[162] demonstrated that SIMV was associated with lower mean Paw and higher variability in V_T than observed with PRVCV. From those studies[161,162] it is not clear whether PRVCV offers advantage over SIMV because the sample size was small (ten to twelve patients), and trial duration was short (20 minutes to 2 hours).

In infants with respiratory distress syndrome, Piotrowski et al[163] studied infants younger than 3 days old whose birthweight was less than 2500 g. Thirty infants received continuous-flow IMV, and twenty-seven received PRVCV; the average Paw were 18.6 and 16.2 cm H_2O, respectively. The IMV rate was selected by the clinician. With PRVCV, the V_T was set at 5 to 6 mL/kg. The primary end point was duration of mechanical ventilation and incidence of bronchopulmonary dysplasia. The secondary end point was complications from mechanical ventilation, consisting of air leaks, intraventricular hemorrhage, and hemodynamic instability. PRVCV did not decrease duration of mechanical ventilation or incidence of bronchopulmonary dysplasia, although it decreased the incidence of high-grade intraventricular hemorrhage (11% vs. 35%). The benefit may have occurred in part because PRVCV delivers a stable volume. In preterm newborns, large fluctuations in intrathoracic and arterial pressures cause variations in cerebral blood flow velocity that is a risk factor for intraventricular hemorrhage.[165] In the second trial, D'Angio et al[164] enrolled a large number of low-birthweight infants (500 to 1249 g) who were younger than 6 hours of age. Infants were assigned to pressure-limited SIMV (n = 108) or PRVCV (n = 104) until extubation, death, or meeting predetermined failure criteria on the assigned mode. With SIMV, no pressure support was applied to the spontaneous breaths. Average Paw measured at 6 hours and 12 hours after SIMV application were 15.0 and 14.0 cm H_2O, respectively, and after PRVCV were 13.8 and 12.7 cm H_2O, respectively. The average V_T for SIMV at 6 hours and 12 hours was 18.4 and 17.8 mL/kg, respectively; whereas V_T with PRVCV was 16.0 and 14.1 mL/kg, respectively. The average set ventilator rate with SIMV at 6 hours and 12 hours was 35 and 30 breaths/min, respectively; with PRVCV, the rate was 40 breaths/min at both 6 hours and 12 hours. Differences in measured ventilator variables between SIMV and PRVCV were not significant. The cumulative percentage of infants alive and extubated at 36 weeks (84%) was similar for both SIMV and PRVCV (88 out of 105 infants for SIMV; 87 out of 104 infants for PRVCV). The percentage of infants who failed the assigned mode tended to be less with PRVCV than with SIMV, 20% versus 33%. Complications associated with prematurity and mechanical ventilation such as bronchopulmonary dysplasia, intraventricular hemorrhage, or retinopathy of prematurity were similar. Interestingly, with both SIMV and PRVCV, V_T was remarkably higher than that recommended with a protective ventilatory strategy.[166] Yet, when ventilator settings are nearly matched, application of SIMV or PRVCV appears to have a similar impact

on survival, extubation rate, or complications rate in preterm infants with acute respiratory failure.

Volume-Support Ventilation. Volume-support ventilation (VSV), or PSV combined with volume guarantee, is PSV that uses V_T as feedback control for continuously adjusting the pressure-support level. All breaths are patient-triggered, pressure-limited, and flow-cycled.[52] Prospective comparisons between VSV and SIMV in preterm infants were conducted during the acute[167] and stable phase of respiratory failure.[162,168] Nafday et al[167] randomized preterm infants following surfactant treatment for respiratory distress syndrome into VSV (n = 16) or pressure-limited SIMV (n = 18) applied for 24 hours. V_T with VSV was set at 5 mL/kg. Ventilator settings were adjusted to achieve predetermined arterial blood-gas values. After 24 hours, attending physicians provided ventilation management as clinically indicated. Mean airway pressure decreased over time in both VSV and SIMV groups, although the decrease was faster in the SIMV group. Both groups had similar survival rates at the time of discharge (86% for VSV, and 94% for SIMV), and complications associated with prematurity and mechanical ventilation. That is, VSV did not offer improved clinical outcomes compared with SIMV.

Two prospective, short-term trials of stable preterm infants during the weaning phase compared VSV and pressure-limited SIMV for either 30 minutes[168] or 20 minutes.[162] In the first trial,[168] following either VSV or SIMV for 30 minutes, VSV was applied for 24 hours. The attending physician, however, had discretion to select a ventilation mode according to the infant's condition. VSV was successfully applied for 24 hours in twenty-one of 25 infants (84%), in those infants a significantly longer duration of rhythmic breathing was observed during the 30-minute trial. VSV provided comparable fluctuations in ventilation and oxygenation, but with a lower Paw than with SIMV (15.4 vs. 19.2 cm H_2O, respectively), and shorter T_I (0.29 vs. 0.35 seconds, respectively). In infants with high respiratory drive, however, hyperventilation occurred with VSV, which dictated a switch to SIMV.[168] Consistent with the first trial, the second trial also demonstrated lower Paw with VSV compared with SIMV (11.2 vs. 18.2 cm H_2O, respectively). In summary, VSV, in the short term, did not offer ventilatory advantage over SIMV in acute or stable preterm infants with respiratory distress syndrome, except for a lower Paw in the stable infants.

Intermittent Mandatory Ventilation as a Weaning Method

INTERMITTENT MANDATORY VENTILATION, PRESSURE SUPPORT, AND T PIECE

IMV was first used in adult patients as a means of discontinuing mechanical ventilation.[5] This method was claimed to be more efficient, safer, and more readily accepted by the patient, and it avoided the necessity of setting up a T-piece circuit. Although preceding ventilator support may be with either ACV or IMV, IMV is applied when the patient is ready to be weaned. The number of mandatory breaths is reduced gradually (1 to 3 breaths/min) at 1- to 4-hour intervals, provided that arterial pH remains greater than 7.30[7] or 7.35,[169] regardless of other physiologic measurements. An IMV rate of zero or close to zero is maintained for several hours, or for as long as 24 hours, before extubating the patient.

With PSV as a weaning method, the pressure level is set initially at a maximum, defined as the level that produces a V_T of 10 to 12 mL/kg; then the pressure support level is reduced according to the patient's respiratory frequency.[170] When the pressure support level reaches 5 cm H_2O, extubation is considered.

With a T piece, once the patient meets predefined weaning criteria, the patient is placed on a T-piece circuit.[171] Progressively longer intervals of spontaneous breathing through a T piece are alternated with ACV. Extubation is considered when the patient can sustain breathing through a T piece for 1 to 2 hours. The early claim for IMV's superiority over a T piece was not based on a controlled study, and subsequent retrospective[172] and prospective studies[173,174] failed to demonstrate IMV's superiority. Studies comparing IMV and PSV showed either a significantly reduced duration[175] or a tendency for a shorter weaning time[176] with PSV. As PSV grew in popularity, two prospective, randomized, controlled multicenter trials[177,178] simultaneously compared the three weaning modalities: SIMV, PSV, and T piece. These trials laid to rest IMV's claim to superiority over T piece and PSV.

Brochard et al[177] studied 109 patients who met three of the four defined weaning criteria and had failed a 2-hour T-piece trial. Patients were randomized to SIMV (n = 43), PSV (n = 31), and T piece (n = 35). Weaning failure was defined as continued inability to be weaned after 21 days on the same mode, the need for reintubation after 48 hours of extubation, or intercurrent events (e.g., cardiac ischemia or nosocomial pneumonia) within 72 hours in the selected mode. The initial SIMV rate was set at half the total frequency during ACV or CMV, keeping V_T and flow rates constant (mean initial SIMV rate of 9.5 breaths/min). Once or twice a day, the SIMV rate was decreased by 2 to 4 breaths/min if patients did not demonstrate signs of poor tolerance. When a patient demonstrated poor tolerance, the SIMV rate was increased to its preceding level. When a patient tolerated a SIMV rate of 4 breaths/min or less over 1 day, tracheal extubation was performed. The T-piece method consisted of a gradual lengthening of the periods of disconnection from the ventilator. The initial T-piece trial was set shorter than the initial tolerance duration (mean duration: 38 minutes). The number of T-piece trials depended on the length of disconnection and on nurse availability and varied from three to eight trials per day. The T-piece periods were lengthened incrementally twice a day. Between the T-piece trials, ACV was applied. When the duration of a T-piece trial had reached 2 hours with adequate gas exchange, tracheal extubation was performed. In the patients assigned to PSV,

TABLE 7-3: TRIALS COMPARING THREE WEANING METHODS: INTERMITTENT T PIECE, PRESSURE-SUPPORT VENTILATION (PSV), AND SYNCHRONIZED INTERMITTENT MANDATORY VENTILATION (SIMV)

	Successful Wean [*n* (%)]		
Trial	**T Piece**	**PSV**	**SIMV**
Brochard et al[177]	20/35 (57)	24/31 (77)	25/43 (58)
Esteban et al[178]	27/33 (82)	23/37 (62)	20/29 (69)
	Risk Difference (%)[a]		
	T Piece vs. PSV	**T Piece vs. SIMV**	**PSV vs. SIMV**
Brochard et al[177]	−20 (−42, 2)	−1 (−23, 21)	19 (−2, 40)
Esteban et al[178]	14 (−5, 32)	7 (−13, 27)	−7 (−20, 16)
	Time to Extubation (Days)		
	T Piece	**PSV**	**SIMV**
Brochard et al[177]	8.5 ± 8.3	5.7 ± 3.7	9.9 ± 8.2
Esteban et al[178]	3 (2, 6)	4 (2, 12)	5 (3, 11)

[a]Risk differences expressed as the difference in proportions of successfully weaned subjects between respective weaning methods. Negative numbers imply lower success rates and positive numbers higher success rates. The 95% confidence intervals follow risk differences in parentheses. Time to extubation is presented as either mean ± SD[177] or median (first and third quartiles).[178]

Sources: Adapted, with permission, from Brochard et al,[177] Esteban et al,[178] and Butler et al[179] for the risk-difference calculations.

the initial pressure was adjusted until the frequency ranged between 20 and 30 breaths/min. Twice a day, the pressure was decreased by 2 to 4 cm H_2O if the patient did not show any signs of poor tolerance; if tolerance worsened, pressure was increased to its preceding level. When the patient tolerated a PSV level of 8 cm H_2O or less throughout a 24-hour period, tracheal extubation was performed. During the 21-day trial, the probability of being weaned was twice as high with PSV compared with SIMV or T piece. Weaning duration did not differ between SIMV and T piece but was significantly shorter with PSV than with the other two modalities (6 vs. 9 days, respectively). The number of weaning success patients was significantly larger with PSV (77%) than with SIMV (58%) or T piece (57%) (Table 7-3).

In the study by Esteban et al,[178] 130 patients who met two of three weaning criteria and had failed a 2-hour T-piece trial were randomly assigned to one of four methods: SIMV ($n = 29$), PSV ($n = 37$), intermittent T-piece trials (two or more per day) ($n = 37$), and a once-daily T-piece trial ($n = 31$). The initial SIMV rate was set at half the frequency during ACV (average 10 breaths/min). When the patient tolerated it, SIMV was reduced twice a day by 2 to 4 breaths/min. Tracheal extubation was performed when the patient tolerated an SIMV rate of 5 breaths/min for 2 hours without signs of distress. With the PSV, the initial pressure was adjusted to achieve a frequency of 25 breaths/min or less (average pressure of 18 cm H_2O). According to patient tolerance, pressure was reduced at least twice a day by 2 to 4 cm H_2O. When the patient tolerated a PSV level of 5 cm H_2O for 2 hours, tracheal extubation was performed. With intermittent T-piece trials, the patient breathed through a T-piece circuit or a continuous-flow CPAP of 5 cm H_2O or less at least twice a day. Trial duration was increased gradually, and when the patient tolerated a 2-hour trial, extubation was performed. Between the T-piece trials, ACV was applied. With the once-daily T-piece method, the patient breathed through a T-piece circuit, after which ACV was resumed for 24 hours. Trial duration was increased gradually. When the patient tolerated a 2-hour trial, extubation was performed. Weaning failure was defined as the need for reintubation within 48 hours after extubation or the inability to extubate the patient after 14 days. The median successful weaning duration was 5 days for SIMV, 4 days for PSV, 3 days for intermittent T-piece trials, and 3 days for the once-daily T-piece trials. The rate of successful weaning for the once-daily T-piece method was three times faster than with SIMV (rate ratio: 2.83) and two times faster than with PSV (rate ratio: 2.05). The rate of success for intermittent or once-daily T-piece trials did not differ significantly. The percentage of patients weaned successfully was 69%, 62%, 82%, and 71% for SIMV, PSV, intermittent T piece, and once-daily T piece, respectively.

These two large randomized studies showed conflicting results. In the study of Brochard et al,[177] PSV was superior to T piece and SIMV. In the study of Esteban et al,[178] T piece was superior to PSV and SIMV. Despite the subtle differences in methodology, both trials demonstrated that weaning time

was the longest with SIMV.[179] Thus, both T piece and PSV were superior to SIMV (see Table 7-3).[180,181]

In weaning preterm infants, Dimitriou et al[182] compared pressure-limited SIMV with ACV in two separate randomized, controlled trials. With both SIMV and ACV (n = 20 each), inspiratory pressure was reduced in decrements of 2 cm H_2O until a defined target pressure tailored to the infant's body weight was reached. With SIMV, in addition to decreasing pressure, the SIMV rate was reduced in decrements of 5 breaths/min until a target rate of 20 breaths/min was reached in the first trial. In the second trial, the target was 5 breaths/min. The frequency of decrements in pressure or SIMV rate was not reported. When the infants tolerated the target pressure (for ACV) or target pressure and rate (for SIMV), ventilation was switched to CPAP for 1 hour before extubation. The end-expiratory pressure was maintained at 3 cm H_2O throughout the study. Weaning failure was defined as either the failure to achieve a reduction in ventilator support within 48 hours or requirement for reintubation within 48 hours of extubation. Reintubation was indicated when respiratory acidosis developed or frequent apneas or one major apnea occurred. In the first trial, there were no significant differences in the success rate with ACV or SIMV (70% vs. 75%) or the duration of successful weaning (median: 33 vs. 30 hours). In the second trial, differences between the weaning success rates were not significant, but the median weaning duration was significantly shorter with ACV (24 hours) than with SIMV (50 hours) ($P < 0.05$). A reduction in inspiratory pressure alone with ACV is favored in weaning preterm infants from mechanical ventilation than with SIMV, in which both inspiratory pressure and rate are reduced.

In weaning children ages 1 month to 4 years, Moraes et al[34] compared pressure-limited IMV (n = 35) and SIMV plus pressure support (n = 35). Weaning began when peak inspiratory pressure was less than 25 cm H_2O and $FI_{O_2} \leq 0.6$ (Time 0). Respiratory rate was reduced gradually by 3 to 5 breaths/min to 10 breaths/min. Then, PEEP was gradually reduced to 7 cm H_2O. These ventilator settings were maintained for 12 to 24 hours. Extubation readiness was assessed daily for 2 hours while on $FI_{O_2} \leq 0.5$ with oxygen saturation as measured using pulse oximetry (Sp_{O_2}) ≥95%, and PEEP 5 cm H_2O; in patients on SIMV plus pressure support, the pressure support level was tailored to the size of the endotracheal tube (pressure support of 10, 8, and 5 cm H_2O for endotracheal tube size of 3.0 to 3.5; 4.0 to 4.5; and >5.0, respectively).[183] The average duration of weaning to extubation was 1 day (range: 1 to 6 days) for both groups. The frequency of extubation failure of 5.7% (because of upper respiratory distress) was also similar in both groups. Unlike adults[177,178] or preterm infants,[182] the ventilator mode has no effects on the outcome of discontinuation from mechanical ventilation in children.[34]

INTERMITTENT MANDATORY VENTILATION AND MANDATORY MINUTE VOLUME, ADAPTIVE-SUPPORT VENTILATION

Mandatory minute ventilation (MMV) allows the patient to breathe spontaneously yet ensures that a preset minute ventilation is maintained should the patient's spontaneous ventilation decline below the set level.[184] MMV was developed to overcome certain ineffective features of IMV.[185] When the set mandatory IMV rate is less than required to achieve adequate ventilation, alveolar hypoventilation will ensue whenever a patient's total minute ventilation falls below a critical level. This drawback of IMV can be circumvented with MMV, which actuates a feedback control so that the ventilator provides pressurized breaths of a fixed volume to achieve a preset total minute ventilation.

Weaning with IMV and MMV was studied prospectively in forty patients recovering from acute respiratory failure caused by parenchymal lung injury and chronic airflow obstruction.[186] After meeting defined weaning criteria, the patients were randomized to IMV (n = 18) or MMV (n = 22). In the IMV group, IMV rate was decreased by 2 breaths/min at 3- to 4-hour intervals during the daytime only until the IMV rate was equal to zero. Weaning was considered complete after 4 hours of breathing on CPAP. In the MMV group, MMV was set at 75% of the total minute volume preceding the weaning trial; this was achieved by decreasing frequency while maintaining a V_T of 12 mL/kg as a reference value. Weaning was considered complete after 4 hours of independent spontaneous breathing. Weaning failure was defined as an inability to complete the trial or the need for ventilator support for the same underlying disease. Successful weaning was comparable: 86% for IMV and 89% for MMV. The weaning trial was longer in the IMV group (33 hours) than in the MMV group (4.75 hours).

In neonates with healthy lungs who were intubated for medical or surgical procedures, Guthrie et al[187] conducted a crossover design, short-term trial (2 hours) of MMV versus SIMV. Mandatory breaths with both MMV and SIMV were flow-limited, volume-cycled (V_T 4 to 6 mL/kg), whereas spontaneous breaths were augmented with pressure support. Both modes had comparable efficacy in carbon dioxide removal, yet with lower mean Paw with MMV. Mean rate of the mandatory breaths was also significantly lower with MMV than with SIMV (4.1 vs. 24.2 breaths/min, respectively). The authors postulated that both the reduced rate of the mandatory breaths and low mean Paw with MMV potentially reduced bronchopulmonary dysplasia complications associated with mechanical ventilation. Nevertheless, a prospective long-term follow-up is required. Moreover, SIMV as a weaning method has not been compared with MMV in neonates.

SIMV and ASV were compared as weaning modalities in a prospective, randomized study in post–cardiac surgery patients.[188] With both ASV (n = 18) and SIMV (n = 16), the patients underwent three ventilation phases. With ASV, in phase 1, the initial settings were the ideal body weight, the desired minute volume at the default value of 100 mL/kg of ideal body weight, and peak airway pressure of less than 25 cm H_2O. Adjustment of minute volume was dictated by a Pa_{CO_2} of less than 38 or greater than 50 mm Hg. Phase 1 ended when there were no controlled breaths for 20 minutes. Phase 2 was a continuation of phase 1; it ended when pressure support was decreased to 10 cm H_2O (±2 cm H_2O)

and maintained for 20 minutes. The patient then entered into phase 3, where pressure support was set manually at 5 cm H_2O for 10 minutes. When the patient showed satisfactory tolerance, tracheal extubation was performed. The initial settings for phase 1 in the SIMV group consisted of a V_T of 8 mL/kg and an SIMV rate adjusted to achieve a Pa_{CO_2} of between 38 and 50 mm Hg. The SIMV rate was then set at 12 breaths/min. When spontaneous breaths exceeded 6 breaths/min for 20 minutes, the patient was switched to PSV of 10 cm H_2O (phase 2). The patient was reassessed 20 minutes later for further reduction of PSV or returned to SIMV. If the patient tolerated it, PSV was reduced to 5 cm H_2O (phase 3), as in the ASV group. There was no difference in duration of tracheal intubation, and all patients except for two (one in each group) were extubated within 6 hours. In the ASV group, patients required fewer manipulations of ventilator settings and endured fewer high inspiratory pressure alarms. This study was performed in postoperative patients who had received mechanical ventilation for less than 24 hours before weaning attempts. Because mechanical ventilation duration before weaning influenced the weaning success rate,[189] the response of critically ill patients to the preceding weaning methods may be different.

VARIATION IN DELIVERY AMONG VENTILATOR BRANDS

No study has yet evaluated the response of various ventilators in the SIMV mode to patient flow demand or vice versa. As part of a study evaluating the response of muscle pressure generation to various unloading conditions with assisted ventilation, Mecklenburgh and Mapleson[190] evaluated the response of three ventilators—Hamilton Veolar, Engstrom Elvira, and Puritan Bennett 7200—in the SIMV mode in healthy subjects. V_T was set at 1.5 times the spontaneous V_T and the SIMV rate at 6 breaths/min. The flow waveform was set to "sine wave." Muscle pressure was calculated using the equation of motion from instantaneous airway pressure, flow, and volume with the respiratory system's known resistance and elastance.[191] Amplitude of muscle pressure generation was similar across the three ventilators. Contraction time for mechanical breaths was shortest with the Engstrom Elvira at 1.03 seconds versus 1.38 seconds for the Hamilton Veolar and 1.37 seconds for the Puritan Bennett. For unassisted breaths, contraction time again was shortest with the Engstrom Elvira (1.33 vs. 1.58 seconds for the Hamilton Veolar and 1.70 seconds for the Puritan Bennett). Because V_T was set constant for all three ventilators, the short contraction time led to higher peak airway pressures with the Engstrom Elvira (9.4 vs. 3.9 cm H_2O for the Hamilton Veolar and 4.0 cm H_2O for the Puritan Bennett). Despite the set sine wave, the Engstrom Elvira flow waveform that accounted for the short contraction time was more of a ramp than a sine wave. The investigators concluded that differences in subject responses to different ventilators were related to flow or pressure waveforms and that different subjects may prefer different waveforms.

ADJUSTMENT AT THE BEDSIDE AND TROUBLESHOOTING

SIMV settings consist of the trigger sensitivity, V_T, flow, and the IMV rate for the flow-limit volume-cycled mandatory breaths. For pressure-limit time-cycled breaths, the ventilator settings include the trigger sensitivity, inspiratory pressure, inspiratory time, pressure attack rate, and IMV rate. If the dual hybrid breath-to-breath volume guarantee is applied, V_T is set instead of inspiratory pressure. With either flow-limited or pressure-limited mandatory breaths, pressure support, but not volume support, can be added to the spontaneous breaths to overcome circuit and endotracheal tube resistance, and unload inspiratory muscle work.[43] Monitoring of the patient and the ventilator output waveforms cannot be overemphasized.[192] For example, palpable abdominal contractions suggest expiratory muscle recruitment and possible encroachment of mechanical inspiratory time into neural expiratory time.[64] Adjustment to reduce mechanical inspiratory time can be made by increasing flow rate (flow-limited breaths) or reducing inspiratory time (pressure-limited breaths). Despite the risk associated with tachypnea when mechanical inspiratory time is reduced, Laghi et al[193] demonstrated an increase in exhalation time and decrease in intrinsic PEEP, changes conducive to improved patient–ventilator interaction.

IMPORTANT UNKNOWNS

IMV has stood the test of time since its clinical application as a primary means of ventilator support in the early 1970s. To date, advanced technology enables most ventilators to be equipped with closed-loop ventilation, which allows full ventilator support with gradual support reduction. Unfortunately, few large, randomized, controlled trials have compared the efficacy of closed-loop ventilation with SIMV with or without pressure support in terms of mechanical ventilation duration, patient–ventilator interaction, sensation of dyspnea, and ventilator-associated complications.

Studies show that inspiratory muscle activity is of the same intensity during machine assistance as during the intervening spontaneous breaths,[57] and that SIMV prolongs weaning.[177,178] Given that the diaphragm is activated with each breath, it is possible that SIMV protects the respiratory muscles from disuse atrophy, which occurs with CMV.[82,84,85] Alternatively, the increased workload at low levels of machine assistance actually may cause overload[194,195] and prolong mechanical ventilation duration or weaning time. Which of those two factors plays a role during a low assistance level of SIMV is unknown.

THE FUTURE

Several studies demonstrate a decline in the application of combined SIMV and pressure support in acute respiratory failure,[10,196] except in less-severity-of-illness, postoperative,

and trauma patients.[12] In patients with ARDS, the proportion of patients managed with SIMV has declined from 22% in 1996 to 3% in 2005.[196] With the availability of closed-loop ventilation with improved patient–ventilator synchrony,[72] SIMV will likely be displaced. In contrast to use of SIMV in adults, the ability to employ simple ventilator settings with SIMV and the options of combining it with pressure support and of guaranteeing volume with use of pressure-limited mandatory breaths, ensures that SIMV will remain an important primary ventilator mode in critically ill pediatric patients.[14]

SUMMARY AND CONCLUSIONS

Few ventilator modes have advanced our understanding of the mechanisms that underlie patient–ventilator interaction as has SIMV. As primary means of ventilator mode in less critically ill and postoperative patients in adults and critically ill pediatrics, SIMV remains one of the most widely used modes of ventilation, as does ACV. No mortality difference has been observed between SIMV and ACV. To date, no large randomized study has compared SIMV with more technologically advanced modes as primary methods of ventilation. As a weaning technique, SIMV has been shown to be inferior to T piece and PSV.

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8

PRESSURE-SUPPORT VENTILATION

Laurent J. Brochard
Francois Lellouche

Pressure-support ventilation (PSV) is a mode of partial ventilator support. Such modes are widely used in intensive care units (ICUs) because most ventilated patients (unless deeply sedated) have preserved respiratory drive. The use of these modes helps to reduce need for sedation, an important issue in the ICU,[1,2] and potentially prevents disuse atrophy of the respiratory muscles that can result from controlled ventilation.[3,4] This preventive effect has been shown experimentally with different modes of partial support.[3,5] Finally, partial support may facilitate both the screening process for detecting patients able to breathe spontaneously as well as the weaning of patients with prolonged or difficult weaning.[6] An ideal mode of partial support should be able to supply both full ventilator support and optimal support during weaning; optimize patient–ventilator synchronization and comfort while reducing the need for sedation and the risk of cardiovascular consequences; and, if possible, facilitate or reduce the duration of the weaning. PSV meets several of these requirements, at least partially, as discussed in this chapter. PSV also has limitations, which are delineated. One important limitation is that overassistance of the patient can be easily reached and improvement in the delivery of the optimal PSV level continues as a field of research.

PSV can be remarkably effective in reducing patient effort and avoiding respiratory distress, and can offer a comfortable ventilator support to many patients. PSV can also deliver support much in excess of patient needs and results in excessive delivered volume, excessive duration of inspiration relative to neural inspiratory time (T_I), or both. Much recent research has been undertaken to understand and analyze the consequences of delivering of excessive pressure. Many benefits of PSV, which provides greater freedom to the patient than traditional modes, can be obscured by improper usage.

EPIDEMIOLOGY

Some clinicians view PSV primarily as a mode devoted to weaning and only consider its use until late in a patient's course.[6] An international survey on mechanical ventilation in 361 ICUs in twenty countries was conducted in 1998 (published in 2002).[7] On the first day, PSV was used in less than 10% of all patients; the combination of SIMV with PSV was used in almost 15%, and assist-control in approximately 60% of the patients. A low level of PSV was used to perform a once-daily weaning attempt in 28% of such attempts, a gradual reduction of PSV was used as the sole weaning method in 21% of cases, and a gradual reduction of synchronized intermittent mandatory ventilation (SIMV) and PSV was used in 22% of all cases. Overall, PSV was used (one way or another) for 45% of weaning attempts, suggesting that clinicians consider weaning as the main indication for PSV.

In 2004, Esteban et al repeated the prospective international observational cohort study, employing a nested comparative study performed in 349 intensive care units in twenty-three countries, and compared the findings with the 1998 cohort.[8] Whereas the use of a T piece was the most common initial method for spontaneous breathing trials, the use of low levels of pressure support for weaning trended upward over time (10% vs. 14%). Among patients not extubated, methods for gradual withdrawal differed: there was a decrease in the use of SIMV and of SIMV combined with PSV, and a major increase in the use of PSV for weaning (19% vs. 55%) between the two observation periods. This international survey was repeated a third time, on a larger scale in 2010 and included more than 8000 patients. The initial results indicate that after more than 6 days of mechanical ventilation, PSV was now the most frequently used ventilator mode, indicating progressive dissemination in the use of this technique over the years.[9]

DIFFERENCES AMONG MECHANICAL VENTILATORS DEFINITION AND PHASES

PSV is a pressure-targeted (or limited) mode in which each breath is patient-triggered and supported.[10–13] It provides breath-by-breath support by means of a positive-pressure boost synchronized with inspiratory effort: patient initiated and flow terminated (Fig. 8-1). During inspiration, airway

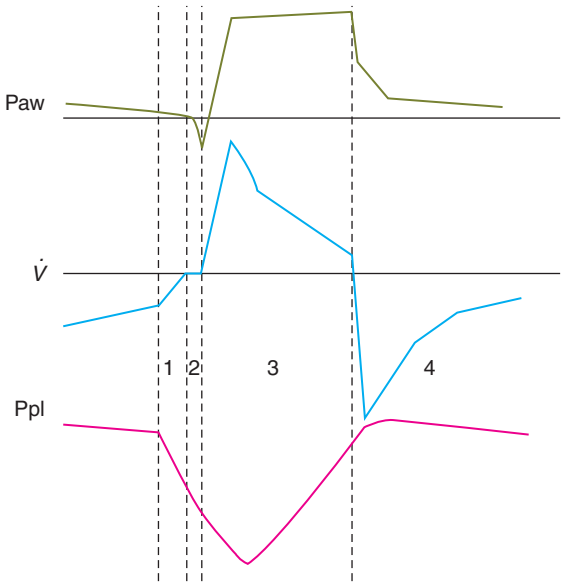

FIGURE 8-1 A pressure-supported breath with tracings of airway pressure (*Paw*), flow ($\dot{V}$), and pleural pressure (*Ppl*). Four phases of patient effort can be discerned. Phase 1 is still expiratory and corresponds to an effort performed against intrinsic positive end-expiratory pressure; it occurs before the triggering system of the ventilator can detect any signal that indicates the onset of patient inspiratory effort. Phase 2 is the time required to activate the triggering system of the ventilator (also called the initiation phase). Phase 3 is the insufflation phase during which the ventilator pressurizes the airway at the level set by the clinician. This phase is terminated by the cycling-off criterion. Patient inspiratory effort may terminate before the end of this phase. Phase 4 is the expiratory phase.

pressure is raised to the preset pressure-support level. The speed of pressurization is system specific but most recent ventilators offer the possibility of adjusting this pressurization rate. Throughout the inspiratory phase, the ventilator works as a pressurized demand-flow system at a predetermined pressure level. PSV is maintained until the machine determines the end of expiration, supposedly reflecting the end of patient demand. The expiratory trigger mechanism is based on decay of inspiratory flow. When inspiratory flow falls below a threshold value, which should indirectly indicate that the inspiratory muscles have relaxed, the ventilator cycles to the expiratory phase releasing the PSV and opening its expiratory port. A level of positive end-expiratory pressure (PEEP) lower than the inspiratory plateau pressure can then be applied. PSV can thus be defined as a patient-initiated (pressure or flow), pressure-targeted, flow-cycled mode of mechanical ventilation.

Three phases of PSV can be distinguished: (a) recognition of the beginning of inspiration, (b) pressurization, and (c) recognition of the end of inspiration. These phases constitute the working principles of PSV, and can vary from one ventilator to another (see Fig. 8-1). As discussed in the section Differences Among Mechanical Ventilators, these variations may induce differences in the effect of PSV for similar levels of pressurization.

Initiation of the Cycle

Triggering of inspiration is initiated by patient effort and is detected by a pressure or flow sensor. Trigger sensitivity is adjustable. This mechanism requires an active effort by the patient, the intensity of which depends on the characteristics of the valve. The opening time delay varies between 50 and 250 milliseconds, depending on the ventilator.[14–18] The most recent data indicate that most ventilators now respond in less than 100 milliseconds.[19–22]

Opening of the demand valve can be triggered by a fall in pressure or a difference in the flow signal between inspiratory and expiratory flows (referred to as *flow-by*). For the latter, a constant flow is delivered to the circuit during the expiratory phase; inspiratory effort is then detected as a small difference between inspiratory and expiratory flow. Flow-triggering avoids the need for a closed demand valve. Aslanian et al[23] showed that the difference between pressure-triggered and flow-triggered systems has become quite small on modern ventilators. The triggering phase represents less than 10% of a patient's overall effort to breathe. A flow-triggering system makes a statistically significant difference but of limited clinical importance.

Pressurization

Once inspiration has been initiated, the ventilator delivers a high inspiratory flow, which rapidly decreases throughout the rest of inspiration. A servo regulatory mechanism maintains the proper flow to reach the appropriate preset PSV level and keeps this pressure approximately constant until expiration occurs. Flow regulation varies among ventilators, thus determining the pressure waveform. Usually, the servo valve is continuously controlled during the breath, such that delivered pressure closely approximates target pressure set by the clinician. In general, the aperture of the proportional servo valve is progressively reduced as the monitored pressure gets closer to the target pressure. For this reason, the wave shape often constitutes a pressure ramp rather than a true square wave. The pressure level can be adjusted between 0 (spontaneous breathing through the ventilator circuit) and a maximum of 30 or 60 cm H_2O (even more with some ventilators). In clinical settings, pressure levels above 30 cm H_2O are rarely used.

Pressure increases according to a rate that is system-specific; formerly, it was nonadjustable. A high speed of pressurization produces a square pressure wave; low achievement of the preset PSV level attenuates this shape. Many ventilators now allow adjustment of the rate of pressurization. Its influence is discussed in the section Pressurization Rate and Inspiratory Flow.

Cycling of Expiration

During PSV, cycling to exhalation is primarily triggered by a decrease of inspiratory flow from its peak to a system-specific threshold value. This critical decrease of inspiratory flow is taken as indirect evidence that the inspiratory muscles have begun to relax. Expiration is triggered when either an absolute level of flow (between 2 and 6 L/min) or a fixed percentage of peak inspiratory flow (12% or 25%) is reached, depending on the ventilator model (Table 8-1). The threshold value for cycling, which can be viewed as sensitivity of the expiratory trigger, was formerly nonadjustable. Adjustment is now offered to clinicians on many ventilators.

Detection of a small degree of pressure (1 to 3 cm H_2O) above the fixed PSV level, consequent to sudden expiratory effort by the patient, can also be used (alone or combined with the flow criteria) to stop inspiratory assistance. Finally, a time limit for inspiration is usually included. This serves as a safety mechanism if a leak develops in the circuit and the two previous methods of terminating inspiration become inoperative. Complications have been reported in the absence of this time-limit mechanism, whereby constant insufflation (at the PSV level) creates a high level of continuous positive airway pressure.[24]

Other Settings

Because no mandatory breath is present with PSV, a safety feature is often available in case of apnea. This may be an automatic feature, or a minimal frequency, or minute ventilation to be set. The time delay for apnea may be adjustable. This safety feature is not available on all ventilators.

PSV can be used in conjunction with SIMV.[25–28] Two approaches have been used: addition of a fixed level of PSV during spontaneous breathing to overcome endotracheal tube (ETT) or circuit resistance,[29] or use of a variable level of PSV between the mandatory breaths. The second approach introduces considerable complexity into ventilator management of patients.

DIFFERENCES AMONG MECHANICAL VENTILATORS

During PSV, specific characteristics of the ventilator may interfere with patient respiratory activity. These differences may be determined by the manufacturer's algorithm to deliver pressure, such as speed of pressurization and/or initial peak flow setting, ability to maintain a plateau pressure and quality of regulation, and termination criteria used to cycle from inspiration to expiration. Nonspecific features include characteristics of the demand valve and/or triggering mechanism, and flow-impeding properties of the expiratory circuits, including PEEP devices.[22] These differences may also vary with the type of ventilator, whether it is designed only for delivery of noninvasive PSV or a full intensive care ventilator.[20,21,30,31] The relative weight of each factor is difficult to determine and may vary from one patient to another. This consideration should, however, be kept in mind when interpreting the results of clinical studies of PSV using various ventilators. One study with old-generation ICU ventilators compared three of them and found major work differences,[32] showing that different characteristics of PSV could

TABLE 8-1: TECHNICAL CHARACTERISTICS OF PRESSURE SUPPORT VENTILATION AND AVAILABLE SETTINGS ON INTENSIVE CARE VENTILATORS

		Inspiratory Trigger		Pressurization	Cycling-off Criterion		
	Manufacturer	**Flow**	**Pressure**		**Flow Cycle**	**Pressure Cycle**	**Time Cycle**
PB 7200	Puritan Bennett/ Covidien	1 to 15	0.5 to 20		5 L/min	+1.5 cm H_2O	3 s
PB 740	Puritan Bennett/ Covidien	1 to 20			10 L/min or 25% PF	+3 cm H_2O	3.5 s
PB 760	Puritan Bennett/ Covidien	1 to 20		5% to 100%	Adjust. 1% to 45% PF	+3 cm H_2O	3.5 s
PB 840	Puritan Bennett/ Covidien	1 to 20		5% to 100%	Adjust. 1% to 80% PF	+1.5 cm H_2O	3 s
Evita 2	Drager				25% PF	High pressure limit	
Evita 2 dura	Drager	0.3 to 15 L/ min		0 to 2 s	25% PF	High pressure limit	
Evita 4	Drager	0.3 to 15 L/ min		0 to 2 s	25% PF	High pressure limit	4 s
Evita XL	Drager	0.3 to 15 L/ min		0 to 2 s	5% to 70% PF	High pressure limit	
Savina	Drager				25% PF	High pressure limit	
Servo 900C	Maquet		0 to 20		25% PF	+3 cm H_2O	
Servo 300	Maquet	0.6 to 2	0 to 20		5% PF	+20 cm H_2O	
Servo-i	Maquet	0.6 to 2	0 to 20	0 to 0.4 s	Adjust. 1% to 80% PF	High pressure limit	
Servo-s	Maquet	0.6 to 2	0 to 20	0 to 0.4 s	Adjust. 1% to 80% PF	High pressure limit	
Veolar	Hamilton				25% PF	High pressure limit	3 s
Galileo	Hamilton	0.5 to 15	0.5 to 10	25 to 200 ms	Adjust. 10% to 40% PF	High pressure limit	3 s
Raphael	Hamilton						
Bird 8400	Viasys Healthcare	1 to 10	1 to 20		25% PF	High pressure limit	3 s
T-Bird	Viasys Healthcare	1 to 20			5% to 30% PF (submenu)	High pressure limit	3 s
Vela	Viasys Healthcare	1 to 8			Adjust. 5% to 30% PF	High pressure limit	0.3 to 3 s
Avea	Viasys Healthcare	0.1 to 20	0.1 to 20		Adjust. 5% to 45% PF	High pressure limit	0.15 to 5 s
Bear 1000	Viasys Healthcare				25% PF		5 s
Bipap Vision	Respironics/ Philips	Automatic (autotrack)		0.05 to 0.4 s	Automatic (autotrak)		
Esprit	Respironics/ Philips	0.5 to 20	0 to 20	0.1 to 0.9 s	Adjust. 10% to 45% PF		
LTV1000	Pulmonetics	1 to 9			Adjust. 10% to 40% PF	High pressure limit	
Elisee	Saime				Adjust. 10% to 40% PF or automatic		
e500	Newport				Adjust. 5% to 50% PF, variable	High pressure limit	
HT50	Newport		0 to –10			High pressure limit	0.1 to 3 s
Infrasonics star	Infrasonics		–0.5 to 20		4 L/min or 10% PF		3.5 s
Inspiration	Event	1 to 25	–1 to 20	Fast/medium/low	Adjust. 10% to 80%		

Abbreviations: *Adjust.*, adjustable; *PF*, peak-flow.

have a major influence on its efficacy (Fig. 8-2). Fortunately, most recent ventilators have designed much better systems of regulation, providing more homogeneous delivery of PSV, but clinically relevant differences still exist.[22]

As with other assisted modes, the triggering mechanism is a key determinant of the efficacy of PSV. A poorly functioning demand valve has two consequences: it imposes an effort to open the valve, and it prolongs the time before

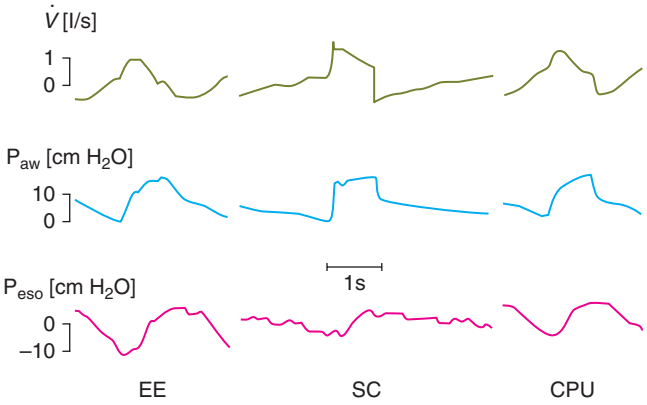

FIGURE 8-2 The influence of a ventilator and its specific algorithm on patient effort. Three ventilators were studied at 15 cm H_2O of PSV. Flow, airway pressure (*Paw*) and esophageal pressure (*Peso*) are presented. Note the different airway and flow profiles, and the impact on esophageal pressure swing. Work of breathing was significantly less with SC. Although modern ventilators tend to homogenize the delivery of PSV, differences still exist and illustrate the effects of varying the pressure ramp. *CPU*, CPU1, Ohmeda, Maurepas, France; *EE*, Erica Engstrom, Bromma, Sweden; and *SC*, Servo 900 C, Siemens, Lund, Sweden. Reproduced from.[28]

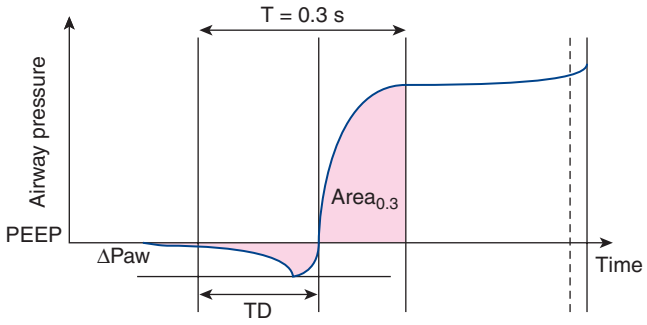

FIGURE 8-3 The method used to calculate the trigger characteristics and pressurization phase during pressure support ventilation based on the airway pressure-time curve. The total trigger phase is evaluated by the time delay (*TD*) between the onset of simulated effort and the time at which airway pressure becomes positive after experiencing a pressure fall (Δ*Paw*). The quality of pressurization is best quantified as the area measured at 0.3 second. (With kind permission from Springer Science and Business Media: Cox D, Tinloi SF, Farrimond JG. Investigation of the spontaneous modes of breathing of different ventilators. *Intensive Care Med*. 1988;14:532–537.)

assistance is delivered. Assisted modes, like PSV, are primarily devoted to reducing or optimizing this effort. Demand valves function with an unalterable delay before delivering gas flow to the patient. For instance, if 200 milliseconds is required between the beginning of an inspiratory effort and the opening of the valve, nearly one-third of the duration of inspiratory effort in a tachypneic patient may take place without any gas entering the lungs. If auto (or intrinsic) PEEP is present, another 200 milliseconds may be wasted (while the respiratory muscles work against this positive alveolar pressure) before any inspiratory flow can start.[33] In addition, if the speed of pressurization of PSV is low, another 200 milliseconds is required to reach the plateau pressure. Thus, assistance will be delivered to the patient 600 milliseconds after the beginning of inspiratory effort, which may correspond to the end of that patient's inspiratory effort.[34]

Comparison of the triggering functions of various ventilators demonstrates that the most recent generation of ventilators, using pressure-sensitive mechanisms, flow-sensitive mechanisms, or both, usually require less effort and open faster than the older generation. This was extensively studied by Richard et al,[19] and subsequently by Thille et al[22] who compared different generations of ventilators, including the new turbine ventilators (Figs. 8-3 to 8-5). The ability of different ventilators to pressurize the airway during PSV was investigated. Different levels of simulated inspiratory demand were used. Pressurization was assessed through the net area of the inspiratory airway pressure-time tracing over the first 0.3 second, 0.5 second, and 1 second at different levels of PSV (Figs. 8-3 and 8-4). Triggering sensitivity was assessed independently by measuring the time delay and the pressure fall with different levels of inspiratory drive (Figs. 8-3 and 8-5). Ventilators released after 1993 achieved significantly better results than most previous generation ventilators regarding the pressure-time area at 0.3 seconds and triggering delay, indicating large improvements in terms of triggering and pressurization. Regarding PSV and trigger performances, this generation of ventilators outperformed most previous generation ventilators; this was also the case for some piston and turbine-based ventilators, including several of those specially designed for noninvasive ventilation (NIV). Six years later, trigger function, pressurization capacity and accuracy of pressure measurements during simulated PSV, and expiratory resistance were again evaluated in a similar bench study.[22] In 2006, new-generation turbine-based ventilators performed as well as, or better than, the best compressed-gas ventilators. The newest ventilators did not perform significantly better than the 2000 ventilators, suggesting that a technological ceiling may have been reached.

Dedicated Noninvasive Ventilators

NIV using PSV can be performed with either turbine ventilators, specially conceived to provide NIV, or conventional ICU ventilators originally designed for invasive ventilation. The rate of use of each of these is variable depending on the care setting, the etiology of respiratory failure, the specialist, and even the geographic region.[35–37] Ventilators delivering PSV and PEEP, termed *bilevel ventilation*, and designed for home ventilation have been evaluated in stable, awake patients with chronic ventilatory failure.[38] Despite some variability in the delivery of pressure, no difference was found in terms of comfort or improvement in inspiratory muscle unloading. These differences, however, might have greater impact in patients with acute respiratory failure.

The presence of air leaks around the mask is a major problem related to use of NIV. When ICU ventilators are not capable of compensating for leakage, leaks generate

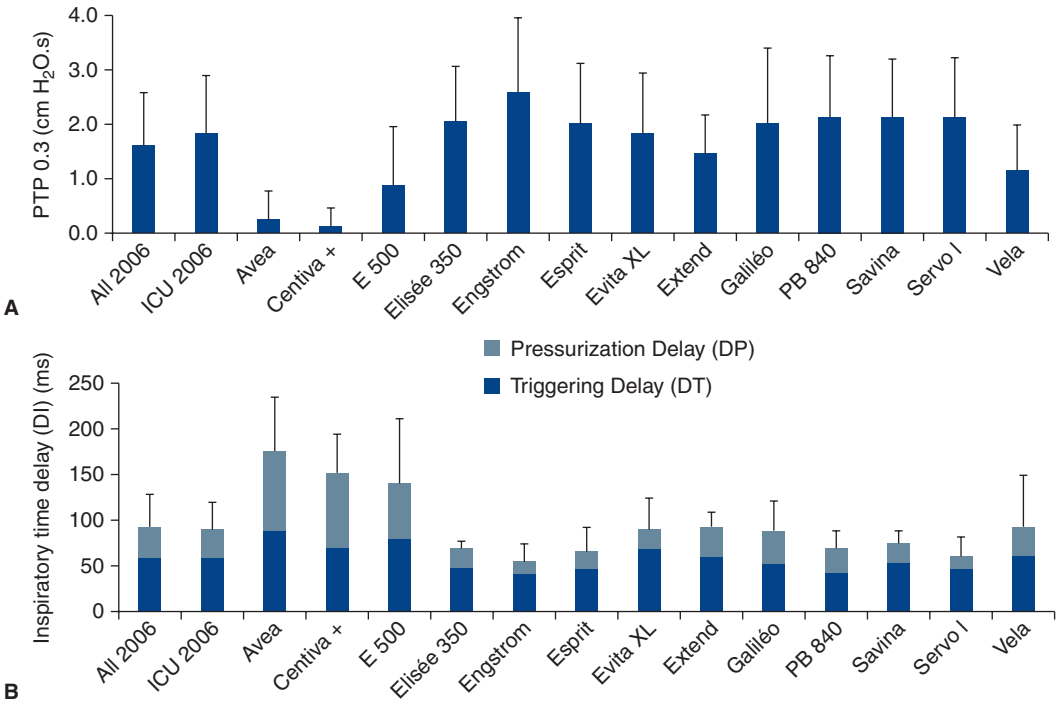

FIGURE 8-4 **A.** Inspiratory area, measured as the integral of the airway pressure-time trace over the first 0.3 second of inspiration (see legend of Fig. 8-3), for a PSV level of 15 cm H_2O for the same simulated level of inspiratory demand. **B.** Inspiratory time delay in milliseconds measured during the same tests, separated into triggering and pressurization delay. The new-generation ICU ventilators proposed in 2006 were evaluated. These included Avea and Vela (Viasys Healthcare, Conshohocken, PA), E 500 (Newport Medical Instruments, Costa Mesa, CA), Elisee 350 (Resmed-Saime, North Ryde, Australia), Engstrom and Centiva (General Electric, Fairfield, CT), Esprit (Respironics, Murrysville, PA), Extend (Taema, Antony, France), Savina and Evita XL (Dräger, Lubeck, Germany), Galileo (Hamilton, Rhäzuns, Switzerland), PB 840 (TYCO, Carlsbad, CA), and Servo I (Maquet, Solna, Sweden). Of these thirteen ventilators, four were turbine-based (Elisée 350, Esprit, Savina, Vela) and nine were conventional servo-valve compressed-gas ventilators. Seven were viewed as ICU ventilators (Avea, Evita XL, Engstrom Extend, Galileo, PB 840, Servo I) and six were mid-level ICU ventilators (Centiva, E 500, Elisee 350, Esprit, Savina, and Vela). The mean values for all ventilators or only ICU ventilator is also presented. (With kind permission from Springer Science and Business Media: Thille AW, Lyazidi A, Richard JC, Galia F, Brochard L. A bench study of intensive-care-unit ventilators: new versus old and turbine-based versus compressed gas-based ventilators. *Intensive Care Med.* 2009;35:1368–1376.)

autotriggering, prolonged cycling, ineffective efforts, and a poor pressurization capacity of the ventilator. For these reasons, manufacturers have developed specific algorithms, called *NIV modes,* which aim to minimize the negative impact of leaks on ICU ventilator performance. Dedicated NIV ventilators are designed to function with leaks and have developed sophisticated algorithms that evaluate online the magnitude of a leak and readjust the triggering thresholds. Several bench studies show variable performance in the ability to ameliorate these key ventilator functions with the activation of the NIV mode,[39,40] and an overall better performance for dedicated NIV ventilators. The clinical effect of "NIV modes" on patient–ventilator interactions has also been evaluated in two recent short-term clinical studies. Vignaux et al compared four ICU ventilators, with and without the activation of the NIV mode, showing a reduction in patient–ventilator asynchronies with the NIV mode.[41] A second study, employing the same schema but also testing a specific NIV ventilator, showed a significant reduction in the rate of these events with the latter.[42] Although clinical studies are needed to clarify this issue, it is advisable to use NIV modes on ICU ventilators or dedicated ventilators.

MAIN PHYSIOLOGIC EFFECTS OF PRESSURE-SUPPORT VENTILATION

Breathing Pattern

During PSV, the patient maintains control over respiratory rate, and has partial control of T_I and tidal volume (V_T). As such, PSV seems to allow the patient to breathe in a "physiologic" way. This is only partially true, because there is a complex interaction between ventilator support and patient control of breathing. This interaction depends on the pressure level and PSV characteristics. For instance, a change in the criterion for cycling from inspiration to expiration will result in a different T_I, different V_T, and may result in more (or less) dynamic hyperinflation.

The addition of PSV modifies the spontaneous breathing pattern.[43–48] Most patients develop an increase in V_T and decrease in respiratory rate with increasing levels of PSV. The breathing pattern adapts rapidly under PSV when the respiratory muscles face a new workload.[49] Adjustment of the PSV level can be guided by noting the breathing pattern response:

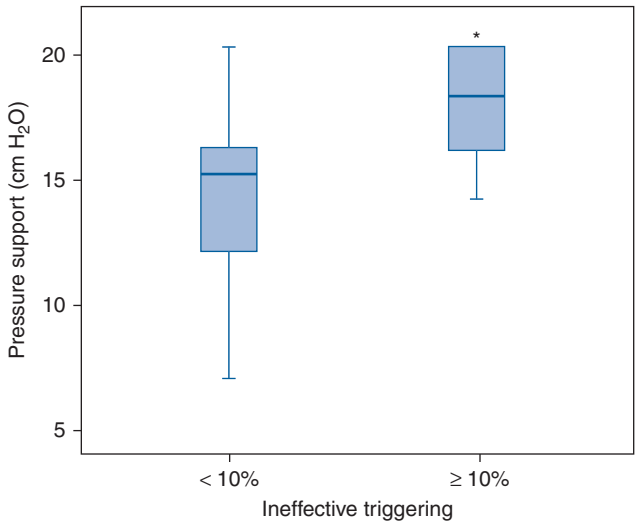

FIGURE 8-5 Relationship between the level of PSV and the frequency of ineffective triggering in a cohort series of sixty-two consecutive patients requiring mechanical ventilation for more than 24 hours. *Box plots* show median, interquartile range (25th to 75th percentiles), and outliers (5th to 95th percentiles) of PSV in patients with and without a high prevalence of ineffective triggering (>10%). PSV was higher in patients with a high incidence of ineffective triggering. *$p < 0.05$. (With kind permission from Springer Science and Business Media: Thille AW, Rodriguez P, Cabello B, Lellouche F, Brochard L. Patient-ventilator asynchrony during assisted mechanical ventilation. *Intensive Care Med*. 2006;32:1515–1522.)

changes in breathing pattern in response to loading conditions usually occur within 1 to 2 minutes.[49,50] Importantly, evaluation of a patient during a low level of PSV is different from evaluation of during a T-tube trial, for instance, even if the clinical outcome of the two approaches may be similar. Two studies show that the use of a low level of PSV during a "spontaneous breathing trial" modifies the thresholds that may be used to predict weaning success or weaning failure.[51,52]

Excessive levels of support, however, can generate hyperinflation, respiratory alkalosis, respiratory depression with apnea, or appearance of missing efforts.[53] A high level of support-induced hyperinflation may indeed result in an inability to trigger the ventilator (so-called ineffective triggering), with a substantial difference in the ventilator's displayed respiratory rate and the patient's true respiratory rate.[54] The frequent occurrence of these findings (discussed below in Degree of patient-ventilator synchrony or asynchrony) illustrates the fact that the insufflation during PSV is often terminated after cessation of the patient's inspiratory time, especially in case of airway obstruction.[55] The higher the pressure level, the longer is this prolongation.[56] Thus, to some extent, PSV artificially forces the patient to decrease respiratory rate as a way of trying to maintain a sufficient expiratory time.[54] As the PSV level is increased, an imbalance almost inevitably occurs between prolongation of the insufflation time and shortening of expiratory time, promoting severe asynchrony.

In patients with acute lung injury, factors other than respiratory muscle load influence respiratory drive. Pesenti et al reported that variation in arterial oxygen (O_2) saturation between 85% to 90% and 100%, obtained by modifying fractional inspired oxygen concentration (FI_{O_2}), had a significant effect on respiratory drive in patients with acute lung injury receiving PSV.[57] Volta et al reported similar findings: modulation of FI_{O_2} produced variation in dyspnea, occlusion pressure, and respiratory frequency.[58]

The influence of PSV on the duty cycle (fractional inspiratory time, T_I/T_{TOT}) is variable and influenced by the setting of the pressure ramp on the ventilator.[59] A decreasing duty cycle with increasing PSV levels was observed in several studies.[44–46]

The influence of PSV on minute ventilation is variable, producing an increase or no change.[43–47] An increase in minute ventilation is often observed when PSV is compared with unassisted breathing through the ventilator circuit. More frequently, an increase in PSV fails to substantially modify minute ventilation whereas it modifies alveolar ventilation. Consequently, the breathing pattern may be markedly modified without significant change in minute ventilation.[43–48] Thus, monitoring minute ventilation is of little help when titrating the level of PSV.

Gas Exchange and Distribution of Ventilation and Perfusion

The primary goal of PSV is to support patient effort while allowing a satisfactory gas exchange. PSV is not primarily aimed at improving oxygenation. The effects of PSV on gas exchange are primarily explained by increased alveolar ventilation resulting from changes in breathing pattern. Indeed, despite lack of change in minute ventilation, an increase in V_T produces a decrease in the ratio of dead space to tidal volume (V_D/V_T). Thus, alveolar ventilation is often increased. Other factors may influence arterial blood gases, such as changes in O_2 consumption, modification of total dead space, and altered distribution of ventilation. During the weaning of patients with hypercapnic respiratory failure, addition of PSV produced a correction of the partial pressure of arterial carbon dioxide (Pa_{CO_2}) and respiratory acidosis compared to spontaneous breathing.[43] In normal, nonintubated subjects, PSV 10 cm H_2O produces significant decreases in Pa_{CO_2} below normal levels.[53] PSV can thus correct hypoventilation but also induce hyperventilation that is not counteracted by respiratory motor output.[60] Consequently, although PSV permits correction of hypercapnia resulting from rapid shallow breathing or helps patients with chronic CO_2 retention to choose their own target Pa_{CO_2}, the level of PSV requires fine adjustment as respiratory alkalosis can easily occur.

Although breathing pattern, especially respiratory frequency, is in part controlled by the patient, an interaction exists between the level of PSV and alveolar ventilation, which is not fully controlled by respiratory center command. MacIntyre and Leatherman showed in a lung model that a biphasic effect can occur with increasing levels of PSV.[61] Above a certain limit, passive (hyper-) inflation will result with high levels of PSV. That excessive assistance with

PSV may induce respiratory alkalosis not controlled by the patient's respiratory centers and has important consequences. Parthasarathy and Tobin found that during sleep PSV was associated with numerous episodes of apneas, desaturation, and microarousals leading to sleep fragmentation.[62] This could be prevented by adding dead space to the circuit. Not tested in this study was the likelihood that reductions in the level of PSV might prevent this problem.

The distribution of ventilation and perfusion during PSV has been assessed in a few studies.[63–68] Valentine et al[63] compared SIMV, PSV, and airway pressure release ventilation in nine patients a few hours following cardiac surgery. The major characteristics of ventilation–perfusion ($\dot{V}_A/\dot{Q}$) distributions were similar with all modes.[63] Dead space was lower during airway pressure release ventilation than during either SIMV or PSV. Gas exchange was assessed with the six-inert-gas technique in a study comparing controlled mechanical ventilation, unassisted spontaneous breathing, and PSV 10 cm H_2O.[64] Using isotopic scanning, they evaluated regional distribution of $\dot{V}_A/\dot{Q}$ ratios in eight patients with chronic obstructive pulmonary disease (COPD). Ventilator discontinuation was associated with rapid shallow breathing and an increase in perfusion to low $\dot{V}_A/\dot{Q}$ regions. Isotopic scans revealed a horizontal craniocaudal difference of $\dot{V}_A/\dot{Q}$ with all modes, and the lowest $\dot{V}_A/\dot{Q}$ ratios were found at the bases. Abnormalities in $\dot{V}_A/\dot{Q}$ distribution observed during spontaneous breathing were also present during 10 cm H_2O PSV, but to a smaller extent.

Ferrer et al assessed whether PSV could improve $\dot{V}_A/\dot{Q}$ imbalance during the transition between positive-pressure ventilation and spontaneous breathing in seven intubated patients with COPD during weaning.[66] PSV avoided $\dot{V}_A/\dot{Q}$ worsening during this transition. Hemodynamics, blood gases, and $\dot{V}_A/\dot{Q}$ distributions were equivalent during PSV and assist-control ventilation (ACV) when the two modes provided similar levels of assistance. Diaz et al studied the reasons for improvement in partial pressure of oxygen (P_{O_2}) and partial pressure of carbon dioxide (P_{CO_2}) in ten patients with acute hypercapnic exacerbations of COPD who were switched from spontaneous breathing to PSV during NIV.[65] Improvement in blood gases was primarily mediated by a higher alveolar ventilation, and not improvement in $\dot{V}_A/\dot{Q}$ relationships. Although O_2 uptake tended to decrease, the respiratory exchange ratio increased, explaining a slight increase in arterial-to-alveolar O_2 difference secondary to increased clearance of body stores of CO_2 during NIV. These results suggested that attaining an efficient breathing pattern rather than high inspiratory pressures should be the primary goal for improving arterial blood gases during NIV with PSV in this type of patient. Lastly, a recent study assessed gas exchange and changes in lung volume through the use of lung diffusion capacity for carbon monoxide (DL_{CO}) in sixteen patients without COPD.[69] An increase in PSV of 5 cm H_2O neither affected lung volume nor increased the volume of the lung participating in gas exchange, but was associated with a slight but significant deterioration in DL_{CO}. Thus, a target V_T closer to 6 mL/kg than to 8 mL/kg of predicted body weight during PSV was associated with better gas exchange.

The effect of PSV on oxygenation varies and depends on many factors, such as the induced changes in alveolar ventilation, O_2 consumption, dead space, and mean airway pressure.[43–46] Most investigators have not found significant changes in arterial oxygenation when PSV was compared with other modalities (primarily spontaneous breathing or SIMV) delivered at the same $F_{I_{O_2}}$. Compared with continuous positive pressure ventilation in surgical ICU patients, Zeravik et al suggested that only patients with a low level of extravascular lung water had improved oxygenation with PSV among patients with moderate acute respiratory failure.[70]

Work of Breathing and Respiratory Effort

A major goal of PSV is to assist respiratory muscle activity in a way that improves the efficacy of patient effort and decreases workload. Many of the initial studies on PSV have focused on this point and have measured work of breathing or indexes of patient effort during PSV.[11,13,43,45,46,71,72]

MacIntyre was one of the first to study the effects of various levels of PSV in patients.[11] The level of PSV was positively correlated with V_T and negatively correlated with respiratory rate. He suggested that PSV alters the characteristics of work of breathing: the change in the pressure-to-volume ratio of the work of each breath decreased progressively with increasing levels of PSV. In intubated patients recovering from acute respiratory failure, Brochard et al compared breathing characteristics during 10 cm H_2O PSV, spontaneous unassisted breathing through a ventilator, and a continuous flow system without a demand valve.[13] PSV produced significant increases in V_T and partial pressure of arterial oxygen (Pa_{O_2}), and a decrease in respiratory rate, transdiaphragmatic pressure (Pdi) swings, pressure-time index, and electromyographic activity of the diaphragm. Subsequently, Brochard et al compared several levels of PSV in eight patients who were experiencing weaning difficulties, four of whom had COPD.[43] During unassisted breathing, patients breathed with a small V_T and a high rate, a pattern associated with unsuccessful weaning, hypoxemia, and hypercapnia. All patients exhibited intense activity of their sternocleidomastoid muscles and the analysis of the diaphragmatic electromyographic recordings suggested impending high-frequency fatigue during PSV0. All these signs or symptoms disappeared at 10 cm H_2O or 20 cm H_2O of PSV, while activity of the sternocleidomastoid muscles was minimized or no longer present. Work of breathing returned to normal, whereas the respiratory rate remained around 30 breaths/min. These findings were later confirmed by another study also analyzing an index of high-frequency fatigue.[73]

The values of respiratory rate described above emphasize that trying to "normalize" respiratory rate much below the point where a patient is no longer in respiratory distress, such as targeting a threshold of 20 breaths/min or even lower values, may not be desirable; we will see later that it may favor asynchrony. A limit of 30 breaths/min was also found by Jubran et al to be predictive of a inspiratory pressure-time

product of less than 125 cm H_2O.sec/min, representing a desirable level of inspiratory effort.[74] This has important clinical implications for the bedside titration of PSV.

PSV acts with great efficiency in decreasing work of breathing. This is more or less proportional to the level of PSV and is accompanied by changes in breathing pattern measurable at the bedside, together with changes in respiratory muscle recruitment. There is, however, an individual limit of pressure above which work of breathing is not decreased and the patient becomes to be overassisted.[44]

Different indexes have been used to assess respiratory muscle activity. Beck et al compared the crural diaphragmatic electrical activity (Edi) with Pdi during varying levels of PSV in intubated patients.[56] Changes in PSV did not alter neuromechanical coupling of the diaphragm: Edi and Pdi decreased proportionally with the addition of PSV. In contrast, Fauroux et al found that diaphragmatic pressure-time product, often used to quantify loading and unloading of the diaphragm, did not exhibit a linear relationship with the diaphragmatic electromyographic activity during PSV and that flow measurements may be necessary when assessing diaphragmatic unloading during PSV.[75]

Compensation for the Work Caused by Endotracheal Tube and Demand Valve

PSV has been used to predict patient tolerance of unassisted breathing and extubation.[76] The idea is based on selecting a level of PSV just sufficient to overcome the circuit resistance. Thus, spontaneous muscular activity should be similar to what a patient would perform in the absence of an ETT or circuit.[77] The pressure needed to obtain a "adequate" breathing pattern during a spontaneous breathing test can provide insight into a patient's ability to tolerate extubation.

It has long been argued that breathing through an ETT and demand valve increases respiratory muscle work[78] and that PSV can compensate for this increased demand.[77,79,80] Part of the confusion, however, comes from the fact that the resistance posed by an ETT is probably close to upper-airway resistance after extubation. Several clinical studies have compared work of breathing before and immediately after extubation.[80–82] These studies demonstrated that the work of breathing was similar or even often higher after extubation than before extubation (while breathing through an ETT). This indicates that there is no rationale for compensating for the ETT in itself. What needs to be compensated for, however, is the ventilator circuit through which the patient is breathing, including the triggering system.

In intubated subjects breathing with various levels of PSV who were disconnected from the ventilator and finally extubated,[77] the level of PSV that compensated for extra work of breathing through the ETT and ventilator circuit was calculated post hoc. In patients with underlying lung disease, the PSV level that compensated for the additional work ranged from 8 to 14 cm H_2O, while it averaged 5 cm H_2O in patients free of lung disease. Based on various studies,[83,84] it has been argued that a PSV level of 5 to 10 cm H_2O be provided when a patient is breathing through a demand valve.

Despite wide individual variation among patients regarding the best pressure to apply in physiologic studies, a simplified approach, based on the same principle, has been applied in several large clinical trials. These studies showed that a low level of PSV (7 to 10 cm H_2O) is overall as efficient as a T-piece trial in testing whether a patient can be separated from the ventilator and eventually extubated, despite the lack of individual titration of PSV.[8,85–87]

Some studies suggested that this low PSV test may be easier to tolerate than a T-piece trial,[88] and measurements of muscular effort support this impression in cardiac patients.[89] Therefore, a T-piece trial seems to constitute a more challenging test than the low PSV test, at least in cardiac patients.

Effect of Instrumental Dead Space

Instrumental dead space is usually constituted by the flex-tube connector, the Y piece, and the humidification system. Heat and moisture exchangers and heated humidifiers constitute a resistive load,[90] but heat and moisture exchangers also add instrumental dead space, because they are positioned between the Y piece and the ETT. The mechanical characteristics of heat and moisture exchangers can substantially modify breathing pattern, effort to breathe, and gas exchange during PSV. These effects were assessed in several studies during PSV and invasive ventilation,[90–95] and also studies during NIV,[96,97] with consistent results. Adding dead space with the heat and moisture exchanger reproduced well-described effects of addition of CO_2 on breathing pattern. In intubated patients during PSV, for instance, Pelosi et al reported that work of breathing increased from 8.8 ± 9.4 J/min with a heated humidifier to 14.5 ± 10.3 J/min with an heat and moisture exchanger.[92] These investigators suggested that increasing the level of PSV by 5 cm H_2O may be necessary to compensate for the increased work of breathing caused by heat and moisture exchangers dead space. Recently, it was shown, however, that small heat and moisture exchangers have a much lower dead space, and that their impact is therefore limited or negligible.[98]

SLEEP

Mechanical ventilation in the ICU is associated with an abnormal sleep pattern characterized by abnormal circadian distribution of sleep and numerous arousals, similar to the pattern found in sleep apnea patients.[99,100] The exact influence of mechanical ventilation on sleep fragmentation in ICU patients remains poorly understood, but the ventilator mode and its settings, as well as patient–ventilator interactions, can influence the degree of fragmentation and the quality of sleep.[62,99,101–103]

The effects of the ventilator mode and settings were investigated in ICU patients by Parthasarathy and Tobin.[62] Sleep fragmentation was increased with the use of PSV as compared with ACV, mostly because of central apneas caused by the level of PSV. The main mechanism of apnea was a decrease in P_{CO_2}, which could be avoided by adding an external dead space. This illustrated an undesirable effect of PSV, resulting from hyperventilation. During ACV, by contrast, the patient can trigger some or all breaths, and a minimal respiratory rate and the V_T are preset, and this backup setting protects against apnea. Conceivably, however, a similar effect could have been achieved by selecting lower levels of PSV. This important study thus raised relevant clinical questions for the selection of ventilator settings.

The hypothesis that the possible deleterious effect—hyperventilation—could be avoided by a more appropriate level of PSV was confirmed in subsequent studies, both in home-ventilated patients and in ICU patients. A study of outpatients with neuromuscular disease compared two settings for NIV with PSV, one based on clinical parameters and the other based on physiologic requirements as estimated by an assessment of the patient's respiratory effort and mechanics.[103] The physiologic setting was associated with improvements in sleep quantity and quality, as well as with a lower level of PSV. An association was found between reductions of ineffective efforts (a marker of patient–ventilator asynchrony, mainly related to hyperinflation) and a higher proportion of rapid eye movement (REM) sleep, a sleep period with extreme physiologic importance. The smaller number of ineffective efforts with the physiologic settings were ascribed to the lower intrinsic PEEP, possibly related to the lower V_T. The apnea index was also lower at the physiologic setting.

The effects of three ventilatory modes on sleep were compared in nonsedated ICU patients.[102] The three modes were ACV, clinically adjusted PSV, and automatically adjusted PSV. With automatically adjusted PSV, the pressure level is adjusted in real-time based on V_T, respiratory rate, and end-tidal CO_2, as described later in this chapter (Closed loop delivery).[104] The goal of automatically adjusted PSV is to adjust the level of PSV to the patient's ventilatory demand so as to avoid underassistance or overassistance. Sleep was severely altered in the fifteen patients, who exhibited reductions in REM sleep and marked sleep fragmentation. No differences, however, were found in sleep architecture, sleep efficiency, or sleep fragmentation between the three ventilator modes. The absence of significant differences may reflect an adequate adjustment of ventilator settings, as minute ventilation was similar with the three modes. In this study,[102] central apneas and ineffective efforts were relatively uncommon and were similar with the three modes. These results suggest that the mode may be less important than adjustment of the settings of each mode.

Newer modes may provide a more continuous and physiologic assistance. The effects of two assist-ventilation modes on sleep quality have been compared.[101] Patients received proportional-assist ventilation (PAV) during one night and PSV during a second night. PAV involves applying a level of pressure that is proportional to the patient's inspiratory effort; therefore, the level of pressure is variable. The patient triggers all the breaths and V_T changes with every breath, reflecting the natural breath-to-breath variability. PSV, in contrast, applies the same level of pressure independently of the magnitude of a patient's inspiratory effort. The working hypothesis was that PAV would improve patient–ventilator interactions and lessen asynchrony, and therefore reduce sleep fragmentation. The ventilator was set to achieve the same reduction in inspiratory effort. The number of patient–ventilator asynchronies was significantly smaller with PAV than with PSV. In addition, PAV was associated with a lower fragmentation index and with higher percentages of slow-wave sleep and REM sleep. V_T and minute ventilation were lower with PAV, suggesting that this mode ensured better matching of the assistance to the patient's requirements than did PSV, thereby decreasing the number of asynchronies linked to overassistance.

DEGREE OF PATIENT–VENTILATOR SYNCHRONY OR ASYNCHRONY DURING PRESSURE-SUPPORT VENTILATION

The fundamental principle of assisted ventilation is to deliver assistance on a breath-by-breath basis in synchrony with patient effort. As discussed, some patient–ventilator asynchrony often exists with most current assisted modes, which can be aggravated by inappropriate settings, chiefly excessive support. Synchrony has been the subject of several investigations, often not specific to PSV.[28,105–109] Patient–ventilator asynchrony has been described during invasive ventilation[28,109–112] and NIV[113] (Figs. 8-6 to 8-14).

Synchrony between the patient and ventilator can be defined as the adequacy of matching with patient neural inspiratory and expiratory time. PSV has often been viewed as offering good synchrony because it is designed to recognize the beginning and end of each spontaneous effort. As discussed above, this is far from true in all cases. The incidence of asynchrony has been studied in three prospective studies, one in ventilator-dependent patients and two in ICU patients.[105,109,114] These studies suggest a strong association between a high incidence of asynchronies (i.e., more than 10% of the breaths, as quantified by an asynchrony index) and a prolonged duration of mechanical ventilation.[105,114]

During PSV, several forms of asynchrony can be identified by inspecting the airway pressure and flow curves on ventilators and it is often possible to rule out the problem by modifying ventilator settings.[115] Many asynchronies are not specific to PSV.[28,105] Descriptions of these asynchronies may help clinicians understand their mechanisms and thus undertake remedial steps.[116] A parallel can be made with cardiac arrhythmias, where each type of arrhythmia has a specific treatment. We describe here the most frequent, gross, and easily recognized asynchronies encountered during PSV, according to recent descriptions.[105,116] More subtle forms of asynchrony, such as simple delays, are difficult to detect at

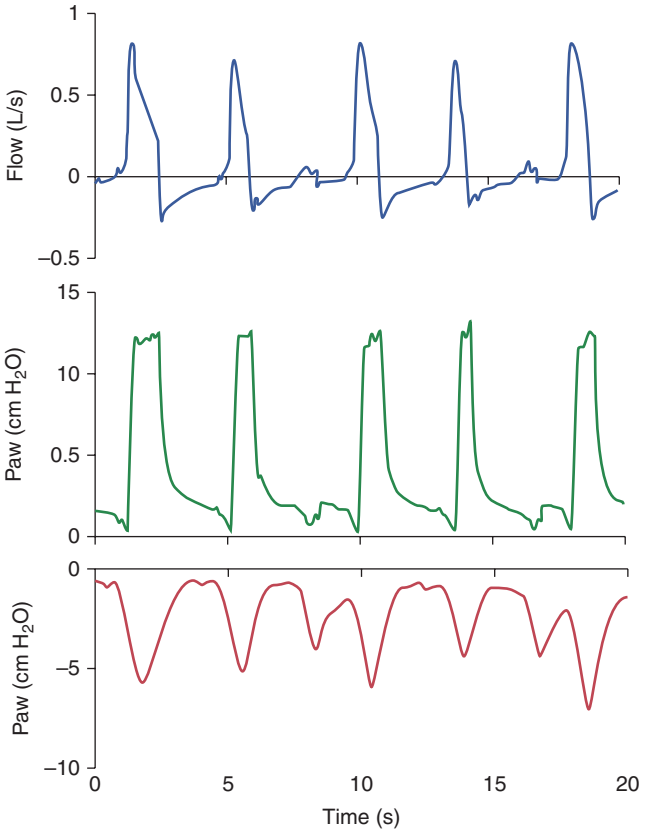

FIGURE 8-6 Ineffective efforts. The third and sixth inspiratory efforts by the patient fail to trigger the ventilator. The efforts by the patient (visible on the esophageal pressure tracing [*Pes*]) are not accompanied by ventilator insufflations. A small and transient increase in flow during expiration and a decrease in airway pressure are visible at the time of the failure-to-trigger events.

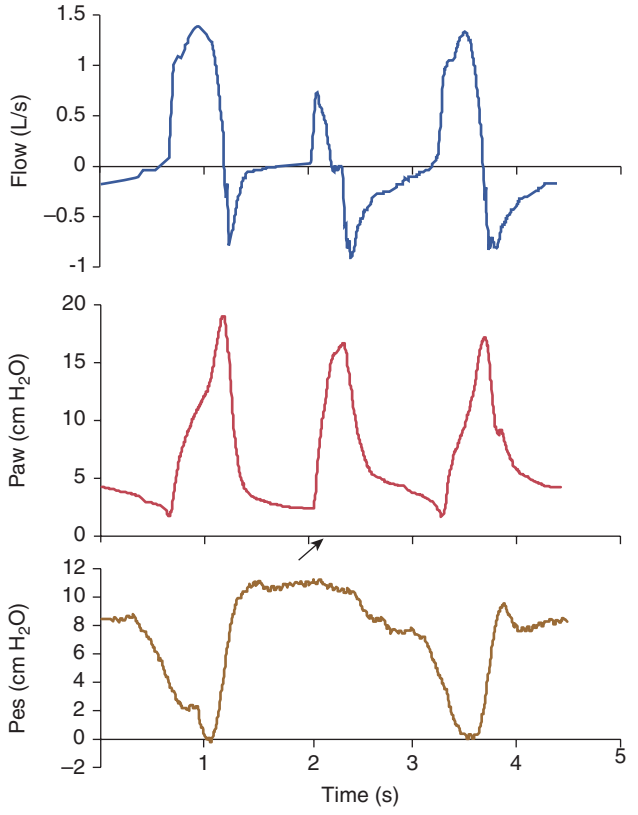

FIGURE 8-7 Autotriggering. This form of asynchrony can occur when the inspiratory trigger is set too sensitive or in the presence of end-expiratory leaks. As on this tracing, a "short cycle" is a frequent result of an autotriggered cycle. The "autotriggered cycle" is accompanied by the absence of an initial airway pressure decay.

the bedside, and need a careful examination of esophageal pressure or diaphragm electromyogram.

At Initiation of the Cycle

Triggering delay, ineffective triggering and autotriggering are all related to lack of synchrony between onset of patient effort and onset of inspiratory assistance but results from different mechanisms (see Figs. 8-6 and 8-7). Short and multiple cycles (see Figs. 8-7 to 8-9) may be related to problems with inspiratory triggering, setting of the pressurization rate, and cycling criteria.

INSPIRATORY TRIGGER DELAY

Trigger delay is almost inevitable with the classical triggering systems and is influenced by the system (pressure versus flow triggering) as discussed previously in the section Differences Among Mechanical Ventilators. Work (or effort) in triggering the ventilator has been evaluated by comparing pressure-triggering and flow-triggering systems.[23,27,117–120] Major delays have also been observed when using the helmet system for NIV.[121] One way to decrease it is to use higher pressure levels with a faster pressurization rate.[122]

INEFFECTIVE TRIGGERING

This asynchrony is illustrated in Fig. 8-6. During invasive ventilation with PSV, asynchrony most often results from ineffective triggering, also called wasted efforts.[28,107–111] The frequency of this asynchrony is directly influenced by the level of PSV and dynamic hyperinflation.[28,54,108,112,123,124] When a patient starts an inspiratory effort, a pressure gradient between the alveoli and mouth necessitates that the respiratory muscles first counteract this gradient before any inspiratory flow can be generated.[27] This constitutes an inspiratory threshold load, which increases breathing effort. The magnitude of positive pressure generated depends on V_T and therefore on set PSV. PSV can worsen hyperinflation by (a) delivering excessive VT, (b) prolonging insufflation time into patient neural expiration, and (c) reducing the respiratory drive. When patient effort is feeble, effort does not reverse expiratory flow or decrease pressure sufficiently to trigger the ventilator. This produces a missed cycle. This

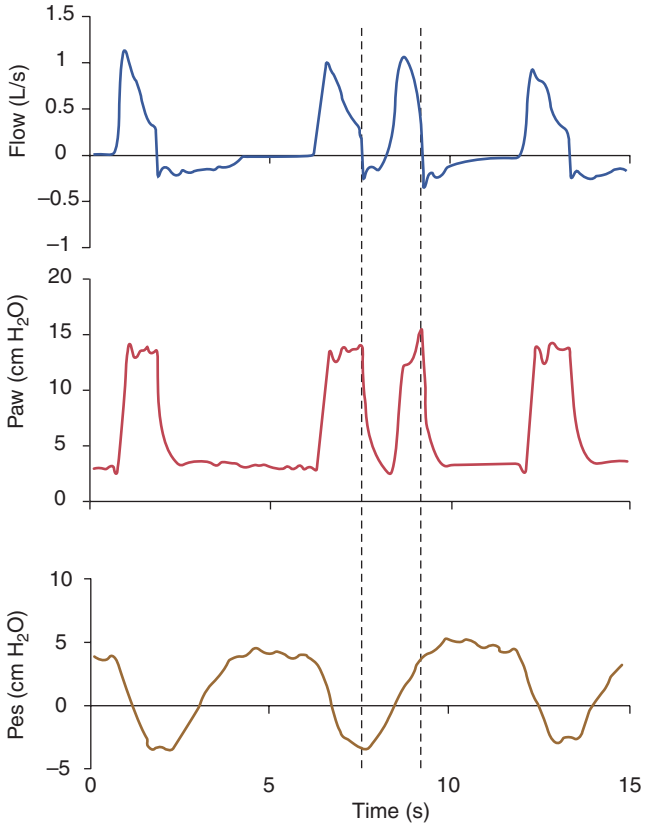

FIGURE 8-8 Double cycles. Two ventilator cycles occur within a single patient's inspiratory effort. Three mechanisms can induce this asynchrony: autotriggering, high pressurization rate (present here with initial overshoot), and early cycling-off (also present in this case).

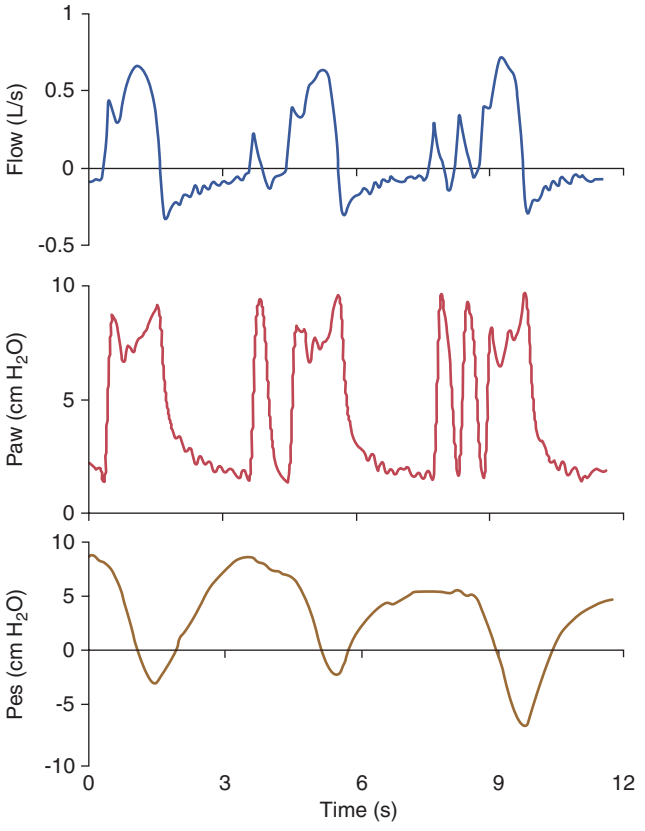

FIGURE 8-9 Multiple cycles. Multiple cycles are frequently associated with autotriggered cycles and frequent "short cycles." A high pressurization rate can favor this form of asynchrony. In this example, both autotriggering and high pressurization rate are present.

type of asynchrony has been described mainly in patients with expiratory flow limitation and intrinsic PEEP.[28,109,111]

In a study where assistance was varied between 0% and 100%, Leung et al found that there was almost no ineffective efforts below 60% of assistance, but they increased gradually when assistance was 60% to 100%.[28] In a cohort of sixty-two intubated patients, Thille et al recently found that ineffective triggering represented almost 90% of all asynchronies during PSV; a quarter of the patients exhibited a high level of asynchrony, that is, more than 10% of their efforts were asynchronous (asynchrony index greater than 10%).[105] COPD was a risk factor for asynchrony, as were a higher V_T, a higher setting of PSV, and progressive alkalosis.[105] In the study by Leung et al, cycles preceding wasted efforts were characterized by higher V_T and lower expiratory time, which lead to greater levels of hyperinflation.[28] Beck et al found that the greater the level of PSV, the longer was the prolongation of insufflation into patient's neural expiration.[56] Therefore, one major reason for ineffective efforts is excessive assistance (PSV), which simultaneously generates dynamic hyperinflation and depresses respiratory drive, both because of high V_T and prolongation of insufflation far beyond the end of patient inspiratory effort.[105]

Ineffective triggering can be detected from irregularities on airway and flow tracings during the expiratory phase (see Fig. 8-6).[27] A respiratory rate lower than 20 breaths/min should also rouse suspicion. Giannouli et al found that ineffective triggering could be detected as accurately on flow and airway tracings as on esophageal pressure tracings.[54] Different approaches are necessary to avoid wasted efforts: check trigger sensitivity, increase PEEP,[108,109,123] lower PSV,[27,28] or decrease instrumental dead space.[92,93] External PEEP decreases the frequency of wasted efforts in some but not all studies.[108,109,115] The two most effective approaches to decrease ineffective efforts are to decrease inspiratory time, achieved by increasing the flow cycling-off criterion or decreasing the level of PSV until the ineffective efforts disappear or the onset of signs of respiratory distress. In patients with COPD, Tassaux et al showed that it was necessary to increase the flow cycling-off criterion to 50% or 75% of the peak flow to reduce ineffective efforts.[125] Thille et al reduced the PSV level in the manner described above, such that VT was around 6 mL/kg. This was associated with a disappearance of ineffective efforts in most, but not all, patients, without significant increase in work of breathing.[115]

Ineffective efforts exist with PSV and with ACV.[105] Thille et al[105] found that a high incidence was significantly

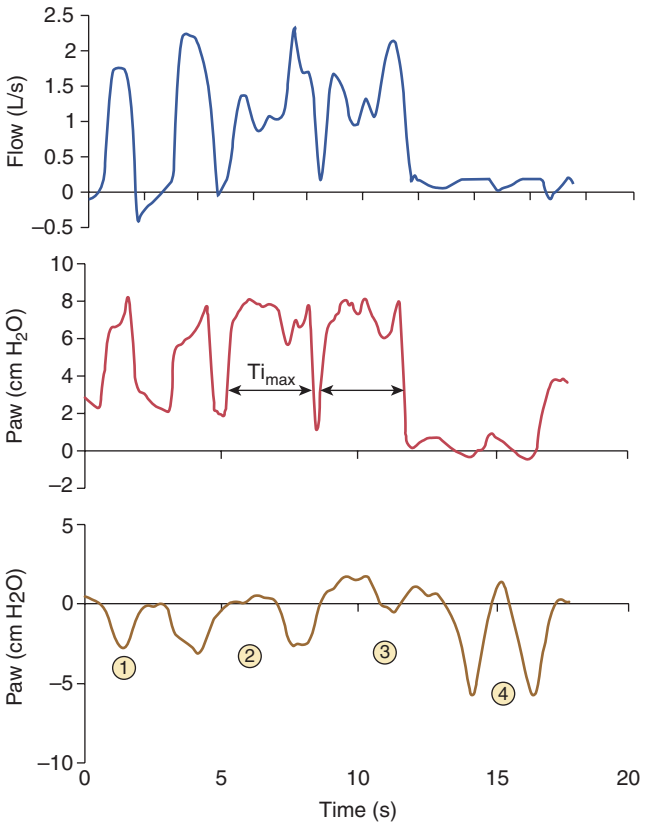

FIGURE 8-10 Prolonged inspiration during noninvasive ventilation. This form of asynchrony during PSV results from a failure to recognize the flow cycling-off criterion. With an end-inspiratory leak, as in this example, the ventilator increases and/or sustains flow to maintain the set airway pressure (here above 2 L/s). This prevents recognition of the decelerating flow threshold and cycling to expiration. Insufflation is stopped only when maximum inspiratory time (Ti_{max}) is reached. Ineffective triggering secondary to hyperinflation may follow the prolonged inspiration, as in this example.

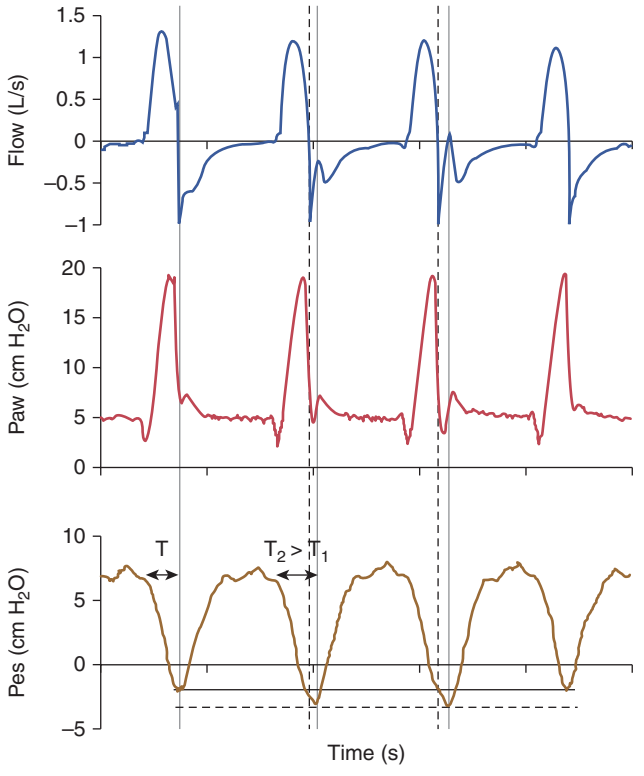

FIGURE 8-11 Early cycling-off. The ventilator ends insufflation (*thick vertical dotted line*) before the patient's inspiratory effort ceases (*second vertical line*). The airway pressure tracing then drops transiently below the baseline end-expiratory pressure level because patient effort is still substantial after ventilator insufflation has ceased. The two cycles with this form of asynchrony are associated with increased effort (*dotted horizontal line*) and prolonged T_I. The duration of T_I on the second cycle (T_2) is longer than T_I on the first cycle (T_1) as reflected with the greater distance between the *arrowheads*. A large T_I favors this form of asynchrony.

associated with prolonged ventilation. The same association was also found by de Wit et al, and was shown to be an independent association by means of multivariate analysis.[114] Because these asynchronies can be avoided by optimized ventilator settings, their treatment and/or prevention may result in a shorter time spent on the ventilator.

AUTOTRIGGERING

Autotriggered cycles (see Fig. 8-7) are falsely triggered by a signal not coming from a patient's inspiratory effort. They can be caused by expiratory leaks around a mask during NIV, or by leaks in the ventilator circuit.[105] It is a special concern when using an ICU ventilator for delivering NIV.[42] An expiratory leak can be misinterpreted by the ventilator as patient effort; an inspiratory cycle is then delivered independently of patient control. Autocycling is also caused by cardiac oscillations,[126] and when the setting trigger is excessively sensitive.

Autotriggering can be difficult to detect on the ventilator tracing. A sudden increase or a persistently high respiratory rate suggest autotriggering. The absence of airway pressure drop at the beginning of an inspiratory cycle is also suggestive (see Fig. 8-7).

Sensitivity of the inspiratory trigger can be reduced, both as a diagnostic test and as a remedy. Triggers based on flow are more sensitive than conventional triggers, and tend to increase of autotriggering.[127] A compromise must be found between triggering that is too sensitive (posing a risk of autotriggering) and too insensitive (with risk of ineffective efforts or increased effort).

MULTIPLE CYCLES

This asynchrony is illustrated in Figs. 8-8 and 8-9. Two or more ventilator insufflations may be delivered within a single patient effort. Auto-triggering can be responsible for multiple cycles (see Fig. 8-9). Ventilator characteristics, such as duration of the refractory period, may

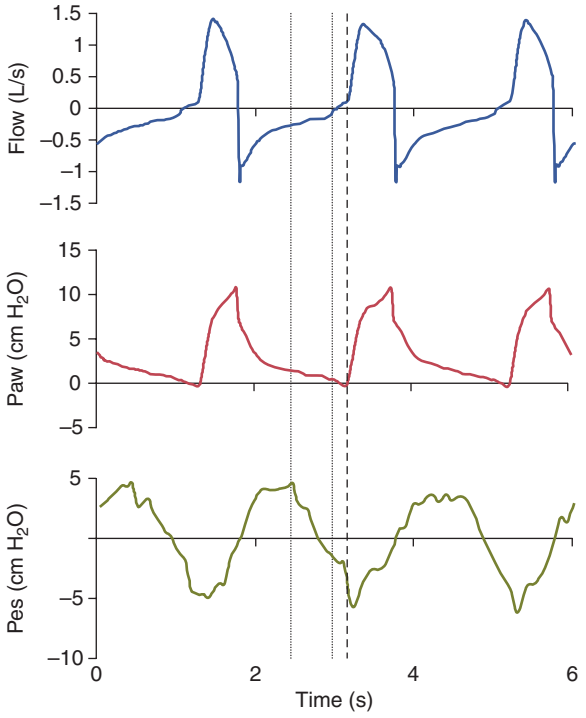

FIGURE 8-12 Inspiratory and expiratory delay. Tracings in an intubated patient with severe COPD receiving PSV. An inspiratory delay secondary to auto-PEEP and triggering delay is evident. The distance between the first and second vertical dotted lines reflects the delay between onset of patient inspiratory effort and positive flow from the ventilator; this delay is caused by auto-PEEP. The delay between the second and third vertical lines is caused by triggering delay (flow triggering). In this patient, mechanical insufflation occurs almost entirely after the patient has terminated inspiratory effort. Consequently, onset of the ventilator's expiratory phase is markedly delayed compared with the patient's neural expiration.

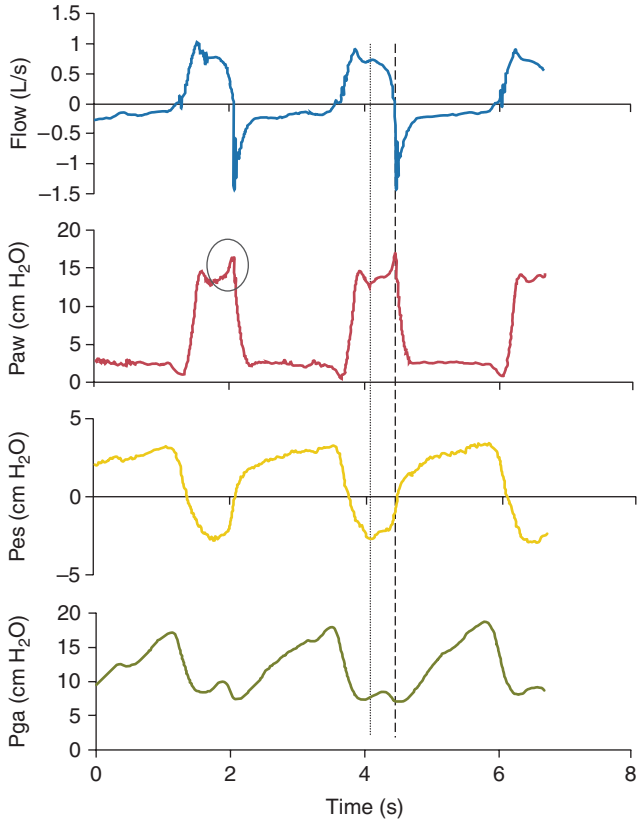

FIGURE 8-13 Expiratory muscle activation. An expiratory increase in gastric pressure (*bottom tracing*) is caused by expiratory muscle activation (at the end of patient inspiration). The apparent "overshoot" on the inspiratory airway pressure tracing (*circle*) indicates, in reality, the abrupt end of patient inspiratory effort. Active expiration is present throughout all of expiration.

also influence this kind of asynchrony. A risk for double-triggering exists with a high inspiratory pressure ramp profile, secondary to a reduction in ventilator T_I relative to neural T_I.[128,129] Tokioka et al described double cycles during PSV in intubated patients with restrictive lung diseases when the cycling-off criteria were high (35% and 45% of maximal inspiratory flow).[130]

Three mechanisms (autotriggering, high pressurization rate, and early cycling-off) should be considered when this asynchrony is detected during PSV.

Pressurization Rate and Inspiratory Flow

The speed of pressurization determines the initial pressure ramp profile and is primarily dependent on the initial peak flow rate. This rate is adjustable on several ventilators. Altering this parameter can directly influence breathing pattern and work of breathing.[131]

Poor matching between patient demand and the provided peak flow may occur as a result of an inadequate rise time during PSV.[32,59,129,132,133] Selecting a low speed of pressurization can cause excessive patient effort, especially when respiratory drive is high and mechanics are poor. Conversely, a very fast rise time may not be optimal[134] and is poorly tolerated by patients.[135] A high speed of pressurization makes it more difficult for the ventilator to properly regulate the pressure throughout inspiration according to its servo-control mechanism.

Patients with the lowest compliance and highest respiratory drive theoretically needed the highest initial flows.[131] In two studies, the longer the time taken to reach the pressure level set on the ventilator, the greater the work of breathing, in patients with obstructive or restrictive lung disease.[59,129] Excessively high pressurization can also lead to an initial overshoot, with possible early termination of the cycle related to high pressure. Chiumello et al found that the relationship between the pressurization rate and dyspnea or work of breathing exhibited a U-shape pattern.[134] During NIV, the highest pressurization rate may increase the amount of leaks and induce double triggering.[135] It can also increase respiratory rate, as previously described with ACV.[136,137]

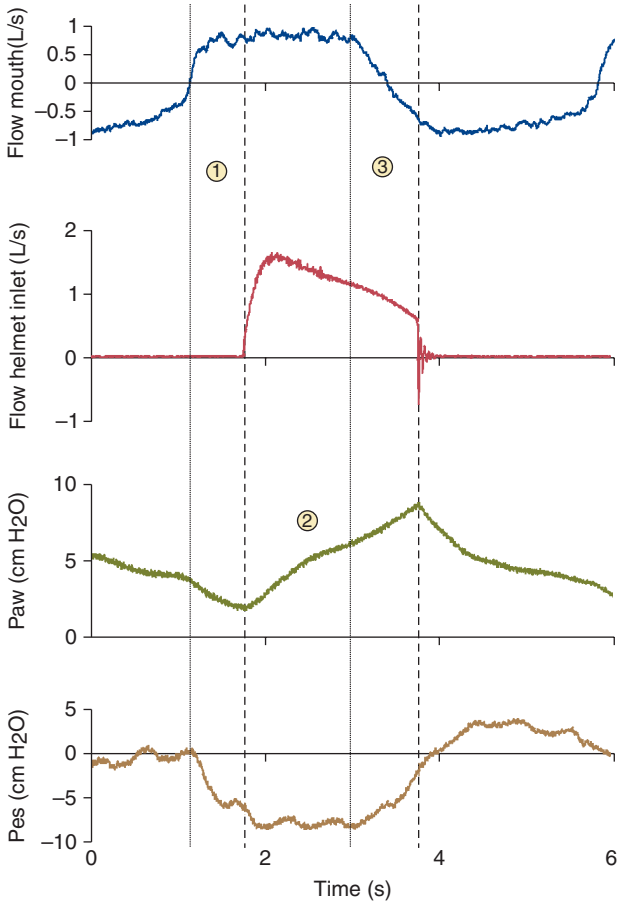

FIGURE 8-14 Inspiratory and expiratory delays and low pressurization during PSV with a helmet system. In this healthy subject, an inspiratory delay is evident between the first vertical dotted line (onset of inspiratory effort) and the second (thicker) vertical line (onset of ventilator assistance) (interval ①). A low rate of pressurization is evident, typical when PSV is delivered via a helmet system (interval ②). Expiratory delay corresponds to the time between the third (end of inspiratory effort) and fourth vertical line (end of insufflation) (interval ③).

Inspiratory Cycling-Off or Cycling to Expiration

DELAYED OCCURRENCE OF EXPIRATION

As with delayed triggering of inspiration, this form of asynchrony is very common and related to the difference between the criterion for inspiration termination on the ventilator and the end of patient neural T_I (see Figs. 8-10, 8-12, and 8-14). Parthasarathy et al[138] studied healthy subjects with simulated airflow obstruction, and found frequent early activation of the expiratory muscles during ventilator insufflation. In intubated patients, Spahija et al compared PSV with neurally adjusted ventilatory assist (NAVA), where ventilator support is driven by the diaphragmatic electromyographic signal. Marked expiratory delays were found with high levels of PSV (1055 ± 1010 milliseconds).[139] These impressive delays may be specific to the ventilator used, Servo 300 (Maquet, Lund, Sweden), which has a low and nonadjustable cycling-off criterion (5% of peak flow).

The inspiratory termination criterion is usually a fixed percentage of peak inspiratory flow rate (12%, 25%, or 30%) and frequently does not correspond to the real end of inspiratory effort.[140] The effect of this setting differs between patients with obstructive and restrictive lung diseases. In general, increasing the flow criterion (expressed as a percentage of peak flow) reduces Ti.[131]

In patients recovering from acute lung injury, Chiumello et al found a low cycling-off criterion (5% of peak flow) was beneficial in terms of breathing pattern (reduction of respiratory rate, increase in V_T), compared with a threshold at 40%.[133] In similar patients Tokioka et al found an increase in V_T and decrease in respiratory rate when the cycling-off criterion was decreased from 45% to 1%.[130] These observations argue for use of a low termination criterion in patients with acute lung injury or restrictive lung disease. Conversely, in patients with COPD, the best cycling-off criterion may be above 50%.[125,141] When the cycling-off criterion is set low (5% with the Servo 300 [Maquet, Lund, Sweden] or 5 L/min with the Puritan Bennett 7200 [Tyco, Carlsbad, CA, USA]), one can expect that insufflation will continue beyond patient neural T_I. Patients may activate their expiratory muscles, and or suffer from increased dynamic hyperinflation.[74,138] The risk of wasted efforts during subsequent respiratory cycles increases.[142]

Some patients exhibit expiratory muscle activity during PSV (see Fig. 8-13).[74,138,143] It has been suggested that an abrupt increase in airway pressure indicates an active expiratory effort from the patient. Although this is indeed possible, a more frequent explanation is the abrupt cessation of patient active inspiratory effort. The release of this effort makes that the airway pressure suddenly reaches the preset level until the end of inspiration.[144]

VERY PROLONGED INSPIRATION DURING NONINVASIVE VENTILATION

This is illustrated in Fig. 8-10. A specific form of the preceding asynchrony may occur in case of large end-inspiratory leaks. Mechanical inflation may be prolonged far beyond the end of patient inspiration, until a limit of maximum T_I has been reached, which is sometimes adjustable. This type of asynchrony can occur during invasive ventilation but is mostly specific to leaks during NIV with ICU ventilators.[113] It occurs because of the impossibility for reaching the cycling-off criterion (e.g., 25% or less of peak inspiratory flow). In the case of end-inspiratory leaks around the mask or in the circuit, the ventilator continues insufflation and flow does not decrease (because of these leaks). The breath does not terminate and is prolonged until a maximum T_I is reached (which can be several seconds). The patient may "fight" against the ventilator and may even attempt additional inspirations. Ineffective

efforts can be observed in this context, either within the same ventilator cycle or in following cycles.

Prolonged inspiration is a common asynchrony in patients receiving NIV for acute respiratory failure with ICU ventilators not having a noninvasive mode.[145] The first step is to reduce leaks and inspiratory pressure by decreasing PEEP or PSV. This asynchrony can also be avoided by adjusting the cycling-off criterion higher. Calderini et al set T_I between 0.8 and 1.2 seconds.[113] This produced better matching between the patient and the ventilator, reducing work of breathing and improving patient comfort.[113] Assist-control pressure ventilation can also be used to deliver pressure with a fixed T_I. Large delays may also result with use of a helmet for NIV (see Fig. 8-14).[146] New ICU ventilators using the NIV mode and dedicated NIV ventilators generally prevent, to a certain extent, the occurrence of these prolonged insufflations.[40,145]

EARLY CYCLING-OFF

This asynchrony is illustrated in Figs. 8-7, 8-8 and 8-11. Very short, aborted cycles can occur during NIV and invasive ventilation. This may indicate either a switch-off mechanism that occurs too early or autotriggering (see Fig. 8-7).[105]

If the cycling-off criterion is reached too early, the ventilator stops insufflation and opens the expiratory valve while patient inspiratory effort continues. This produces an initial drop in airway pressure and flow, followed by an increase related to patient inspiration, resulting in a characteristic contour (see Fig. 8-11).[130] This asynchrony is observed during invasive ventilation and NIV. In patients recovering from acute lung injury,[133] the cycling-off criterion may be set lower to minimize this risk.

Yamada and Du[141] designed a mathematical model to analyze the mechanisms of expiratory asynchrony during PSV.[141] The ratio of flow at the end of patient neural inspiration (neural T_I) to peak inspiratory flow during PSV is determined by the ratio of respiratory time constant (τ) to neural T_I and by the ratio of set PSV to maximal inspiratory muscle pressure. They found that with selected respiratory mechanics, the ratio of flow at the end of neural T_I to peak inspiratory flow ranged from 1 to 85%, and had an excellent linear correlation with the τ-to-neural T_I ratio. The highest values of the cycling-off criterion corresponded to obstructive patients with high resistances and high compliances (resulting in a high time constant). The lowest values corresponded to patients with acute lung injury, who have low resistances and low compliance (resulting in a short time constant).

Hotchkiss et al used linear and nonlinear mathematical models to investigate the dynamic behavior of PSV. Predicted behavior was confirmed with a test lung.[147] In the setting of airflow obstruction, PSV was accompanied by marked variations in V_T and end-expiratory alveolar pressure, even when patient effort was unvarying. Unstable behavior was observed in the simplest plausible linear mathematical model, and it was an inherent consequence of the underlying dynamics of this mode. Because of its complexity and the frequent changes in ventilatory pattern during PSV,[147] automatic adjustment of triggering, based on mathematical models, might be helpful.[148] Du et al proposed an automatic adjustment of the cycling-off criterion based on the measured time constant in a patient.[149,150]

CLINICAL DETECTION

Major asynchronies can be detected at the bedside on the ventilator screen by looking at airway pressure and flow tracings.[116] New ventilators permit clinicians to adjust ventilator settings in order to reduce the frequency of asynchrony.[116] During invasive PSV, a major goal is recognition of ineffective efforts. During noninvasive PSV, an important issue is recognition of prolonged inspirations, caused by leaks, or autocycling.[42] Adjustment of settings (simple decrease of pressure level or change in the cycling-off criterion) avoids or minimizes the problem. This step is likely to improve the efficacy and comfort of PSV.

DIFFERENCES FROM OTHER MODES OF VENTILATION

Intermittent Positive-Pressure Breathing

PSV has some similarities with intermittent positive-pressure breathing (IPPB), an assisted mode used widely in the 1960s for physiotherapy.[151–154] With both IPPB and PSV, cycles are triggered by the patient and limited by pressure, and both can assist patients in acute respiratory failure (with or without endotracheal intubation). They differ in that PSV, but not IPPB, maintains a constant level of pressure during inspiration. The mechanisms that cycle between inspiration and expiration are also different. The end of inspiration is flow-cycled with PSV and is pressure-cycled with IPPB. In normal, nonintubated patients, work of breathing was lower with PSV than with IPPB,[155] a difference considerably exaggerated in the presence of CO_2 stimulation. Expiratory work was also greater and comfort poorer with IPPB devices than with PSV.

Assist-Control Ventilation

Both PSV and volume-controlled ACV can provide full ventilator support but ACV is used more frequently, especially during the early phase of mechanical ventilation because it offers a more stable ventilation with regards to changes in respiratory mechanics.[7] The modes differ in ways that explain their relative advantages and disadvantages. During ACV, V_T is guaranteed and independent of respiratory mechanics, and a minimal frequency and minute ventilation is set. During PSV, by contrast, V_T may change with alterations in respiratory system compliance or resistance.

For any inspiratory effort, addition of PSV augments the pressure difference between the circuit and the alveoli,

leading to a higher inspiratory flow rate and higher V_T than during spontaneous breathing. Until high PSV levels are reached, it increases inspiratory flow rate in a way that remains partially under patient regulation. During ACV, patient inspiratory effort does not modify flow or volume. Therefore, the use of volume ACV is essential when strict control of V_T or transpulmonary pressure is considered important, such as acute respiratory distress syndrome to avoid excessive distension.[156,157] Use of PSV in unstable patients with a high respiratory drive has the major disadvantage of offering no control over V_T, and the pressure level used does not give any indication of what is the real transpulmonary pressure.[158] Conversely, PSV may adapt better to variation in patient demand.

Effects of PSV and ACV on breathing pattern, gas exchange, and indexes of work or effort have rarely been compared. Cinnella et al compared breathing pattern and respiratory muscle effort during ACV and assisted pressure-control ventilation.[159] Although the latter mode differs from PSV in that T_I is preset, this comparison enabled the study of the comparison of a pressure-targeted and a flow-targeted mode. Pressure was adjusted to achieve a similar V_T and T_I as with ACV. With a high V_T (12 mL/kg), the modes did not differ for respiratory muscle effort. At a moderate V_T (8 mL/kg), the decelerating flow pattern of the pressure-targeted mode better matched patient demand than did the constant-flow pattern and work of breathing and pressure-time index were significantly lower with assisted pressure control ventilation. This difference was abolished, however, when inspiratory peak flow rates were increased. Thus, with adequate settings, both modes could adequately unload the muscles. Leung et al also showed that high levels of assistance was equivalent with PSV, ACV, and SIMV.[28]

Synchronized Intermittent Mandatory Ventilation

SIMV combines delivery of assisted breaths with spontaneous unassisted breaths. SIMV differs from PSV, where every breath is supported to the same extent. On a breath-to-breath basis, the effort performed by a patient during SIMV is almost equivalent for assisted and unassisted breathing,[160,161] although differences between assisted and unassisted breaths have been found during SIMV when the mandatory breaths were delivered as pressure-targeted breaths.[27]

MacIntyre compared SIMV (V_T set at 10 to 15 mL/kg), and PSV (set at 13 to 41 cm H_2O) in a crossover study of fifteen patients recovering from acute respiratory failure.[11] Sense of comfort was increased and respiratory rate slower with PSV. In patients ventilated for at least 3 days, Knebel et al compared similar levels of partial support provided by SIMV and PSV in terms of breathing comfort, defined by subjective ratings of dyspnea and anxiety.[162] Preweaning levels of dyspnea and anxiety did not differ significantly between the modes at any level of support. Comfort was not influenced by the level of support, and was similar with the two modes.

Leung et al compared the effects of PSV, SIMV, and their combination at varying levels of support in the same patients.[28] Patient effort was similar with SIMV and PSV at high levels of assistance, but was higher with SIMV than with PSV at lower levels of assistance (20% to 40% of maximal support). The same difference between the two modes was found in animal experiments.[163] The studies suggest that when reducing the level of ventilator support, unloading of the respiratory muscles occurs earlier with SIMV than with PSV.[164] Whether this could explain the different clinical outcomes with the two modes during weaning is unclear.

Proportional-Assist Ventilation

PAV was developed several years after PSV.[165,166] Promising initial results and great physiologic interest has characterized this mode. PAV, however, has essentially remained a physiologic tool, and results of the first clinical comparisons with PSV have been disappointing. Most of physiologic comparisons of PAV and PSV favor PAV in terms of breathing pattern variability, patient–ventilator interaction, and comfort. In clinical trials, mainly during NIV, these physiologic effects did not produce any outcome benefit until recent developments.[167–171]

PAV is designed to deliver assistance in direct proportion to patient effort.[165,166,172]

ADVANTAGES OF PROPORTIONAL-ASSIST VENTILATION COMPARED WITH PRESSURE-SUPPORT VENTILATION

During invasive ventilation and NIV, PAV is consistently superior to PSV on physiologic end points. In response to variable loads (dead space, resistive or restrictive loads), PAV adapts the level of assistance to patient demand. With PSV, in contrast, the level of inspiratory pressure remains constant whatever the load. In response to acute hypercapnia, Ranieri et al showed that PAV adapted more efficiently to ventilatory demand than did PSV.[173] Levels of inspiratory pressure increased during PAV with a relative increase in V_T and no change in respiratory rate, while a small increase in V_T and a large increase in rate were observed with PSV. This resulted in lower work of breathing and better comfort with PAV.[173] In intubated patients, the response to a restrictive load (chest and abdominal binding) resulted in less work and better comfort when compared with PSV.[174] Such adaptations to loads with PAV and PSV were also found in healthy subjects.[175,176]

Several studies found less ineffective triggering with PAV than with PSV in intubated patients.[54,177–179] With PAV, ventilator T_I exactly matches neural T_I, even in patients with a long time constant. Thus, insufflation continues while the patient has begun to exhale with PSV, but not with PAV. Many studies also reveal a greater variability of V_T with PAV than with PSV,[176,180–183] and better patient comfort.[167,168,173,176,181,184–188]

CLINICAL TRIALS

Two prospective randomized controlled studies with clinical end points compared PAV and PSV during NIV.[167,168] The first study enrolled forty-four patients and the second enrolled 117 patients.[168] Intubation and mortality rates were equivalent despite better comfort and less intolerance with PAV. These early clinical trials of PAV are disappointing when contrasted with the promising physiologic studies.

PROPORTIONAL-ASSIST VENTILATION WITH LOAD-ADJUSTABLE GAIN FACTOR

A new method now enables automatic measurement of respiratory mechanics with PAV. The initial results are encouraging.[189,190] In contrast with any other mode (including PSV), greater knowledge of resistive and elastic characteristics of the respiratory system is necessary when setting PAV. It is often difficult to obtain simple and reliable measurements in awake patients triggering the ventilator and the values frequently vary. The setting of PAV is thus complex, and constitutes an obstacle to its wide acceptance. The time needed to set PAV is much longer than for PSV.[182] Also, a major drawback of PAV is the occurrence of a specific asynchrony: flow and pressure runaway.[172] Runaway is mainly related to an excess of volume and elastic assistance because elastance is overestimated.[54,177,184] Methods to automatically and intermittently determine respiratory resistance and elastance were recently described.[189,190] These methods could be incorporated into a closed-loop adjustment of PAV, and possibly constitute a major step forward. A potentially important advance regarding the clinical use of PAV is the possibility to get automated reliable repeated measurements of elastance and resistance of the respiratory system. Few clinical comparisons exist, again mostly with PSV. The effect of modifications in the respiratory loading conditions were compared between PAV with load-adjustable gain factor, referred to as PAV+, against PSV.[191] Adaptation was more physiologic with PAV+, allowing patients to keep the same V_T and minute ventilation, by contrast with PSV. One clinical evaluation of PAV+ randomly compared it to PSV for 48 hours of assistance.[192] In this study, failure to maintain assisted spontaneous ventilation was higher with PSV than with PAV+, and PAV+ was associated with a major reduction of ineffective efforts.

Neurally Adjusted Ventilatory Assist

NAVA is a promising mode of ventilation, although it still lacks clinical data to precisely define its clinical application. Like PAV, it provides assistance in proportion to patient effort but it depends on continuous recording of Edi, which is obtained via a nasogastric catheter incorporating a multiple array esophageal electrode (nine electrodes spaced 10 mm apart). The ventilator thus acts like a muscle under a patient's neural command. Inspiratory airway pressure applied by the ventilator is determined by the following equation:

$$Paw_{(t)} = Edi_{(t)} \times NAVA\ level$$

where $Paw_{(t)}$ is the instantaneous airway pressure (cm H_2O), $Edi_{(t)}$ is the instantaneous diaphragmatic electrical activity signal (μV), and NAVA level (cm H_2O/μV or per arbitrary unit) is a proportionality constant set by the clinician.

The onset and end of assistance and the level of assistance are directly driven by the Edi signal.[193] In theory, NAVA should provide much better patient–ventilator synchrony than achieved with pressure-targeted modes, and both experimental and clinical results support this expectation. Unlike all other modes (including PAV), NAVA should not be influenced by intrinsic PEEP or by the presence of leaks as in the case of standard triggering systems. The initial reports on NAVA revealed advantages compared with PSV in terms of triggering and cycling-off of the ventilator.[193] In a rabbit model of acute lung injury,[194] diaphragmatic unloading was much more efficient with NAVA than with PSV, with an absence of wasted efforts. In intubated patients, Spahija et al compared the trigger delay and cycling-off of inspiration with NAVA and PSV[139] at low and high levels of assistance. Inspiratory trigger delay was around 100 milliseconds with NAVA and around 200 milliseconds with PSV. Cycling-off delays were markedly different: 40 milliseconds (whatever the level of assistance) with NAVA and 500 to 1000 milliseconds with PSV (low and high assistance). The same group also reported an evaluation of an original closed-loop system, using Edi as a target to select the level of PSV: target-drive ventilation.[195] This system was evaluated in eleven healthy subjects, before and during exercise, and without ventilator support. Without target-drive ventilation, Edi increased, as did indexes of effort and end-tidal CO_2 during exercise. With target-drive ventilation, the level of pressure increased during exercise, maintaining the Edi constant.

In the more recent comparisons with PSV, NAVA reproducibly decreased triggering delay by more than 50%, in addition to significantly reducing cycling delay and total asynchrony events.[139,196] Terzi et al showed that beyond a pure proportional assistance, Edi triggering further decreases patient–ventilator asynchrony.[196] These studies also demonstrated that NAVA limits overassistance in contrast to PSV. NAVA prevents overassistance because excessive assist downregulates respiratory center activity (hence Edi) and, thus, inspiratory pressure. NAVA reveals the patient's natural breathing variability that is otherwise masked by constant PSV assist.[197] This finding could be relevant in explaining the oxygenation improvement with NAVA compared to PSV in a 24-hour crossover study of twelve postoperative patients.[198] Thus, the most recent studies have confirmed that NAVA improves patient–ventilator interaction compared to PSV and prevents overassistance. Nevertheless, it remains to be demonstrated that providing control over breathing pattern to a patient will improve clinical outcome.

HEMODYNAMIC CONSEQUENCES OF PRESSURE-SUPPORT VENTILATION

Unique hemodynamic consequences have not been described with PSV.[11,12,45,47,63,76,199] Despite a wide range of pressures, most studies have found little or no deleterious effects of PSV on cardiovascular function in patients after cardiac surgery or in patients with respiratory failure. The negativity of pleural pressure during PSV and the control of airway pressure reduces the risk of negatively influencing venous return or right ventricular afterload. One study found that PSV during NIV may lead to a reduction in cardiac output without change in mixed venous P_{O_2}.[65] Whether this reflects adaptation to a decrease in CO_2 production or a deleterious effect could not be inferred from these data.[200]

In patients with cardiac dysfunction, it was shown that weaning-induced left-ventricular dysfunction appears sooner during T-piece trials than during PSV trials because the workload is higher during the T piece.[89] Whether T piece better predicts postextubation problems in cardiac patients cannot be directly inferred from these data.

ADJUSTMENT OF PRESSURE LEVEL AT BEDSIDE

Precise guidelines for the bedside use of PSV are lacking because the pressure level has been adjusted in various ways in many studies.[11,201,202] Recent data reinforce the notion that targeting a V_T lower than traditionally used and a higher respiratory frequency offers benefit for the patient.[69,115] Assessment of accessory muscle activity, especially the sternocleidomastoid, by inspection and palpation was suggested for deciding optimal assistance.[43] A decrease in respiratory frequency below 30 to 32 breaths/min was also associated with an optimal level of PSV. Respiratory frequency can be used as a simple indicator of the adequacy of PSV[43,76]; and less than 30 breaths/min has been recommended.[74,76,203] As indirectly suggested by weaning trials, targeting a low frequency (25 breaths/min or less) can prolong weaning duration. The latter may also be explained by increased occurrence of asynchrony when a low frequency is displayed on the ventilator.

In early studies, PSV was adjusted to reach a predetermined V_T (8 to 12 mL/kg).[12,47,70] A setting of closer to 6 mL/kg V_T seems more advisable to avoid patient–ventilator dyssynchrony. One study suggested, however, that patients who could be weaned controlled their own V_T and were only mildly influenced by the PSV level.[204]

In patients who display major asynchronies, such as ineffective efforts, reducing the level of pressure support[115] and reducing the insufflation time through an increase in the flow-cycling criterion[125] are recommended. This leads to a smaller V_T than usually recommended, around 6 mL/kg. Interestingly, a recent study using the DL_{CO} technique showed that gas exchange was overall better with a V_T of 6 mL/kg versus 8 mL/kg.[69]

CLOSED-LOOP DELIVERY OF PRESSURE-SUPPORT VENTILATION

Dual Modes

The potential for variation in delivered ventilation has led many manufacturers to develop servo-controlled modalities of PSV. In one ventilator, the PSV level was automatically adjusted to achieve a preset breathing frequency.[205] Several servo-controlled modes have been proposed to adjust the PSV level to keep V_T constant. Pressure can be varied from breath to breath using various algorithms. These options have been designed to provide a better ventilator response to changes in respiratory mechanics.[206,207] An increase in resistance or elastance during PSV normally leads to a drop in V_T if no compensation is made by the patient or the ventilator.

These modes, often called *dual-control modalities*, use closed-loop feedback control systems that enable the ventilator to adapt output based on the difference between measured ventilation and a predefined target. The modes go by different names. Volume-support ventilation (VSV) was introduced in the 1990s on the Servo 300 ventilator (Siemens Elema, Solna, Sweden). VSV is a pressure-limited mode that uses a target V_T and minute ventilation for feedback control. The level of PSV is adjusted continuously to deliver a preset V_T. Two anecdotal reports with VSV[208,209] and one randomized controlled trial[210] have yielded variable results. Several modes are now working on the same principle—volume targeted pressure-regulated mode—and have been extensively developed by manufacturers without clinical validation. Physiologic studies have not assessed the efficacy of VSV in terms of adjustment to spontaneous changes in mechanics. The response of such modes to changes in ventilatory demand can be problematic. Changes in demand frequently occur with different states of, for example, wakefulness, nutrition, episodes of sepsis, pain, and anemia. With a fixed level of VSV, but not of PSV, it was shown that an increase in ventilatory demand resulted in a decrease in the level of support provided by the ventilator, the opposite of a desired response.[211–213] Conceivably, VSV may result in respiratory distress in clinical settings.[211] In general, these modes are not able to cope correctly with changes in ventilator demand. They also make rapid alterations in the level of support, thus potentially interfering with a patient's own response time.[50]

Knowledge-Based Systems

More complex knowledge-based systems have been developed with the aim of providing an automatically performed, patient-adapted ventilator support, which is superimposed on an automated weaning strategy.[104,214–216] Such systems have been implemented in computers that drive a ventilator. These approaches using SIMV plus PSV or PSV alone have

been evaluated in patients. Sophisticated modes have been developed through improvements in computer science.[217,218]

When the physiologic and clinical knowledge needed to manage a well-defined clinical situation is acquired, it can be embedded within a computer program that drives the ventilator using artificial intelligence techniques, such as production rules, fuzzy logic, or neural networks.[219] These techniques allow planning and control. Control is a local task, which consists of determining what the immediate next step is. Planning is a strategic task, aimed at regulating the time-course of the process. For control and planning, numerous techniques have been developed in the fields of control theory and artificial intelligence, respectively. The main difference between these two fields lies in the process models used. It is important to avoid both oversimplification and excessive complexity.[209] Strickland and Hasson tried to develop a controller incorporating an active clinical strategy represented by production rules using SIMV and PSV (IF conditions, THEN actions). Their work did not lead to commercial development.[215,216]

The Smart Care system is an embedded version of the initial NeoGanesh system. The NeoGanesh system drives the ventilator with PSV, keeping a patient within a zone of "respiratory comfort" as defined by respiratory parameters, and superimposing an automated strategy for weaning.[104,214,220] The designers of the knowledge-based NeoGanesh system intended to build a closed-loop system that (a) was efficient for automatically controlling PSV and planning of the weaning process, (b) could be evaluated with the goal of gradually improving its reasoning and planning capabilities, and (c) could be subjected at the bedside to performance measurements at each step of its operation. The NeoGanesh system is based on modeling of the medical expertise required to perform mechanical ventilation in PSV mode. It does not include mathematical equations of a physiologic model. Several types of evaluation have been performed: (a) to determine how well the system adapts the level of assistance to patient needs (evaluation of the control level),[220] (b) to assess the extubation recommendation made by the system (evaluation of the strategic level),[214] and (c) to estimate the impact on clinical outcomes.[221,222] This system reduces periods of excessive respiratory efforts and predicts extubation time with good accuracy.[214,220] It has been used safely during prolonged periods of mechanical ventilation and often predicted earlier than clinicians the time at which patients were ready to be separated from the ventilator.[221] A multicenter study comparing this system of automated weaning to usual weaning was later performed.[222] Five academic centers recruited 144 patients in 1 year; patients were included as soon as they could tolerate PSV. It was compared to usual care, as performed in the various ICUs participating in the study. Weaning duration was reduced by a median of 2 days, which resulted in a shorter duration of mechanical ventilation and ICU stay. These impressive results have not been consistently reproduced. A smaller randomized study showed no difference with a strict weaning approach,[223] whereas other reports a reduction of weaning duration in surgical patients.[224]

Noisy Pressure-Support Ventilation

Introducing a random noise on the distribution of pressure during PSV produces interesting physiologic effects.[225–227] In two animal models of acute lung injury, noisy PSV increased the variability of the respiratory pattern and improved oxygenation by a redistribution of perfusion toward the ventilated nondependent lung regions.[225,226]

Predicting the Effect of Pressure-Support Ventilation Based on Load Estimation

It has been suggested that a noninvasive method allowing load estimation could be used to titrate the level of pressure support.[228] Noninvasive measurement of the power of breathing, and tolerance of these loads, reflected by spontaneous breathing frequency and V_T, could be considered for deciding the level of PSV, so that muscle loads are not too high or too low. Such a computerized PSV advisory system provided recommendations for setting PSV to unload the inspiratory muscles that were essentially the same as the recommendations from experienced, critical care respiratory therapists.[229]

CLINICAL APPLICATIONS

Weaning

The usual weaning methods are once-daily trials of spontaneous breathing, most often with a T piece, resulting in abrupt discontinuation of mechanical ventilation, SIMV, and PSV, with a gradual reduction in the level of assistance. A low PSV level can be used to mimic spontaneous breathing trials, as mentioned earlier (Compensation for the Work Caused by Endotracheal Tube and Demand Valve); the latter trial thus constitutes the final step in the approach of gradual reduction in PSV or as a substitute for a T-piece trial. PSV can also been used in combination with SIMV, although very few data support the use of this combination.[26–28] In a 1998 international survey of the use of mechanical ventilation,[7] PSV was used one way or another in 45% of weaning attempts, indicating that PSV is considered an important weaning technique.

Studies comparing T-piece trials, SIMV, and PSV were rare before the mid-1990s. Studies had included a large percentage of postoperative patients who exhibited no persistent weaning problem; no conclusions were drawn regarding the type of support to use.[230] PSV as a sole mode of ventilation has first been tested in two large prospective, randomized, controlled trials.[201,202] These trials share common conclusions: (a) patients who tolerated 2 hours of breathing on a T-piece constituted 60% to 80% of patients and were easily separated from the ventilator on first attempt; (b) weaning outcome in the remaining patients depended heavily on the

weaning strategy used; and (c) SIMV was consistently the worst weaning method. The two trials, however, differed regarding efficacy of PSV. PSV was found superior to other methods in the study of Brochard et al, but not in the subsequent study of Esteban et al.

At 21 days, a significantly higher percentage of patients had been separated from the ventilator with PSV than with the other two methods in the trial of Brochard et al,[201] and this was accompanied by a shorter duration of weaning with PSV. Esteban et al adjusted the pressure level to achieve a respiratory rate lower than 25 breaths/min, much lower than the 35 breaths/min upper limit in the trial of Brochard et al.[202] PSV was found to be inferior to once-daily T-piece trials and multiple daily T-piece trials in the trial of Esteban et al. This PSV approach seemed to lengthen the weaning process compared with once-daily T-piece trials. In the study of Esteban et al, the final test before extubation was a T-piece trial, during which respiratory rates of up to 35 breaths/min were tolerated. In the same study, the final step with PSV was a level of 5 cm H_2O, during which respiratory rates above 25 breaths/min were considered a sign of poor clinical tolerance. Thus, the use of PSV differed markedly in the two studies and likely explains differences in efficacy. No study has compared the PSV approach in the trial of Brochard et al to the once-daily T-piece method in the study of Esteban et al. Another trial, however, found no difference between T-piece trial and PSV in patients with prolonged weaning difficulties.[231]

PSV and T piece have been compared as a final test before extubation. Use of a low level of PSV has been found equivalent or slightly superior to a T-piece trial both in adults and infants.[85,86,232] A low level of PSV was slightly superior to T piece in terms of short-term success after extubation.[85,232] At 48 hours, the success rate was not significantly different in the largest trial.[85] A small study suggested that patients who do not tolerate a T-piece trial may tolerate a low level of PSV without increasing the risk of reintubation.[88] The study was too small to render definite conclusions, but concurs with recent data showing that the T-piece trial imposes a higher load on the respiratory muscles.[89]

A comparable approach was used in the NeoGanesh closed-loop system that employs automatic adjustment of PSV. Although different from standard clinical use of PSV, the results of computer-driven system constitute a form of validation of PSV weaning, in a system that applies it on a 24-hour-a-day basis.[222,233]

Noninvasive Ventilation

NIV has been used in many patients with acute respiratory failure since the early 1990s.[8,9,36,110,146,234–240] PSV is used preferentially for NIV. Delivered via a face mask, PSV markedly decreases respiratory muscle activity in patients with COPD in acute exacerbation.[235,241] During exercise, which also constitutes a high ventilatory workload, noninvasive PSV improves performance in patients with COPD.[242]

Bi-level ventilation, as PSV is often called when combined with PEEP, is by far the most frequent mode of ventilation. In a large, multicentric French survey of NIV in ICUs, PSV was used in 67%, ACV in 15%, and continuous positive airway pressure in 18% of patients.[243] PSV is often considered better tolerated than ACV during NIV.[244]

Determinants of the success of NIV have been described in several studies. They relate to patient characteristics (severity scores, etiology of the respiratory failure, nutritional status)[111,241,243] and immediate outcome variables (evolution of arterial blood gases over 2 hours, comfort, level of leaks).[111,243,245–248] These determinants are in part related to technical aspects: ventilator performance, modes,[110,244] settings,[20,31,110,113,123,249] interfaces,[146,250,251] and patient–ventilator asynchrony.[113,145]

Use of Noninvasive Ventilation with Pressure-Support Ventilation for Weaning

In patients with acute exacerbations of COPD, prolonged mechanical ventilation is associated with complications. In this setting, Nava et al suggested that deliberate extubation followed by a switch to NIV might improve weaning outcome.[239] Using PSV for such a goal achieved greater weaning success and higher survival rate. A subsequent study did not confirm these results; patients switched to noninvasive PSV experienced a longer time of ventilator support.[252] In patients with stable chronic respiratory disorders who were unable to sustain spontaneous breathing, Vitacca et al found that invasive PSV, delivered while patients were still intubated, and noninvasive PSV were equally effective in reducing respiratory muscle work and improving arterial blood gases.[253] In addition, noninvasive PSV was slightly better tolerated.

The best indication for NIV with PSV after extubation seems to be the prevention of subsequent respiratory failure in patients at risk of reintubation, as shown in several randomized clinical trials.[254,255] By contrast, applying NIV at the time of postextubation respiratory distress has not proved efficient and can even delay reintubation.[256,257]

CONCLUSION

PSV is a mode of partial ventilator assistance that has proved very efficient in reducing work of breathing and can offer often acceptable synchrony with patient effort. As such, PSV has constituted an enormous change in the way patients have been ventilated over the last 15 years, and has also provided a model to increase understanding of patient–ventilator interaction. Its place has been first assessed during weaning and NIV but is by now largely increasing. It can be used early in the course of ventilation, enabling the patient to be ventilated without need for sedation and in preparation for weaning. In the early phase, its use was limited by lack of control over the volume delivered and the lack of knowledge of the transpulmonary pressure generated. One of its main drawbacks,

however, is the possibility of overassisting patients, causing dyssynchrony between a patient's rhythm and that of the ventilator, inducing hyperventilation, episodes of apneas and potentially sleep fragmentation, especially in patients with obstructive lung disease. For clinical use, lower tidal volumes than usually recommended and relatively higher frequencies should be targeted together with clinical assessment of patient comfort.

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9

PRESSURE-CONTROLLED AND INVERSE-RATIO VENTILATION

Marcelo B. P. Amato
John J. Marini

The use of pressure-controlled ventilation (PCV) increased substantially after 1995, when intensivists became increasingly aware of ventilator-induced lung injury (VILI) and the risks of high inspiratory pressures. Familiarity with the concept of permissive hypercapnia contributed to this change, helping physicians to overcome the old and stringent mindset on arterial blood gases.[1–4] Tidal volume or minute ventilation requirements were increasingly regarded as secondary goals during mechanical ventilation and the apparent security provided by PCV, keeping airway pressures under strict limits, gained broader acceptance. Recent surveys in intensive care units demonstrate that PCV is now used in up to 25% of ventilated patients, usually in the most severe cases[5,6] (including pediatric patients[7]). Studies, describing the implications of PCV on the cardiovascular system, work of breathing, regional mechanics, risks of VILI, and recruitment maneuvers are now available. These studies increase physician comfort in moving away from volume-controlled ventilation.

In contrast to the increasing acceptance of PCV, the use of inverse-ratio ventilation (IRV)—that is, the prolongation of inspiratory time to the point of inverting the conventional inspiratory-to-expiratory (I:E) ratio—is now very rare. This decline was caused by recent progress in our understanding on the pathophysiology of lung collapse, and demonstration of unnecessary hemodynamic compromise. The original benefits in terms of oxygenation ascribed to IRV,[8–14] and the apparent reduction of peak inspiratory alveolar pressures[11,12] are now supplanted by more consistent effects of recruiting maneuvers followed by optimization of positive end-expiratory pressure (PEEP),[15–20] especially during controlled mechanical ventilation. It is only in the more specific context of airway pressure release ventilation (APRV) that the use of IRV has still survived, although surrounded by great skepticism and controversy.[21,22]

In this chapter, we do not revitalize IRV. We believe there are always safer, more predictable, and more efficient ventilatory solutions to be implemented at the bedside. IRV was extensively discussed in the second edition of this book. At the end of the present chapter, we present a few aspects of IRV that still offer great insights about the pathophysiology of acute respiratory failure.

TYPES OF CONTROLLED VENTILATION AND SELECTION OF THE "CONTROLLED" PARAMETER

Ventilators regulate the pressure profile applied to the airways or the pattern of flow delivery. Somewhat imprecisely, flow-controlled ventilation has been designated

"volume-controlled" ventilation (VCV). We avoid this convention because the criterion by which the ventilator ceases to pressurize the airway (initiates deflation) may be a specified value of delivered volume, pressure, elapsed time, or flow. The variable, however, actively controlled by the ventilator during "volume-controlled" breaths is in reality inspiratory flow. Therefore, the modes of ventilation currently used in medical practice should be classified as *pressure-controlled* or *flow-controlled* and as *time-cycled, volume-cycled, flow-cycled,* or *pressure-cycled.* Pressure-support ventilation (PSV) is an example of a pressure-controlled, *flow-cycled* mode, whereas PCV is an example of pressure-controlled, *time-cycled* mode.

In flow-controlled modes, the waveform theoretically can be of any desired contour; in practice, however, the flow waveforms usually are rectilinear (square), linearly decelerating, and sinusoidal. Setting tidal volume as the "off switch" criterion (*volume-cycled*) means that the pressure applied to the airway opening can rise to any value required by impedance to inflation that does not exceed the pressure-limit alarm. For instance, very high absolute airway pressures can develop during acute airway obstruction, acute lung edema or expulsive efforts or bouts of coughing, without consequences to delivered tidal-volume (except if the alarm is activated).

Although once used extensively, *pressure-cycled* ventilation is now considered obsolete for continuous support, and its application in intermittent positive-pressure breathing has been restricted greatly as a backup cycling-off criterion during flow-controlled, *volume-cycled* ventilation (when airway pressures reach a preset alarm threshold), or as a backup for flow-cycling during pressure support ventilation.

To improve safety or decrease the need for repeated adjustments at the bedside, flow-controlled and pressure-controlled algorithms have been combined recently to form new modes (*dual modes*, such as "volume-assured pressure support" and "pressure-regulated volume control"), incorporating the desirable characteristics of each category.[23,24]

The equation of motion of the respiratory system confines the clinician to setting independently the inspiratory flow and tidal volume or just the applied pressure profile. Flow and pressure cannot be selected independently at the same time because their relationship is intrinsically defined by the mechanical properties of the respiratory system. Because modern ventilators can provide online feedback information about output variables (airway pressures during flow-controlled ventilation or flow and tidal volume during pressure-controlled ventilation), either flow-controlled, *volume-cycled* ventilation or pressure-controlled, *time-cycled* ventilation (PCV) can be used interchangeably during specific conditions. For instance, instead of using the original pressure-control algorithms during IRV, some investigators proposed the equivalent use of IRV through flow-controlled, *volume-cycled* breaths,[13] although doing so requires careful monitoring and frequent readjustments. Depending on particular combinations of compliance and resistance in the respiratory system, the pressure profile generated in the airways can be similar in both modes.

The major differences between *flow-controlled* and *pressure-controlled* breaths appear during prolonged use, after unpredictable changes in respiratory system characteristics. By using the traditional flow-controlled, *volume-cycled* mode, minute ventilation is guaranteed safely over prolonged periods of time, although airway pressures may rise significantly when respiratory system impedance increases. Conversely, during prolonged use of pressure-controlled, *time-cycled* ventilation, airway pressure limits are guaranteed, although minute ventilation is at risk whenever lung impedance changes.

Independent of selection of the controlled parameter, inspiration can be triggered by elapsed time or by small perturbations in pressure and flow in the airways (usually indicative of patient effort). Elapsed time defines a totally controlled breath, whereas small perturbations in pressure and flow define an assisted (patient-triggered) breath. In recent years, modern ventilators have incorporated algorithms providing pressure-controlled breaths triggered by either elapsed expiratory time, characterizing traditional PCV, or patient effort (*assisted* pressure-controlled ventilation), analogous to the traditional flow-controlled assist-control ventilation.

During *assisted* PCV, some important and relevant differences between VCV and PCV may appear. For instance, in the presence of a sustained inspiratory effort, extending from the beginning until end-inspiration, the *pressure*-controller will respond with an increased delivery of flow and tidal volume so as to keep airway pressures close to target. The result is an increased transpulmonary effective pressure (which is the sum of the positive airway pressure generated by the ventilator plus the modulus of the negative perturbation in pleural pressure driven by inspiratory muscles). In contrast, the *flow*-controller keeps inspiratory flow close to the target, while peak airway pressures decreases in proportion to the negative perturbation in pleural pressures. The result is a near constant transpulmonary effective pressure (Fig. 9-1, which shows that the modulus of positive airway pressure from the ventilator decreases in direct proportion to the modulus of the negative perturbation in pleural pressures; thus, the sum of the two is almost constant). This is why some investigators believe that VCV is safer during acute lung injury in the presence of strong patient effort and a persisting need for lung protection.[25,26] The drawback of this "forced" maintenance of transpulmonary pressures by VCV, however, is the increased workload to inspiratory muscles and the promotion of a regimen of more negative pleural pressures, which, when excessive, may promote lung edema.[27]

SPECIFIC CHARACTERISTICS OF PRESSURE-CONTROLLED VENTILATION

Many recently introduced ventilator modes can be considered as variants of pressure-controlled or *pressure-preset* ventilation. This includes traditional PCV,[8,27] PSV,[28,29]

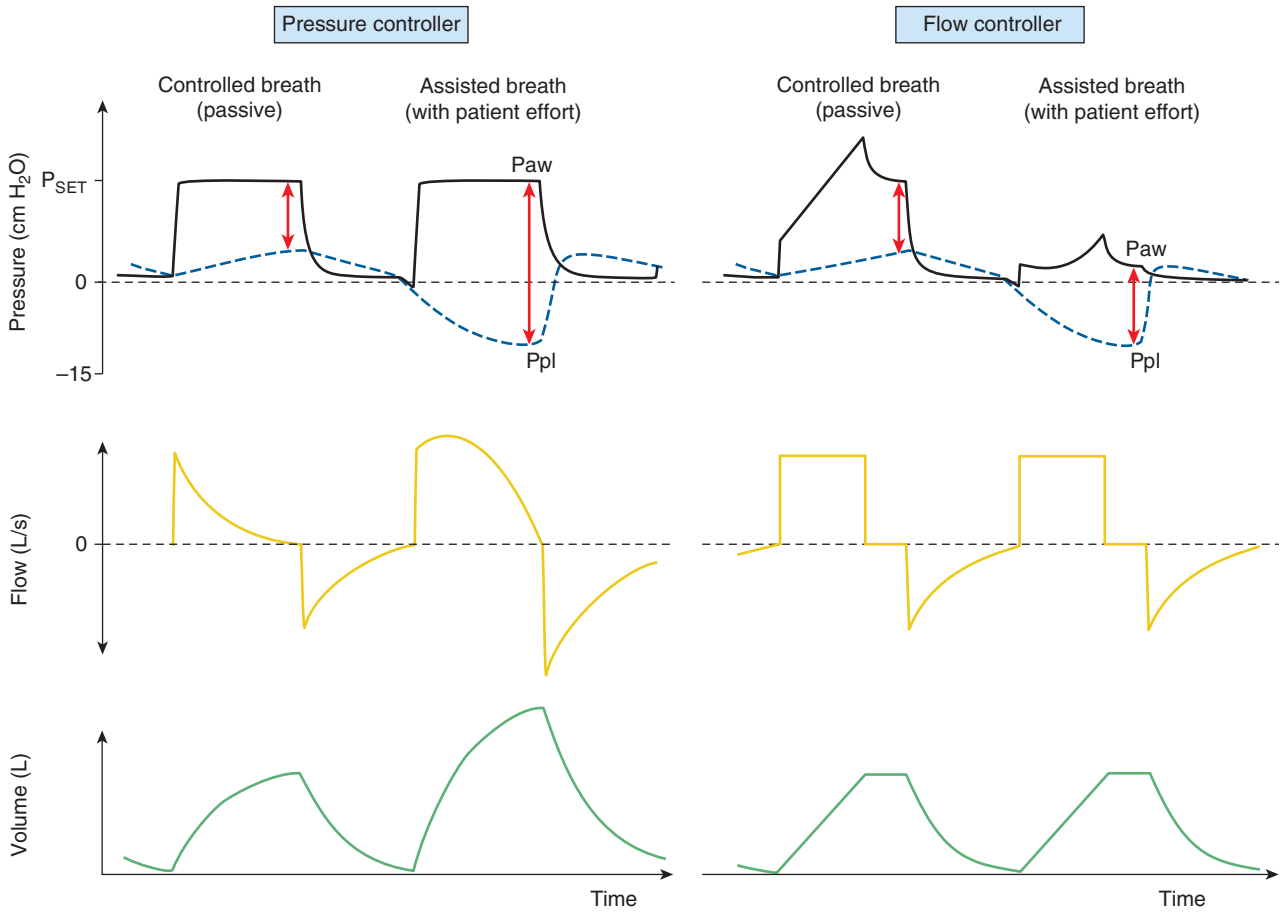

FIGURE 9-1 Airway opening pressure (Paw), pleural pressure (Ppl—*blue dashed lines*), flow and volume tracings during pressure-controlled ventilation (PCV, *left panel of curves*) and during flow-controlled ventilation (VCV, *right panel of curves*). In this simulation, pleural pressures are +1 cm H_2O at relaxed end expiration, which corresponds to the midpleural pressure in a supine patient under anesthesia. In the second cycle of each panel, a patient effort is simulated (muscle pressure = –15 cm H_2O). *Red arrows* at end-inspiration represent the total amplitude of effective transpulmonary pressure at end-inspiration. Note that transpulmonary pressures may increase during assisted PCV, in conjunction with increases in inspiratory flow and tidal volume (second breath in the left panel). In contrast, the assisted-VCV breath (*second breath in the right panel*) is associated with a drop in airway pressures, and with sustained inspiratory flow and tidal volume. The result is a near-constant transpulmonary pressure at end-inspiration. Because of safety concerns, some modern ventilators do not operate as pure flow controllers during VCV if airway pressure drops to below baseline pressure (PEEP); they may provide an extra demand flow to compensate excessive drops in Paw. In this case, the effective transpulmonary pressure might also increase during VCV, although to a lesser degree.

biphasic continuous positive airway pressure, and variants of APRV.[30,31] In some modes, spontaneous respiratory efforts continue. In others, none occur. These modes vary both in their intended objectives and in their criteria for initiating and terminating the machine's inspiratory cycle. Yet all can be viewed as modes in which the machine applies approximately square waves of pressure to the airway opening. In concept, any pressure profile can be regulated. In current practice, however, most *pressure-controlled* modes build pressure rapidly, toward a preset value, attempting to maintain pressure nearly constant throughout the remainder of the higher-pressure phase. During exhalation, pressure is released abruptly, allowing passive deflation to occur unimpeded or against a set PEEP level. By fixing the level of applied pressure during inspiration, the physician imposes an upper limit to the machine's energy transferred to lung tissue.

The specifics of the new pressure-controlled modes are discussed in other chapters. The physical principles governing pressure-controlled, *time-cycled* ventilation—which serves as the prototype for this group—and its major "outcome" variables, such as tidal volume, minute ventilation, and intrinsic PEEP, are addressed here. Some discussion of the concepts of mean airway pressure ($\overline{P}_{aw}$) and mean alveolar pressure ($\overline{P}_{\phi A}$) also are presented because these concepts are essential tools for understanding the physiologic implications of all pressure-controlled modes.

Input Parameters of Pressure-Controlled Ventilation

Apart from the external PEEP, the clinician sets only three parameters during PCV: the applied inspiratory pressure, backup or mandatory frequency, and fractional inspiratory time (duty cycle, T_I/T_{TOT}). The most salient feature of PCV is that maximal airway and alveolar pressures are restricted by the cap of preset pressure, whereas tidal volume, flow, minute volume, and alveolar ventilation depend on the impedance of the respiratory system in conjunction with the three input variables just described. Once the impedance (resistance and compliance) of the respiratory system is known, the machine's contributions to ventilation and alveolar pressure can be characterized completely from knowledge of just those three input parameters.

Machines vary in the rapidity (*rise time* or *inspiratory slope*) with which airway pressure builds toward the preset maximum value. Faster rates of pressurization are needed in certain situations when flow demands are high (during assisted *pressure-controlled* ventilation) so as to achieve high peak inspiratory flows that exceed patient demands. Because of limitations in the controlling system of most ventilators, however, a faster (shorter) *rise time* has to be selected during low-impedance conditions (in large patients), whereas a slower one has to be selected during high-impedance conditions (to avoid overshoots in airway pressure at the beginning of inspiration). Some newer machines allow the clinician to adjust rise time to suit the situation at hand, whereas others adjust it automatically.

With most machines today, physicians set the pressure increment above external PEEP to be applied during inspiration. This means that absolute inspiratory pressures increase as external PEEP increases. With a few machines, the physician has to set the absolute inspiratory pressure, which is independent of external PEEP.

Mean Airway and Alveolar Pressures

When considering a plot of airway-opening pressure (Paw) over time, mean airway pressure is the integral of Paw over time divided by the time span of the breath. Two input parameters that the clinician sets during PCV bear direct relationships to mean airway pressure ($\bar{P}_{aw}$): preset inspiratory pressure and T_I/T_{TOT}. Because of the square waveform of pressure during PCV, $\bar{P}_{aw}$ can be expressed simply as

$$\bar{P}_{aw} = P_{SET} \times T_I / T_{TOT} + PEEP_E \times (1 - T_I / T_{TOT}) \qquad (1)$$

where $PEEP_E$ is external PEEP. Therefore, variations in either set pressure (P_{SET}) or T_I/T_{TOT} influence $\bar{P}_{aw}$ predictably. Frequency variations leave $\bar{P}_{aw}$ unaffected.[28,29]

Under passive conditions, airway pressure represents the total pressure applied across the respiratory system. Under this circumstance, it can be demonstrated mathematically that mean alveolar pressure $\bar{P}_A$ bears a close relationship with $\bar{P}_{aw}$, and its bedside estimation requires only some previous assessment of inspiratory and expiratory resistances

$$\bar{P}_A = \bar{P}_{aw} + \dot{V}_E \times (R_E - R_I) \qquad (2)$$

where R_E and R_I are mean expiratory and mean inspiratory resistances, respectively, and $\dot{V}_E$ is the minute ventilation.

Some practical conclusions can be drawn from this simple formulation. First, changing frequency alters mean alveolar pressure very little if inspiratory and expiratory resistances are similar. In this particular situation, mean airway pressures will reflect alveolar pressures consistently. Conversely, when expiratory resistance exceeds inspiratory resistance, a frequent condition in chronic obstructive lung disease, mean airway pressures can seriously underestimate mean alveolar pressures, especially when minute ventilation is high. Under such conditions, variations in frequency do influence mean alveolar pressure, and physicians easily could overlook the hemodynamic consequences of a ventilator setting.

Figure 9-2 illustrates some additional features related to alveolar and airway pressures during PCV. Alveolar pressure (P_A) can rise no higher than P_{SET}, the pressure to which it equilibrates at end inspiration when sufficient inspiratory time is provided (in Fig. 9-2 there is no equilibrium). Peak P_A falls rather than rises with increasing frequency. One also can grasp from the figure that intrinsic PEEP increases with increasing frequency, reducing the *effective* ventilating pressure (P_{SET}–total PEEP) and consequently reducing tidal volume. As frequency increases further, P_A oscillations decline to the point that $\bar{P}_A$ sets the upper bounding value for intrinsic PEEP.

Under conditions of passive inflation, mean airway pressure reflects the average distending pressure of the respiratory system. Understandably, therefore, mean airway pressure has been associated with two beneficial physiologic effects (ventilation and oxygenation) and three potentially noxious effects (hemodynamic compromise, fluid retention, and barotrauma). These effects, however, are nonlinear, and there are exceptions. For instance, as discussed later, the relationship between $\bar{P}_{aw}$ and oxygenation is very dependent on the extent of pressure-volume hysteresis of the lung, which is greatly affected by lung disease. The greater the hysteresis, the greater is the dependency of oxygenation on PEEP and previous lung history (i.e., the maximum alveolar pressure achieved in previous breaths), and the looser is the correlation between the current $\bar{P}_{aw}$ and oxygenation. In situations of negligible lung hysteresis, for instance, during partial liquid ventilation, the correlation between $\bar{P}_{aw}$ and oxygenation is straight forward.[30] The complex relationship between $\bar{P}_{aw}$ and oxygenation is further elaborated in the short discussion of IRV below.

Mean airway pressure is also a measurable correlate of the back pressure for venous return. Raising $\bar{P}_{aw}$ during passive ventilation increases both lung and chest volumes by similar amounts. Lung expansion tends to increase right-ventricular afterload, which is already high in many patients

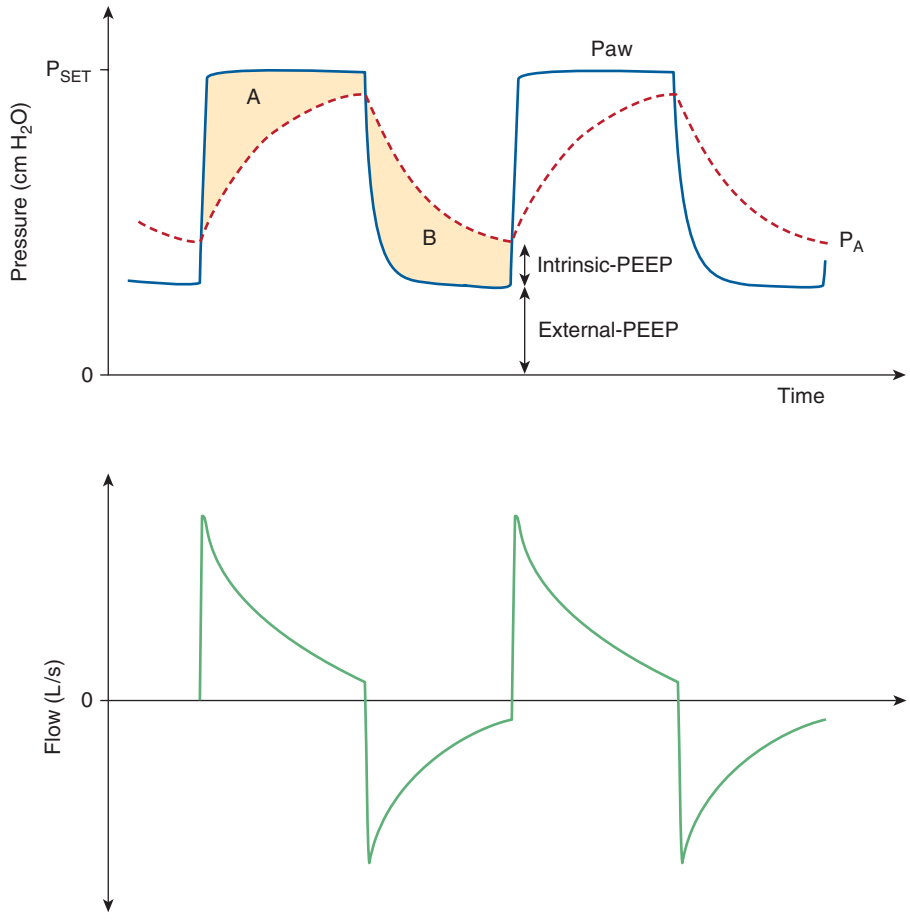

FIGURE 9-2 Airway opening pressure (Paw), alveolar pressure (P_A, red *dashed line*) and flow during pressure-controlled ventilation. Intrinsic-PEEP presents a backpressure that opposes the applied pressure (P_{SET}) and reduces the effective ventilating pressure, which is equal to P_{SET}–total-PEEP (total-PEEP = intrinsic-PEEP + extrinsic-PEEP). Areas *A* and *B* represent the pressure-time product dissipated during inspiration and exhalation, respectively. These areas are proportional to mean inspiratory and expiratory resistances.

with acute respiratory failure. More important, the increase in intrapleural pressure may raise right-atrial pressure, often impeding venous return. Rising back pressure can have clinical consequences in patients with impaired systemic venous tone and reduced tissue turgor (e.g., consequent to sedation or paralysis). Sodium and water retention also tends to correlate with the magnitude of $\bar{P}_{aw}$. Although high $\bar{P}_{aw}$ may not be directly implicated in the *generation* of barotrauma (barotrauma seems to be mainly associated with high inspiratory plateau pressures or high inspiratory driving pressures[31]), a high level of $\bar{P}_{aw}$ may *exacerbate* damage or *accentuate* gas leakage through rents in the alveolar tissues, thereby bringing barotrauma to clinical attention.

Output Variables of Pressure-Controlled Ventilation

As discussed earlier, the major "output" variables of PCV are tidal volume, intrinsic PEEP, minute ventilation, alveolar ventilation, and inspiratory flow.

TIDAL VOLUME

When maximal airway pressure is preset, the tidal volume actually delivered varies with several key variables: the pressure gradient existing between the airway opening and the alveolus at the onset of inflation, the resistance to airflow, the compliance of the respiratory system, and the time available for inspiration. Theoretically, inspiratory time should be longer than the three time constants of the respiratory system to allow near-complete (>95%) lung filling, thus maximizing delivered tidal volume. This scenario would guarantee that alveolar pressures are in equilibrium with airway pressures at the end of inspiration. In adult patients with orotracheal intubation, equilibration usually requires 1.0 to 1.5 seconds of inspiration. In the presence of severe obstructive disease, this value can be as high as 2 to 4 seconds, whereas in patients with reduced compliance (acute respiratory distress syndrome [ARDS]) this value can be as short as 0.8 to 1.0 second. To improve synchrony during *assisted* PCV, sometimes it is necessary to match the spontaneous inspiratory time of the patient. In this case, inspiratory time rarely should exceed 1.2 seconds, usually resulting in incomplete lung filling but promoting comfort.

Any residual end-expiratory pressure (intrinsic PEEP) detracts from the total pressure difference available to accomplish ventilation (*driving pressure*). Therefore, incomplete lung emptying is also an important factor affecting the delivered tidal volume. To allow near-complete lung emptying, expiratory time should be longer than three expiratory time constants. The aggravating factor is that expiratory resistance is usually higher than inspiratory resistance, implying that the expiratory time constants are longer. An expiratory time shorter than 1.5 seconds in an adult patient should be considered a potential source of intrinsic PEEP, reducing the potential for tidal volume delivery.

Such relationships are also valid during low tidal ventilation (used for lung protection, often combined with tidal volumes of approximately 6 mL/kg or lower), which means that incomplete lung filling or emptying are common at respiratory rates above 25 to 30 breaths/min. Because the *absolute* values of intrinsic PEEP, however, in this setting tend to be negligible (from a clinical perspective),[32] clinicians have used PCV with respiratory rates up to 40 breaths/min without great concern about intrinsic PEEP.

INTRINSIC PEEP

Intrinsic PEEP (auto-PEEP) that results from dynamic hyperinflation is a complex function of the input parameters of PCV in conjunction with the impedance characteristics of the respiratory system.[33] The general principles affecting it can be summarized as follows: (a) higher-frequency, longer T_I/T_{TOT} ratio, and higher P_{SET} tend to increase intrinsic PEEP; (b) increments in T_I/T_{TOT} cause a monotonic increase in intrinsic PEEP from external PEEP up to P_{SET}; (c) pure increments in frequency also cause an increase in intrinsic PEEP but with a saturation effect that limits intrinsic PEEP to half (approximately) the range between external PEEP and P_{SET}, which arises because as frequency rises, inspiratory time is curtailed, preventing equilibration between applied airway and alveolar pressures, keeping maximum P_A well below P_{SET} (Fig. 9-3); and (d) the higher the compliance and the higher the expiratory resistance, the higher is the intrinsic PEEP for the same input parameters. Figure 9-3 illustrates some of these relationships.

MINUTE VENTILATION

The relationships just described are responsible for important and nonintuitive effects on minute ventilation (Figs. 9-4 and 9-5). When frequency increases at constant values for P_{SET} and T_I/T_{TOT}, the durations of inspiration and expiration both decrease, and intrinsic PEEP rises. As tidal volume falls, minute ventilation exponentially approaches an upper bound mainly determined by resistance.[33] In obstructed adult patients breathing at respiratory rates above 40 breaths/min, changes in compliance have a minor influence on minute ventilation generation, because most of the *driving pressure* is spent in overcoming resistive losses. For instance, a decrease in compliance from 100 to 50 mL/cm H_2O will produce a maximum fall in minute ventilation of 10%. This

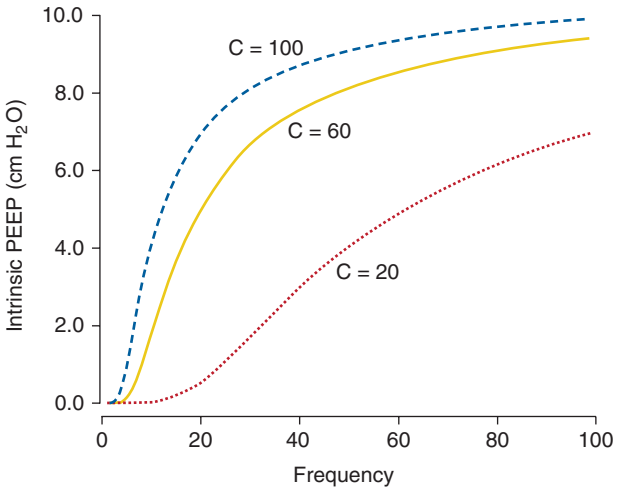

FIGURE 9-3 Effect of frequency on intrinsic-PEEP generation during PCV. Three impedance combinations with moderate airflow obstruction and varying respiratory system compliance (expressed in mL/cm H_2O). A decrease in compliance causes both a reduction in intrinsic PEEP and alteration in the curvature of the intrinsic PEEP-to-frequency relationship. Note that curves converge to an asymptote at 10 cm H_2O, which corresponds to approximately half P_{SET}. *Simulated conditions:* P_{SET} = 20 cm H_2O above PEEP; T_I/T_{TOT} = 0.4; R_E = 25 cm H_2O/L/s. (Adapted from Marini JJ, Crooke PS 3rd. A general mathematical model for respiratory dynamics relevant to the clinical setting. *Am Rev Respir Dis.* 1993;147(1):14–24).

situation resembles a condition commonly observed during high-frequency oscillation,[34,35] when the distribution of ventilation is mainly driven by the distribution of regional resistances, rather than regional compliances.

Figure 9-4 suggests that in patients with moderate to severe airway obstruction (resistance ≥25 cm H_2O/L/s), the benefits of increasing respiratory rate above 12 breaths/min is negligible (this is an important hint when ventilating patients with asthma). The situation changes considerably, however, under conditions of low compliance (≤25 mL/cm H_2O): any increase in frequency becomes an effective mechanism to increase minute ventilation (see Fig. 9-4, *top*).

Important differences between obstructed and restricted patients also can be seen in the relationship between minute ventilation and duty cycle. Minute ventilation becomes very sensitive to changes in duty cycle for obstructed patients but not for restrictive patients. As shown in Figure 9-5, if one wants to maximize minute ventilation for a given P_{SET} (a common target during intensive care of patients with asthma), T_I/T_{TOT} has to be titrated according to the ratio between inspiratory and expiratory resistances. For patients with fixed obstruction and equivalent values for inspiratory and expiratory resistances (as sometimes occurs in asthmatic patients), the ideal T_I/T_{TOT} for maximizing minute ventilation is 0.5.

ALVEOLAR VENTILATION

Over the lower frequency range, increasing frequency tends to improve alveolar as well as total ventilation, decreasing partial pressure of arterial carbon dioxide (Pa_{CO_2}); however,

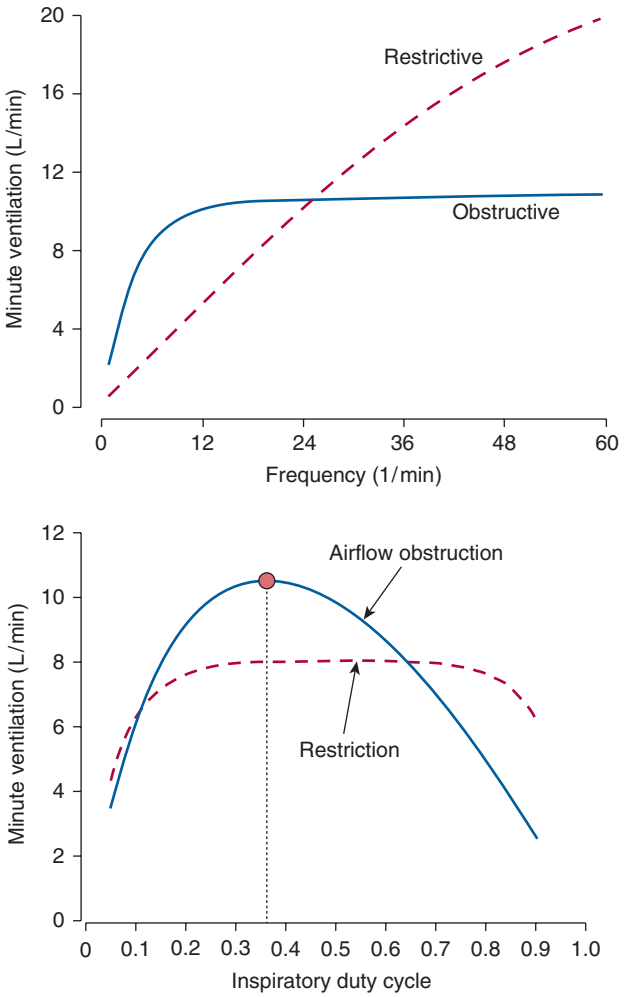

FIGURE 9-4 *Upper plot.* Effect of frequency on minute ventilation during PCV. An increase in frequency causes tidal volume to fall so that minute ventilation approaches a mathematically defined plateau value mainly determined by the applied pressure and resistance. The approach is more gradual for a restrictive ventilatory defect with low compliance. *Bottom plot.* Unlike minute ventilation in the obstructed condition, for which a distinctly optimal T_I/T_{TOT} is evident (*red dot*), minute ventilation in the restricted condition remains essentially unaffected by changes in this parameter. *Simulated conditions:* P_{SET} = 20 cm H_2O above PEEP; T_I/T_{TOT} = 0.4; restrictive, C = 20 mL/cm H_2O, R_I = R_E = 10 cm H_2O/L/sec; obstructed, C = 100 mL/cm H_2O, R_I = 15, R_E = 45 cm H_2O/L/sec. (Adapted from Marini JJ, Crooke PS 3rd. A general mathematical model for respiratory dynamics relevant to the clinical setting. *Am Rev Respir Dis.* 1993;147(1):14–24.)

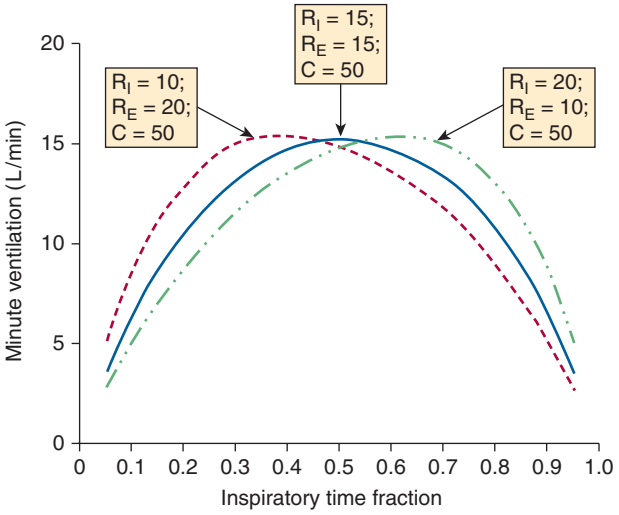

FIGURE 9-5 Effect of inspiratory time fraction(T_I/T_{TOT}) on minute ventilation according to the balance between inspiratory and expiratory resistances (R_I and R_E, respectively). As is true for tidal volume, the apogee of the curve is reached at T_I/T_{TOT} = 0.5, provided that R_I = R_E. Note that optimum T_I/T_{TOT} is shifted leftward, when $R_E > R_I$, exemplifying a common situation in clinical practice. (Adapted from Marini JJ, Crooke PS, 3rd, Truwit JD. Determinants and limits of pressure-preset ventilation: a mathematical model of pressure control. *J Appl Physiol.* 1989;67(3):1081–1092.)

the same is not necessarily true when high frequencies are used. As frequency rises at a fixed, noninverse T_I/T_{TOT}, inspiratory time is curtailed, preventing equilibration between applied airway and alveolar pressures.

From a practical standpoint, the ventilator itself becomes less able to generate the nominal pressure waveform, especially when flow impedance is low and *rising-time* is not optimal. As tidal volume declines, the wasted fraction of each breath (dead-space-to-tidal-volume ratio [V_D/V_T]) increases owing to the predominance of the series ("anatomic") dead-space component. Under certain conditions, this increase in dead space actually may cause Pa_{CO_2} to rise rather than fall with increasing frequency.[36] In practical terms, there is an important message for the bedside: For a given P_{SET} and T_I/T_{TOT}, increments in frequency may cause a decrease in Pa_{CO_2} up to the point that tidal volume decreases by 25% to 30%. Beyond this limit, even when minute ventilation increases with frequency, it is likely that further increments in frequency will be counterproductive because of excessive amounts of dead space.

Because the principles just outlined are rooted in physics and mathematics, hypercapnia can be an unavoidable consequence of a pressure-targeted strategy for managing acute lung injury.

INSPIRATORY FLOW

Decelerating inspiratory flow necessarily is observed during pressure-controlled breaths with rectilinear pressure waveforms—provided that there is no patient effort. Under such conditions, the theoretical maximum of flow associated with a square wave of pressure (P_{SET}) depends on inspiratory resistance (R_I) and end-expiratory alveolar pressure ($PEEP_{TOT}$), and is achieved at inflation onset:

$$Peak\ flow = \frac{P_{SET} - PEEP_{TOT}}{R_I} \quad (3)$$

where $PEEP_{TOT}$ = intrinsic PEEP + external PEEP.

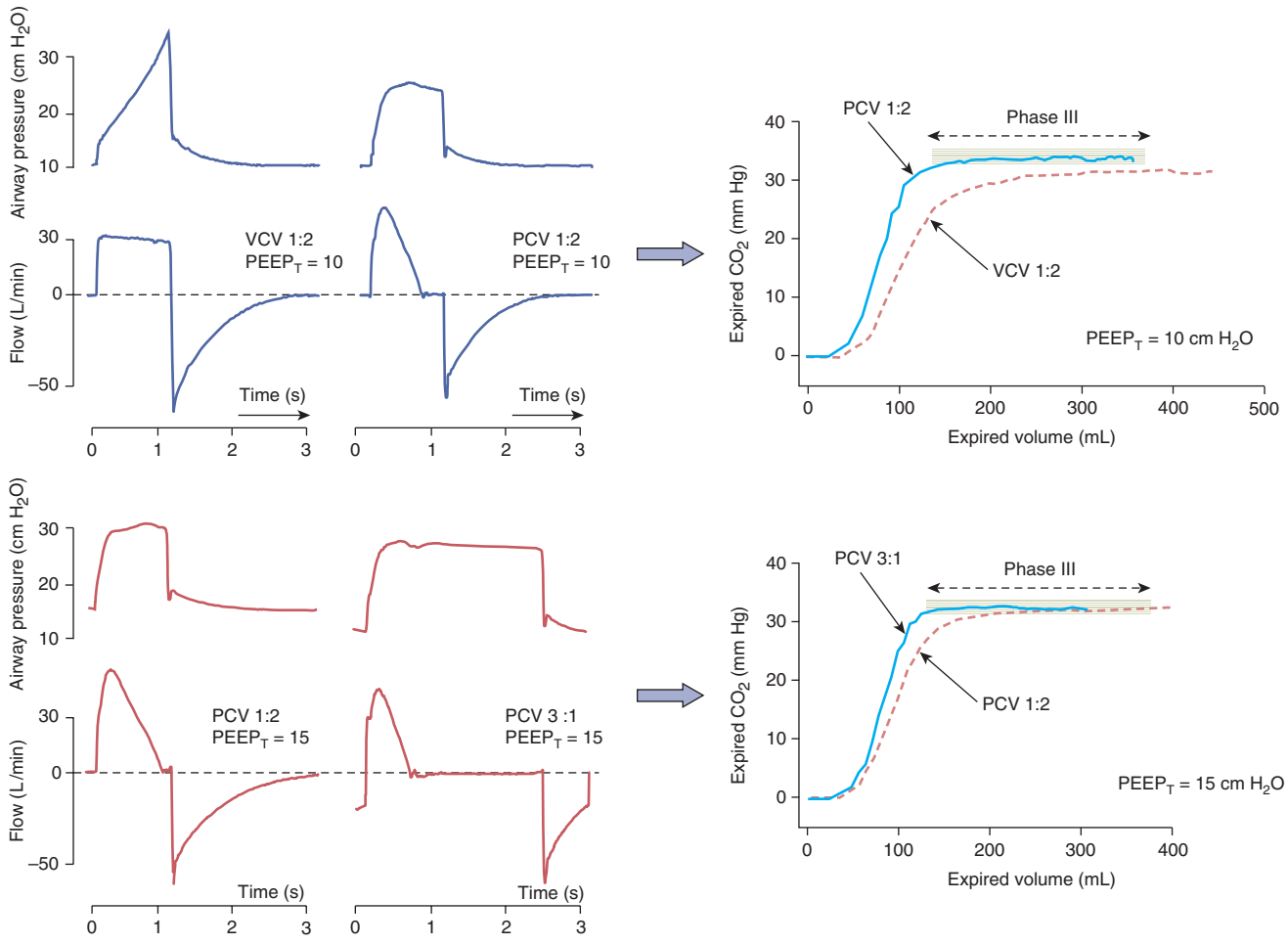

FIGURE 9-6 Effects of inspiratory flow profile on CO_2 elimination per breath (CO_2 single-breath tests obtained in a mainstream volumetric capnograph). *Top.* The change from *flow-controlled, volume-cycled* ventilation (VCV) to PCV, while keeping the same inspiratory time, resulted in more efficient elimination of CO_2 per breath, reflected by the large area under the curve of CO_2 versus exhaled-volume (especially in the first 200 mL, and consequently reflecting a lower dead space). Note that inspiratory flow decayed to zero before exhalation and that the phase III slope is almost flat during PCV, reflecting less heterogeneity among lung units. Arterial P_{CO2} was the same (38 mm Hg) in both conditions, despite the lower tidal volume during PCV. *Bottom.* Changing PCV with an I:E ratio = 1:2 to PCV with an I:E ratio = 3:1 (when part of external PEEP was replaced by intrinsic PEEP) resulted in a further increase in the area under the curve of CO_2 versus exhaled volume. The benefit, however, was much less evident than in the *top panel.*

In practice, however, the abruptness of the rise to the nominal peak value is a set characteristic of the particular ventilator, which may be modulated by the *slope* or inspiratory *rise-time* adjustment. Under conditions of quiet breathing, a precipitous buildup to peak flow often is associated with some pressure overshoot, which may be annoying for monitoring purposes because of alarm triggering. Because most of this pressure overshoot represents pressure dissipation as frictional work across the endotracheal tube, it does not cause elevation of peak alveolar pressure and probably is *not* associated with any harm.

Conversely, under high flow demands (especially in large patients, or in patients using the helmet for noninvasive ventilation), a slow "attack rate" up to peak flow can cause some pressure undershoot or a slow ramp of pressure at the initial phase of the breath, forcing the patient to expend considerable effort and causing delaying filling of the lung.[37,38] Because of limitations in the hardware controlling system, the flow performance of most ventilators, especially at the first 300 milliseconds of inspiration, tends to be poor when P_{SET} is less than 10 cm H_2O. Under such conditions, maximizing rise time or slightly increasing P_{SET} (in association with some procedure to avoid too prolonged T_I, such as shortening the set T_I during assisted PCV, or increasing the cycling-off criterion during PSV[39]) can be very helpful.

The decelerating-flow pattern found in PCV usually improves the distribution of ventilation and limits the end-inspiratory gradient of regional pressures among units with heterogeneous time constants. When inspiratory time is long enough, inspiratory flow may decrease down to zero before exhalation, a phenomenon that further favors redistribution of air or pressure among heterogeneous units and collateral ventilation.[40,41] The consequences of such a flow profile are reflected mainly in the CO_2 eliminated per breath (Fig. 9-6).[42]

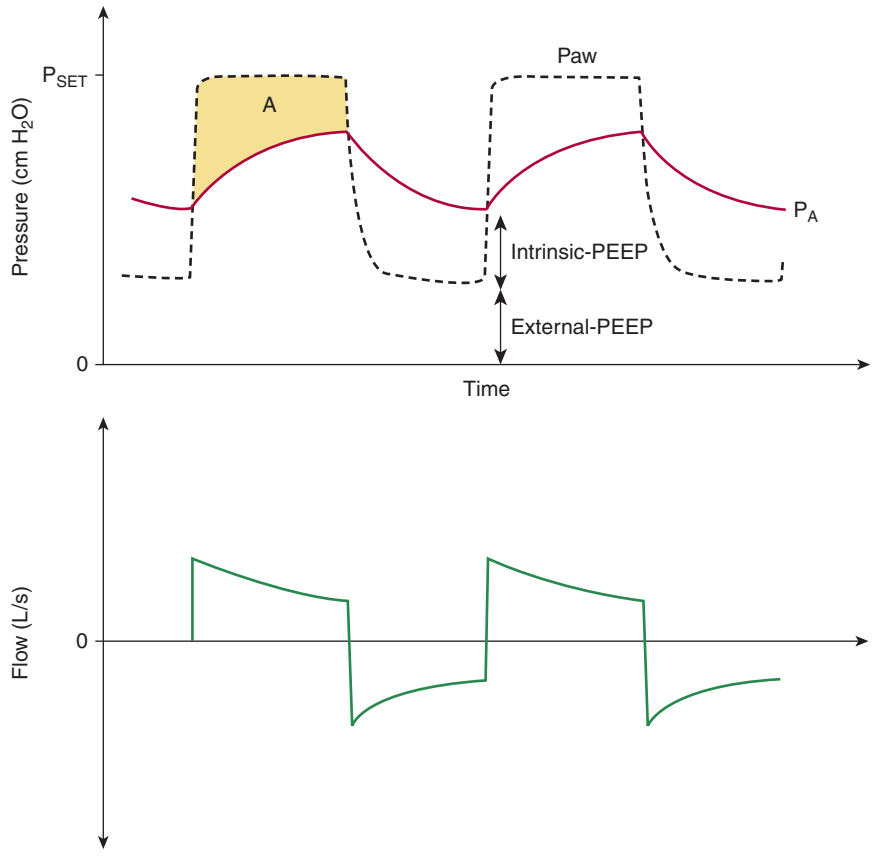

FIGURE 9-7 Typical tracings in an obstructed patient receiving PCV. Note that the flow pattern resembles a square waveform, mimicking *flow-controlled, volume-cycled* ventilation. Intrinsic PEEP is evident and end-inspiratory alveolar pressures (in *red*) are much lower than end-inspiratory airway pressures (*black dashed line*).

The longer the inspiratory time, the more effective is the clearance of CO_2, although most of the benefit may be seen already when T_I slightly exceeds the point of zero flow (Fig. 9-6). This topic is discussed further in "The Controversy on Optimal Distribution of Ventilation" below.

Figures 9-7 and 9-8 illustrate the effects of resistance and compliance on flow profile. Because of the consequent increase in time constant, increments in resistance tend to produce a less decelerating flow pattern (presenting reduced peak flow, with more squared appearance) and rendering tidal volume very sensitive to reductions in inspiratory time. In contrast, decrements in compliance tend to accelerate flow decay. It is obvious, therefore, that restrictive patients tolerate a shorter inspiratory time without marked consequences to their tidal volume.

PHYSIOLOGIC EFFECTS OF PRESSURE-CONTROLLED VENTILATION

Advantages of Controlling Airway Pressures

A major feature of PCV is that peak alveolar pressure cannot rise any higher than P_{SET}. In critical situations, when one attempts to minimize ventilator-induced lung injury, this aspect of PCV may be convenient. Specifying the maximum achievable alveolar pressure, however, does not cap the upper limit for *transalveolar* pressure (equivalent to transpulmonary pressure during an end-inspiratory pause) unless the patient's own breathing efforts also have been silenced (see Fig. 9-1). As suggested by many studies, transalveolar pressure, rather than alveolar pressure, is the key determinant of ventilator-induced lung injury and barotrauma.[43,44]

In the absence of patient efforts, keeping peak alveolar pressures within a safe range makes sense. Under these circumstances, controlling airway pressure effectively controls maximal alveolar pressure. Obviously, the same peak alveolar pressure always can be achieved by flow-controlled, volume-cycled ventilation, although more bedside adjustments are necessary. The subtle difference here is that by selecting *pressure* as the controlling parameter, the physician better defines the priority of his or her strategy (i.e., to minimize peak alveolar pressure at the expense of minute ventilation and possible hypercapnia) and probably minimizes violations to the target during ongoing tidal ventilation (see the section The Controversy on Optimal Distribution of Ventilation).

When thinking in peak alveolar pressures as opposed to peak airway pressures, it is important to stress some important aspects of PCV. When inspiratory time is brief,

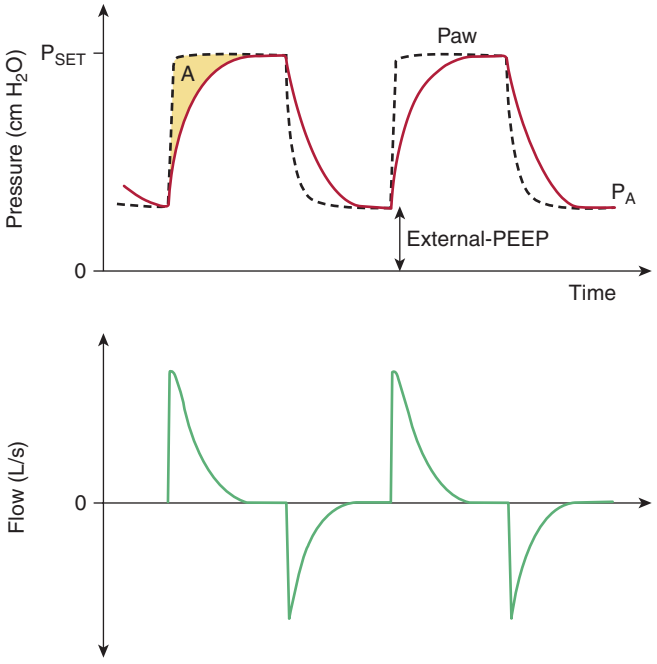

FIGURE 9-8 Typical tracings observed in a restricted patient receiving PCV. Note that inspiratory flow decelerates quickly, achieving zero-flow conditions well before the end of inspiration (generating a small area *A*; compare with Fig. 9-7). There is no intrinsic PEEP and end-inspiratory alveolar pressures (in *red*) equilibrate with end-inspiratory airway pressures (*black dashed line*).

end-inspiratory airway and alveolar pressures fail to equilibrate, so the maximal alveolar pressure is considerably *less* than the set value. This is reflected by persistent end-inspiratory flow, which frequently occurs in obstructed patients.

For a given inspiratory time and peak airway pressure, however, PCV is the waveform that applies the greatest cumulative pressure to the respiratory system.[45] Therefore, for the *same* peak airway pressure—and provided that inspiratory time is long enough—PCV generates a higher peak alveolar pressure and a higher tidal volume than VCV (flow-controlled, volume-cycled breaths delivered with a square-wave profile). Such characteristics of PCV are advantageous during laryngeal mask ventilation: for the same delivered tidal volume, PCV generates lower peak laryngeal pressures during inspiration (approximately 3 to 4 cm H_2O lower than during VCV), resulting in less inadvertent gastric insufflation,[46] and keeps peak airway pressures at a safer distance from the threshold leak pressures.[47]

The consequences of PCV on $\bar{P}_{aw}$ were discussed earlier. It is an important parameter for evaluating the hemodynamic consequences of PCV. Unlike in flow-controlled VCV, $\bar{P}_{aw}$ relates linearly to P_{SET} and T_I/T_{TOT} (see Eq. 1). As its defining equation indicates, $\bar{P}_{aw}$ is unaffected by changes of respiratory system impedance and frequency. Provided that changes in inspiratory and expiratory resistance are roughly balanced, mean alveolar pressures follow mean airway pressures very consistently. Consequently, the impact of adjustments in $\bar{P}_{aw}$ on $\bar{P}_A$ can be predicted much more easily during PCV than during VCV.

Such a straightforward relationship between $\bar{P}_{aw}$ and the input parameters of PCV may be convenient during short-term procedures such as recruiting maneuvers. By adjusting PEEP, P_{SET}, and T_I/T_{TOT}, one can easily predict the generated $\bar{P}_{aw}$ (or $\bar{P}_A$) and hence the hemodynamic consequences. Recent studies demonstrate the relative safety of recruitment maneuvers using PCV for 1 to 2 minutes,[15–17] which achieved equivalent or superior efficacy as sustained pressure maneuvers (continuous positive airway pressure [CPAP]) adjusted to equivalent P_{SET}.[15,48–51] Because the motor of effective recruitment is the surpassing of threshold opening pressures of terminal airspaces,[52] applied long enough to overcome the forces of viscosity and adhesion,[53] cyclic pressurizations with PCV provide an interesting alternative. At the same time that repeated waves of inspiratory pressure promote progressive recruitment, repeated relief of pressure during exhalation minimizes impairment of venous return. Theoretically, one should adjust P_{SET} above the threshold opening pressures, adjust PEEP above the closing pressures, and ensure that inspiratory time is long enough to favor slow, sequential stepwise recruitment of clumps of alveolar units.[52] As suggested by Neumann et al,[54] inspiratory times exceeding 0.6 second (ideally closer to 3 seconds)—for instance, obtained during PCV with a frequency of 8 to 10 breaths/min and an I:E ratio of 1:1—would be enough to maximize the potential for recruitment at a certain P_{SET}. The great appeal of such PCV maneuvers is their reasonable hemodynamic tolerance: because the $\bar{P}_{aw}$ generated during a PCV maneuver is substantially less than the $\bar{P}_{aw}$ generated during a CPAP maneuver (at equivalent P_{SET}), the hemodynamic consequences are less pronounced.[48,50,51,55] Preceding volume expansion with colloids further improves hemodynamic tolerance of the maneuver.[50]

Some investigators, such as Schreiter et al,[56] have applied PCV recruiting maneuvers over much shorter periods (approximately 10 to 15 seconds) but reached higher inspiratory pressures (50 to 80 cm H_2O) and reported good success in patients with severe chest trauma. Comparative data of the relative efficacy and safety of shorter, more intensive application of recruiting pressures[57–60] versus longer (1 to 2 minutes) application of less intensive (45 to 60 cm H_2O) recruiting pressures[15,17,61–63] do not yet exist.

When some active patient effort is present during PCV, the primary control of airway pressures (instead of flow) might offer the potential benefit of introducing some variability in the flow or tidal volume profiles among breaths. By design, an assisted PCV breath provides more freedom (lower machine impedance) for the intrinsic variability of a patient's respiratory motor output to manifest. Besides the likely improvement in comfort, recent research suggest that some random variation (within certain limits) in the effective driving pressure applied to the respiratory system may bring additional benefits in terms of oxygenation, mechanics, and surfactant function.[64–69] The benefits of such extra freedom, however, have to be tempered in conditions where lung protection is a priority, especially when patient effort becomes too vigorous (see Fig. 9-1).

As with any time-cycled mode of ventilation, PCV invites dyssynchrony when the patient breathes spontaneously. The implications of slow *rising-time* settings were discussed earlier. It is important to think about the other end of the inflation period, however, when the airway continues to be pressurized to the nominal value until the set inspiratory time has elapsed. As with flow-controlled VCV, the patient may attempt to cycle to expiration before the ventilator completes its pressurization cycle. One could imagine, however, that unlike the situation with flow-controlled ventilation, patient effort never could force airway pressure higher than the preset value during PCV. Unfortunately, this is not always true (see the section Activation of Exhalation Valve During Pressure-Controlled Ventilation: Airway Pressure Release Ventilation) because of hardware limitations in some ventilators.

Another feature related to dyssynchrony is the fact that by fixing T_I, as required with many commercial ventilators, one allows T_I/T_{TOT} to vary with frequency whenever the patient retains control of the cycling rhythm. As frequency increases, T_{TOT} decreases and T_I/T_{TOT} tends to increase, often provoking dynamic overinflation and generation of intrinsic PEEP. Even with ventilators in which the direct input is "duty cycle," most of them calculate the inspiratory time based on the *set* frequency rather than on *measured* frequency. Therefore, the resulting T_I/T_{TOT} can be very different from the originally set T_I/T_{TOT}.

The Controversy on Optimal Distribution of Ventilation

Several studies have attempted to demonstrate a definitive advantage of PCV over VCV (squared flow pattern) in terms of ventilation distribution, oxygenation, hemodynamics, lung injury, and patient outcome. At first glance, results seem inconclusive. By separating the studies according to key ventilator parameters measured, however, some consistency emerges.

First, it is important to distinguish studies that compare PCV-IRV from studies comparing PCV with normal I:E ratio against other modes. As discussed within this section, the effects of IRV are complex and depend on intrinsic PEEP generation. Thus, during IRV, the choice of the controller (*flow* versus *pressure*) is just a minor issue inside a complex and broader picture. Second, it is important to observe whether all the remaining variables (I:E ratio, tidal volume, intrinsic PEEP, total PEEP, frequency, and O_2 fraction) were kept constant during the comparison and whether they were consistent. For example, studies displaying different plateau pressures or tidal volumes during PCV and VCV can hardly be considered to be perfectly matched if one is interested in the effects on oxygenation[70] or lung overdistension.[71] Thus, they should not be used to draw important conclusions on this controversy.

Keeping such boundaries in mind and by considering only the effects of a pure change in the type of controller (from squared *flow control* to squared *pressure control*, while keeping similar values of I:E ratio, tidal volume, frequency, total PEEP, and plateau pressure), most studies have demonstrated that:

- The resulting decelerating flow during PCV decreases peak airway pressures but increases $\bar{P}_{aw}$.[71–79] Such reduction is helpful during laryngeal mask ventilation,[46] avoiding high peak pressures at the esophageal entrance and avoiding gastric insufflation.[80]
- Pa_{CO_2} and V_D/V_T decrease slightly (ΔPa_{CO_2} approximately 2 to 4 mm Hg), with modest clinical significance,[72,75–77,79] in accordance with the example shown in Figure 9-6. PCV seems to favor ventilation of units with slow time constants, increasing also the *mean distribution time* (defined as the time available for gas distribution and diffusion during inspiration[41,42]). The fast delivery of flow during early inspiration is probably responsible for this effect.
- Such selective benefit in terms of ventilation distribution has been explored theoretically and clinically in obstructed patients.[81–83] PCV is certainly an interesting option in conditions of severe CO_2 retention. Theoretically, however, if obstruction is too severe, the decelerating flow waveform of PCV may become relatively "squared" (see Fig. 9-7), and some benefits reported for decelerating *flow-controlled* VCV[84] (which necessarily achieves zero flow at end-inspiration) may not be directly translated to PCV.
- Minor, if any, changes in dynamic (within the breath) or static lung aeration (end-expiratory or end-inspiratory pause) are observed by computed tomography.[71,74,78] or by mathematical modeling.[85] Regional lung strain measured by computed tomography was also equivalent.[86] Peak alveolar pressure distribution across lung units, however, seems to be more favorable during PCV, guaranteeing a lower exposure to high pressures in more diseased areas of the lung.[85]
- Minor changes are seen in the partial pressure of arterial oxygen (Pa_{O_2}),[72,74,84] slightly favoring PCV.[75,79,87,88] Numerous studies have evaluated the advantages of PCV during anesthesia and one-lung ventilation (during thoracic surgery)[89,90] or during laparoscopic exploration of abdominal cavity,[91–93] including in morbidly obese patients.[94–96] All showed equivalence or minor advantages of questionable clinical relevance.
- No hemodynamic impairment is seen on switching from VCV to PCV, provided that the increments in $\bar{P}_{aw}$ are moderate (usually the case when using I:E<1:1).
- No differences are seen in barotrauma or patient outcome. Studies suggesting benefit of PCV had imbalanced randomization,[88] whereas some studies suggesting benefit of VCV were poorly controlled (including crossovers and rescue procedures).[97–99]

Taken together, the evidence suggests a clear physiologic difference between the two modes of flow delivery, although the clinical implications are modest. At the bedside, the most consistent effects are a reduction of peak inspiratory airway

pressures, increase in $\overline{P}_{aw}$, and small reduction in Pa_{CO_2}. Because of the increment in $\overline{P}_{aw}$, Pa_{O_2} tends to increase with PCV, but this depends on PEEP and plateau pressure in the particular case.

Some concerns are raised repeatedly about the potential generation of greater shear forces at the beginning of inspiration during decelerating-flow patterns. It is suggested that the squared-flow waveform might distribute stress more evenly throughout inspiration, theoretically decreasing VILI. This notion, however, is just theoretical speculation, valid in only extreme conditions. The isolated effects of high inspiratory flow rates on VILI[100–109] have been investigated in recent years. Most studies suggest a deleterious effect,[100,104,106–109] although a few suggest a neutral or protective effect.[102,103,105] The deleterious effects, however, could be demonstrated only in association with tidal volumes above 20 mL/kg, and in conditions where PCV caused an approximate three fold increment in inspiratory flow, as compared to VCV.

In the context of protective ventilation, the peak flow rates observed during PCV are much lower, usually within the same range as those achieved during VCV.[25] When the driving pressure set on the ventilator is within the 15 to 20 cm H_2O range, the resistance across the endotracheal tube and connectors is usually enough to avoid peak flow rates above 1.5 L/s. Thus, consistent differences in VILI will hardly be linked to PCV as opposed to VCV, at least during controlled ventilation and during ventilation with small tidal volume (≤6 mL/kg). Isolated short-term changes in the controller, from flow to pressure control, could probably induce mild perturbations in the effective stress applied on the parenchyma.[85,86] But when compared with the potential for iatrogenic damage associated with other parameters set on the ventilator, such as the choice of tidal volumes or resulting driving pressures (plateau pressure minus PEEP during controlled ventilation), the controller option is most likely insignificant.

As discussed earlier, with adequate feedback it is usually possible to obtain the same ventilator output with either a *flow controller* or a *pressure controller* under specific conditions. For instance, a flow-controlled breath with a decelerating-flow waveform can be generated by modern ventilators, mimicking the flow and airway pressure waveforms commonly observed during PCV[79,110] and producing some of its physiologic effects. Because it is practically impossible to match the degree of deceleration with the impedance characteristics of different patients (e.g., more obstructed patients would present a less accentuated deceleration during PCV), peak airway pressures are frequently higher during such pressure-control "imitations."[110,111]

Considering the evidence presented above, we again suggest that the choice for PCV should be decided in terms of a global bedside strategy and not based on subtle physiologic differences. Minor differences between PCV and VCV may have an impact only when considering the associated clinical problems. For instance, in a patient requiring high PEEP levels, in whom Pa_{CO2} and alveolar dead space are also increased, and who thus requires high plateau pressure to achieve satisfactory ventilation, a change from VCV to PCV might be appropriate because (a) plateau pressures will rarely exceed the physician-adjusted P_{SET}; (b) any decrease in dead space afforded by decelerating flow may allow further reduction in tidal volumes and, thus, in P_{SET}; (c) an eventual rise in respiratory rate triggered by the patient will not be translated into increased plateau pressures despite the possible generation of intrinsic PEEP; and (d) paralyzing agents and sedation may thus be reduced.

Paradoxically, however, such advantages may be quickly nullified if spontaneous efforts become too strong. By decreasing pleural pressures, diaphragmatic activity may cause transpulmonary pressures to be excessive, despite rigid control of maximum alveolar pressures (capped at P_{SET}, see Fig. 9-1). In fact, during strong patient efforts, a *flow controller* avoids excessive transpulmonary pressure more efficiently than a *pressure controller*, because airway pressures follow changes in pleural pressure more closely, being transiently reduced during patient effort (there is no extra "demand" flow to maintain airway pressure). The result is an almost constant transpulmonary pressure. This important physiologic difference may explain some evidences pointing to a better outcome in neonates during *flow-controlled* VCV[112] versus pressure-limited ventilation (which is essentially similar to PCV working with an open exhalation valve; see below the section "Variants of Pressure-Controlled Ventilation and Activation of Exhalation Valve"). Irregular breathing patterns and strong spontaneous efforts are especially common in neonates; the eventual coupling of such efforts with a *pressure-controlled* breath can transiently promote excessive transpulmonary pressures.

This is why we strongly recommend the close monitoring of the extra tidal volume generated by a patient during assisted PCV. Even when P_{SET} is relatively low, it is important to infer the effective driving pressures applied to the respiratory system by observing the resulting tidal volume during synchronous efforts. The simple division of tidal volume by respiratory compliance provides a good estimate of the effective driving pressure (the driving pressure applied across the respiratory system [the lung plus chest wall in series]). It is common to observe patients with ARDS submitted to PCV with P_{SET} at 10 cm H_2O, and producing tidal volumes of 500 mL during synchronous efforts. If respiratory system compliance is 20 mL/cm H_2O, such a presentation means that the effective inspiratory driving pressure is equivalent to 25 cm H_2O. Failure to adhere to these principles can make PCV more dangerous than VCV.

Another point considered here is that peak-flow rates during PCV at low levels of P_{SET} may be equal to lower than during VCV, increasing work of breathing.[25,113] This might appear quite surprising, considering the previous rationale that the *free* inspiratory demand-flow during assisted PCV is an effective tool to reduce the work of breathing.[114] One should note, however, that this rationale was developed in an era when high levels of P_{SET} were common in clinical practice. This topic is discussed in the section Assisted Pressure-Controlled Ventilation.

Assisted versus Controlled (Time-Triggered) Ventilation

Most reasons to control ventilation can be classified as needs to regulate the ventilatory pattern, reverse life-threatening abnormalities in blood gases, reduce agitation and the O_2 cost of breathing, or prevent excessive excursions of the injured lung. Perhaps the most common indication is to provide ventilator support to a patient with marginal cardiorespiratory reserve in whom breathing efforts compromise comfort, gas exchange, or cardiac function. Reducing O_2 consumption in a patient with critical coronary ischemia, for example, may prove lifesaving, especially in the setting of circulatory shock or acute pulmonary edema. Silencing ventilatory effort also can improve arterial oxygenation and lung volume recruitment in agitated patients with ARDS,[115–119] probably by reducing expiratory efforts that may reduce end-expiratory transpulmonary pressures. The silencing of vigorous patient efforts during the first few hours of protective ventilation may also help by decreasing lung inflammation,[119,120] and reducing double triggering ("breath stacking").[121] The active control of minute volume to achieve normocapnia or to achieve transient hypocapnia, when reductions in cerebral blood volume and intracranial pressure are urgent priorities, are also common indications for controlled ventilation. Controlling ventilation greatly facilitates the monitoring of respiratory mechanics but in itself is seldom sufficient reason to undertake deep sedation or pharmacologic paralysis.

Apart from reducing O_2 consumption and preventing spontaneous efforts from interfering with intended patterns of *conventional* ventilation, establishing ventilatory control facilitates the therapeutic application of "nonphysiologic" breathing patterns. Interventions such as IRV,[9,13] independent lung ventilation,[122] continuous-flow ventilation,[123] and permissive hypercapnia[1,3,4,124] usually require cessation of patient effort. In patients with acute lung injury, use of small tidal-volume ventilation is a priority, but this pattern is not easily tolerated by patients unless deep sedation, ventilator overriding,[125,126] or complete paralysis is applied.[120] This is especially true when tidal volume is set at 4 to 6 mL/kg.[125,127]

Sedation is commonly used to enhance comfort or inhibit excessive respiratory drive. Muscle relaxants, however, should be used sparingly because of their injurious potential. A better understanding of the sequelae of prolonged paralysis, especially when combined with sepsis and systemic inflammation,[128] high-dose corticosteroids and hyperglycemia,[129–131] has forced physicians to minimize the magnitude and duration of paralysis in ventilated patients. Recent work suggests that severe diaphragmatic dysfunction occurs after only 2 to 3 days of controlled mechanical ventilation,[132–134] independent of the use of paralyzing agents, with loss of more than 40% of power generation. It is likely that paralyzing agents magnify or trigger such effects[135] by blocking protective mechanism against atrophy. Independent of its precise mechanism, critical illness polyneuropathy increases the duration of mechanical ventilation significantly.[136]

Recent evidence suggests that calm assisted ventilation, with efforts just sufficient to trigger the ventilator, can avoid excessive muscle wasting.[133] Because spontaneous efforts also can improve oxygenation during pressure-controlled breaths,[65,137–139] probably secondary to redistribution of blood flow to nondependent, well-ventilated lung areas, it is tempting to conclude that some level of spontaneous effort always should be promoted in patients receiving PCV. Such approach consistently reduces sedation requirements.[139] An anticipated drawback of such a strategy, however, is an undesirable increase in I:E ratio when the patient respiratory rate is much higher than the set respiratory rate. Another problem is the generation of unpredictably high transpulmonary pressures during strong and synchronous effort by the patient (see Fig. 9-1). In both circumstances, however, deeper sedation or partial paralysis could control the situation easily. By keeping the spontaneous respiratory rate close to the set rate, one easily can avoid changes in the I:E ratio. Also, by keeping the exhaled tidal volume close to a value associated to low driving pressures during totally controlled breaths (see the section The Controversy on Optimal Distribution of Ventilation), one may ensure that a patient's spontaneous effort does not cause significant increments in inspiratory transpulmonary pressures.

VARIANTS OF PRESSURE-CONTROLLED VENTILATION AND ACTIVATION OF EXHALATION VALVE

As discussed earlier, the variants of traditional PCV[10,75] include assisted PCV,[25,114,140] PSV,[141,142] and variants of APRV.[143–147]

Assisted Pressure-Controlled Ventilation

Assisted PCV is similar to PSV in that the breaths can be triggered by the patient (physicians set the sensitivity and triggering mechanism). The difference is that cycling off is determined by time instead of flow. Another obvious difference is that assisted PCV possesses the same backup mechanism available with traditional assisted flow-controlled breaths: breaths can be triggered by patient effort or by elapsed expiratory time, whichever occurs first.

Compared with assisted VCV at equivalent tidal volumes, assisted PCV decreases peak airway pressures. Although irrelevant during invasive ventilation, this characteristic is relevant during noninvasive ventilation, minimizing leaks through the mask[80,148] and avoiding uncomfortably high pressures in the upper airways.[46,149] When comparing the level of patient assistance during invasive ventilation, the characteristic decelerating flow (*on demand*) provided by PCV seems to reduce workload more efficiently than most flow-controlled, volume-cycled breaths.[114,140] The reduction in inspiratory muscle

load is especially prominent during moderate to high tidal volume (8 to 10 mL/kg) ventilation or use of a low inspiratory flow during VCV (<0.7 L/s). It is important to stress, however, that with use of low tidal volume (≤6 mL/kg), this assumption is not always valid.[25,113,125] Because physicians have to set low values of P_{SET} during *pressure-controlled* breaths (to keep tidal volume in a safe range), peak inspiratory flow rates are commonly at lower during PCV than during *flow-controlled* VCV. To circumvent this problem, it is tempting to use higher levels of P_{SET}, guaranteeing a high peak flow at the beginning of a breath, but keeping inspiratory time short enough so that a high tidal volume is not delivered.[39] This maneuver, however, must be used under close monitoring, or combined with some inspiratory pause so as to avoid double triggering and "breath stacking."

The algorithm configured for assisted PCV also may carry some advantages over PSV. First, in patients with unstable respiratory drive, the backup rate works as a safety and stabilizing mechanism, avoiding central apneas and sleep fragmentation, especially in patients with cardiac failure or in those receiving heavy sedation.[150] Second, although PSV is popular during noninvasive ventilation, serious concerns have been raised about potential dyssynchrony at end inspiration. During PSV, transition from inspiration to expiration is triggered by flow (i.e., when inspiratory flow decays below a certain threshold). Hence the presence of mask leaks or severe airway obstruction can render this mechanism inefficient—both conditions cause a relatively high inspiratory flow at end inspiration. Leaks simply mislead the inspiratory flow regulator of the ventilator, which cannot detect that inspiratory flow is not being delivered to patient. Conversely, severe obstruction changes the shape of inspiratory flow (see Fig. 9-7), making it less decelerating and pushing end-inspiratory flows closer to peak flow. With both conditions, the default expiratory triggering threshold for PSV (usually 25% of peak inspiratory flow) may never be reached, causing excessive prolongation of inspiratory time and patient overinflation.[39,151–153] Under such conditions, pressure-controlled, *time-cycled* ventilation could be convenient: The intensivist needs only to adjust inspiratory time to match the patient's spontaneous inspiratory time, usually 0.6 to 1.2 seconds.[39,151,152] By changing from PSV to PCV, the intensivist necessarily decreases the freedom of ventilation pattern (restraining, for instance, the possibility of a spontaneous sigh and potentially increasing discomfort) but also avoids dangerous prolongation of inspiratory time. This is a difficult balance that has to be judged at the bedside.

During assisted PCV, especially under high flow demands, a fast "attack rate" to peak flow (at the initial phase) of the breath is desirable and decreases the work of breathing.[37] Thus, when changing from totally controlled (time-triggered) PCV to assisted PCV, it is advisable to increase the speed of pressurization (i.e., to decrease the *rise time* or to increase the inspiratory *pressure slope*).

Activation of Exhalation Valve During Pressure-Controlled Ventilation: Airway Pressure Release Ventilation

OPENING OF THE EXHALATION VALVE

In theory, any pressure-controlled breath should limit airway pressures to P_{SET} independent of patient demand, dyssynchrony, premature expiratory efforts, or cough. In practice, however, hardware and software limitations of most ventilators preclude such ideal configuration. Usually, ventilators can overcome an increase in inspiratory-flow demands efficiently during PCV (caused by leaks or strong inspiratory efforts) by boosting flow through the demand valve. Airway pressures are raised quickly back to P_{SET}. Additionally, during the period in which the demand valve is still open, any sudden increment in alveolar pressure (cough) can be counterbalanced promptly by a sudden decrease in demand flow, attenuating the potential raise in airway pressures. Once the demand valve is already closed, however—because alveolar pressures have equalized airway pressures—the ventilator is no longer able to control airway pressures. Because most ventilators do not actively control the exhalation valve during inspiration (they just close it tightly until the end of inspiratory time), any unexpected increment in airway pressures can only be counterbalanced by total closure of the demand valve, but this is already at its minimum position. The end result is a steep increment in airway pressures, as in *flow-controlled* breaths.

Physicians have to keep this limitation of PCV in mind because it may be responsible for undesirable increments in airway pressures above P_{SET} in most ventilators. This situation has been observed during continuous tracheal gas insufflation,[154] during cough, and during strong efforts in assisted PCV breaths. In the latter circumstance, marked elevations of airway pressures can be found even in the absence of active expiratory efforts. This is so because the patient effort can increase effective driving pressures in early inspiration, increasing tidal volume and, consequently, the elastic recoil pressure at end inspiration (when diaphragmatic contraction already has ceased). An inactive exhalation valve could not release this extra tidal volume before the beginning of next exhalation, thus increasing airway pressures.

To overcome such limitations, some modern ventilators have incorporated improved hardware in their exhalation system that allows the simultaneous control of both valves (the inspiratory demand-flow valve and the exhalation valve) during the inspiratory phase of PCV. The end result is a smoother control of airway pressures during cough or during continuous tracheal gas insufflation.[155] Whenever available, such active control of the exhalation valve enhances ventilator operation.

The opening of the exhalation valve and its active control during inspiration are the technological basis for incorporation of APRV in microprocessed ventilators.

AIRWAY PRESSURE RELEASE VENTILATION AND ITS VARIANTS

APRV is a form of partial ventilatory support intended originally to offload a portion of the work required to ventilate during a primary crisis of oxygenation.[143,144] In its original conception, APRV elevated mean airway pressure by maintaining a moderately high level of CPAP, delivered through a specially designed high-flow CPAP system linked to a release valve operated by a time controller. The system was design to work independently of any commercial ventilator. Spontaneous breaths were planned to occur around this pressure baseline. Periodically, the airway was depressurized rapidly during one of the patient's deflation cycles, exhausting waste gas from the expiratory reserve before replacing it with fresh gas as CPAP rebuilt to the baseline level. Total time for both phases of the release cycle generally was brief, ideally occupying only a single breath of the patient's rhythm. The release pattern was repeated at a clinician-selected frequency. As predicated by the mathematics of pressure-preset ventilation,[33] ventilator support (achieved by the machine) was necessarily a function of the number of release cycles, the magnitude of the pressure drop during release, the duration of the release period, and the impedance to inflation and deflation. Synchronization between the patient's own exhalation and airway depressurization also affects the effectiveness of ventilation. Ineffectual inspiratory efforts during the deflation phase could impair the released volume. Despite such concerns, the original system was not designed to be synchronous.

Subsequently, different names were used for similar systems and arrangements, *biphasic positive airway pressure*, *intermittent mandatory pressure-release ventilation,* or simply *PCV+* (this latter mostly used in the United States). Despite the similarity, the term *bilevel airway pressure,* commercially known as *biphasic continuous positive airway pressure,* represents something different, being simply a combination of pressure-supported ventilation and CPAP; this product is designed for noninvasive use. The basic difference among these systems is the duration of each phase, although all the systems can be approximated to periodic alternation between two CPAP levels according to a time controller. A longer period at the lower CPAP level, enough to allow one or more spontaneous breaths, is characteristic of biphasic positive airway pressure ventilation. This definition, however, is not consistent in the literature, with considerable ambiguity in the use of terms.[21] Commercial ventilator branding further add to confusion. The specific transition from low to high CPAP levels differs among these variants, whether it is synchronized or not.

Adjustment of all these features is now possible in modern ventilators, and this does not represent any important conceptual modification. Accordingly, we believe that the confusing proliferation of names should be simplified under a single acronym: *APRV*.

In modern ventilators, provided that the ventilator works with an *active* (open) exhalation valve during inspiration, APRV can be perfectly imitated by PCV breaths with a single difference. During APRV, if the expiratory time is set long enough to allow the patient to complete one or more spontaneous breaths during the low-pressure phase, the spontaneous breath will be assisted by an efficient CPAP system (equivalent to PSV set at zero driving pressure). Conversely, during the exhalation phase of PCV, the spontaneous effort cannot be well assisted in most ventilators, because the bias-flow systems responsible for PEEP maintenance are not designed to support strong efforts. The end result may be some drop in PEEP unless sensitivity is adjusted to allow triggered inspirations (this latter, however, will result in an *assisted* PCV breath, which will necessarily cause an increase in the I:E ratio).

During the inspiratory phase, the opening of the exhalation valve during PCV assures that both systems perform identically, allowing spontaneous breaths to occur around highly sustained airway pressures. When spontaneous breaths are abolished by paralysis, APRV is not different from PCV.

It is important to remember that spontaneous cycles and ventilator cycles are completely uncoupled in the most frequent usage of APRV. This means that spontaneous breathing can occur at any phase of the ventilator cycle without any synchronization mechanism. Switching between the two CPAP levels obeys a timed-cycled mechanism, and patient inspiratory work is mechanically supported only when it coincides with the restoration of the high CPAP phase. In view of such inherent dyssynchrony, more sophisticated APRV algorithms have been introduced in recent years, although without a clear rationale or clinical benefit. These include triggered transitions between low and high CPAP levels and use of PSV during one or both phases, on top of the corresponding baseline pressures.

Regarding the synchronized transition, it is important to remember that whenever commercial ventilators allow the patient to trigger the CPAP transition, usually during a time-window that spans the last 25% of the preset low-pressure phase, the actual time intervals at high and low pressures (equivalent to I:E ratio) may vary according to the respiratory drive of the patient.[156] Furthermore, even when some synchronization with CPAP transitions is attempted, most spontaneous breaths during APRV are still nonsynchronous because of the long duration of both phases. Under such conditions, the real advantage of synchronized systems is questionable. *From a workload perspective, APRV is an inefficient way of assisting the patient, imposing a higher workload and greater discomfort as compared with equivalent levels of PSV or assisted PCV*.[65,139,157,158] The benefit, if any, of providing some synchronization has to be balanced against the loss of control over T_I/T_{TOT}. Synchronization would only make sense if applied to most spontaneous efforts, meaning that APRV should be set at higher frequencies and shorter inspiratory times, as with assisted PCV. Another potential disadvantage of synchronization is the creation of high driving pressures

during this upward transition, caused by the coupling of muscle effort with the positive-pressure wave from the ventilator. The high inspiratory volume generated, however, will not be evident when looking at the next exhalation, because the release will occur against a higher PEEP level. To compute this hidden, large, inspired volume, one should carefully look at the next downward transition, a few breaths ahead, when most of the insufflated volume will be finally released.

Whenever APRV is applied in its common configuration, with long time intervals set for both phases, the intermittent mechanical assistance (applied only when the spontaneous effort coincides with transition from low to high pressures) shares some similarities with intermittent mandatory ventilation. As with synchronized intermittent mandatory ventilation, the presence of alternating levels of assistance probably impairs smooth accommodation of patient drive,[159] potentially causing some distress in patients when sedation is removed. Therefore, it is still an open question as to whether APRV will prove helpful during weaning or for patients with extreme weakness, very high workloads, or conditions in which release cycles are relatively inefficient in achieving ventilation (e.g., severe airflow obstruction).

For the sake of simplicity, whenever the patient gets too distressed during APRV and sedation is contraindicated, it is preferable to change to PSV or assisted PCV, assisting the patient in a more predictable way. The combination of PSV with APRV introduces unnecessary complexity, making little sense in terms of physiologic benefit or as an attempt to minimize driving pressures and ventilator-induced lung injury.

By extending the higher CPAP level further, APRV gets closer to inverse-ratio PCV. The shorter the time at low CPAP levels, the lower is the ventilator contribution to minute ventilation,[156] and the higher is the Pa_{CO2}. On the other hand, Pa_{O2} tends to increase because intrinsic PEEP increases. The full consequences of the duty-cycle settings on oxygenation are discussed in the section Intrinsic Positive End-Expiratory Pressure versus Extrinsic Positive End-Expiratory Pressure.

Comparison of APRV associated *with* spontaneous breaths versus APRV *without* spontaneous efforts (identical to conventional PCV), when both modes are set at *equivalent end-expiratory* and *end-inspiratory* airway pressures, showed that the former achieved better oxygenation,[147] higher cardiac output,[147,160] higher renal blood flow,[161] higher lung aeration, and higher functional residual capacity.[145] Whereas the hemodynamic benefits seem to be related to lower intrathoracic pressures generated during spontaneous efforts,[146] the benefits in lung function seem to be mostly related to higher transpulmonary pressures.[145,162] When equivalent transpulmonary pressures are accomplished by controlled PCV without any patient effort (with P_{SET} adjusted at higher levels, matching the transpulmonary pressures observed during APRV), the oxygenation benefits are no longer observed.[162]

It is also important to stress that equivalent physiologic benefits can be achieved during simple CPAP application (matched to the high-pressure phase of APRV), in fact, with better outcomes in terms of oxygenation.[163] These findings demonstrate that *most of the benefits attributed to APRV relate to the replacement of mechanically applied driving pressures by patient-generated driving pressures.*

When considering the overall implications on hemodynamics, lung injury, and muscle function, APRV still poses a well-defined set of potential problems. Central vascular congestion and exacerbated pulmonary edema are natural consequences of lower intrathoracic pressures and increased cardiac workload. Interstitial pressures are expected to be lower in this setting, potentially increasing transcapillary pressures and interstitial edema.[26] Thus, in patients with cardiac failure, APRV should be used with caution. Conversely, to unload inspiratory muscles significantly, the high-pressure CPAP in APRV first must be raised to a considerable degree, obscuring the major advantage of APRV, which is the use of lower airway pressures. Moreover, inspiratory muscles will be disadvantaged by the resulting hyperinflation, promoting a sense of dyspnea that APRV is designed to relieve.

Finally, the intrinsic design of APRV raises important concerns about VILI. Because relaxation of inspiratory muscles is common during end-exhalation, even during spontaneous effort, we should not expect any significant advantage of APRV in terms cyclic lung collapse and its related damage.[164–167] Also, because inspiratory transpulmonary pressures are unpredictable, probably higher than during passive PCV breaths (supposing a situation where P_{SET} matches the high CPAP level of APRV) we should not expect much improvements in terms of overdistension.[18,43,168–170] Conceptually, the same principles of protective ventilation should be respected during APRV: the need to reduce effective driving pressures, whatever their source of generation, and the need to avoid cyclic collapse and tidal recruitment. The practical implications are that the releasing pressures of APRV should be titrated carefully (as during any PEEP titration), and, similarly, driving pressures should be estimated carefully and minimized (as during any attempt to reduce plateau pressures during controlled ventilation). Unfortunately, the general use of APRV rarely follows such protective principles.[21]

In conclusion, the important message provided by studies of APRV is that the preservation of spontaneous efforts is an important aspect of mechanical ventilation that should be employed prudently. Often, the simple use of assisted PCV, instead of fully controlled PCV, is the required change to promote profound benefits in hemodynamics, lung recruitment and oxygenation.

COMBINED MODES

In recent years, attempts have been made to combine the desirable features of both *flow*-controlled, volume-cycled and *pressure*-controlled, time-cycled ventilation. These modes include *pressure-regulated volume-control, volume-assured pressure-support ventilation*,[24] and *autoflow* among others; they guarantee any tidal volume compatible with the physician-set upper pressure limit. Some modes accomplish

a dual target over a few breaths, whereas others, like volume-assured pressure-support ventilation, guarantee a dual target within the same breath. Despite limited research, the original rationale for theses modes was the desire to combine the benefits of *pressure* and *flow* controllers while avoiding their problems.

A major advantage of such modes is their use in patients in whom some level of spontaneous ventilation is desirable, but in whom some control over transpulmonary pressures is necessary. Provided that the patient is not extremely agitated, a volume-cycled target promotes a decrease in inspiratory airway pressures in proportion to the magnitude of patient effort, still allowing the patient to choose inspiratory flow pattern. Such feedback limits transpulmonary pressures and, theoretically, would be a convenient strategy to avoid ventilator-induced lung injury. Also, such feedback usually provides a smooth transition from *ventilator-imposed* driving pressures to *patient-generated* driving pressures. The drawback of such strategy is the increase in the work of breathing, especially when the volume target is set below 6 mL/kg.[125,127]

INVERSE-RATIO VENTILATION

After the tremendous enthusiasm that followed Reynolds' original publication in 1971,[8] especially over the subsequent two decades,[9–13,171–175] IRV has today become an almost extinct mode, with the exception of its incorporation into APRV (see the section Activation of Exhalation Valve during Pressure-Controlled Ventilation: Airway Pressure Release Ventilation). Most studies on IRV used duty cycles (T_I/T_{TOT}) between 0.5 (the lower limit consistent with its definition) and 0.8. The original concept behind IRV was the attempt to increase $\overline{P}_{aw}$ and $\overline{P}_A$ without violating the desired upper limits for airway and alveolar pressures.

In initial studies, IRV was implemented either with *pressure-controlled*, time-cycled forms of ventilation or with *flow-controlled*, volume-cycled ventilation. Over time, the pressure-controlled application gained wider acceptance because of its better performance in terms of gas exchange[28,176] and the lower risks of over inflation when paralysis was not total. Specific details and advantages of those earlier implementations can be found in Chapter 10 of the second edition of this book.

The enthusiasm associated with IRV was driven by the original report of three main physiologic advantages: (a) oxygenation improvement despite the use of low external PEEP,[9–12,171] (b) apparently lower peak inspiratory pressures for equivalent tidal-volumes,[177–179] and (c) very low levels of dead space and efficient CO_2 removal.[72,76,176,177,179–183] Over time, it became clear that these advantages had a high price, and that we have better alternatives while maintaining conventional I:E ratios (<1:1).

The oxygenation benefits of IRV were shown to be the result of two basic mechanisms: (a) higher $\overline{P}_{aw}$ and $\overline{P}_A$ (when compared to conventional I:E ratio at same levels of external PEEP and plateau inspiratory pressures), and (b) higher intrinsic PEEP, promoted by the shorter exhalation time. Other mechanisms, like better gas distribution, were initially proposed and later found to be irrelevant. The relative efficacy of these two basic mechanisms was shown to be related to lung history and the degree of lung *hysteresis*. Some of the intricate relationships between the two mechanisms are shown in Figures 9-9 and 9-10, which can be used as a guide to understand most studies on IRV(even those suggesting an apparent controversy).

The major lesson to be learned from the studies on IRV is that lung hysteresis plays a greater role in the oxygenation response, irrespective of the I:E ratio, than was initially thought. Irrespective of its basic mechanism—which is linked to a complex sequence of lung opening and closing at the microscopic level—hysteresis can be generally understood as a lung *parenchymal memory* to pressure challenges. As schematized in Figures 9-9 and 9-10, one can regard hysteresis as representing an asymmetry of lung status or configuration according to the direction (in time) of pressure variations across the lung. Hysteresis means that there is a transitional state (representing a corresponding window of pressures) in the parenchyma that keeps "memory" of the previous state; if many lungs units were closed in the previous state, it is likely that the system will stay partially or totally closed during subsequent increments in pressure. It is only when pressures reach a certain limit (*opening pressures*), defined by the transitional window of pressures, that we can see a change in status. And the opposite is also true: a previously opened lung state will favor an open lung state during subsequent application of airway pressures, even if airway pressures are brought down to below the opening pressures.

The range of such a transitional window of pressures depends on the distribution of opening and closing pressures of lung units. The higher the mean threshold opening pressure and the lower the mean threshold closing pressure, the larger is this transitional range, and the more the entire system depends on lung history. If we assume, for the sake of simplification, that the blood flow through a lung unit does not change much from inspiration to exhalation, we can grasp the consequences of a large hysteresis on pulmonary shunt and, consequently, on oxygenation.

If hysteresis is large, with a wide transitional window, it is likely that inspiratory plateau pressures will remain below *opening pressures* in a large portion of the lung. In this scenario, a single recruitment maneuver might have a profound impact on those units and, consequently, on oxygenation. Symmetrically, the subsequent use of a proper PEEP, by keeping (or not) alveolar pressures above the threshold closing pressures, would also have a profound impact on oxygenation, preserving (or not) the new status achieved by the recruitment maneuver. In clinical practice, the range of this transitional window of pressures (representing hysteresis) exceeded 30 to 40 cm H_2O in patients with severe ARDS or trauma.[15,56] Such a large hysteresis explains the apparent discrepancy in oxygenation responses across many studies on IRV. A careful match of previous pressure challenges, as well

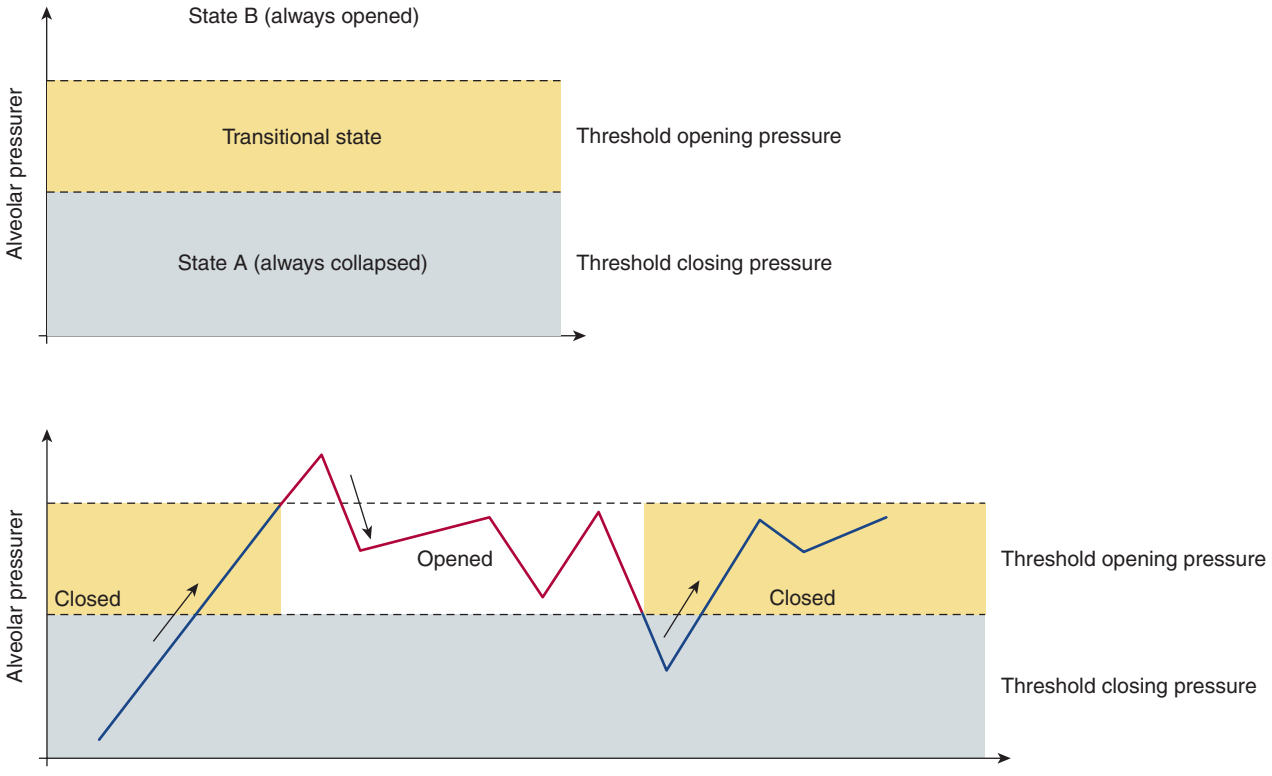

FIGURE 9-9 Representation of lung hysteresis according to the pressures applied on the system (for simplicity, we considered alveolar pressures as roughly representing transpulmonary pressures). The system changes its status according to the direction (in time) of the transition. The transitional state keeps some "memory" of the previous state, behaving like in *state A* when coming from lower pressures, or behaving like in *state B* when coming from higher pressures. Once inside the transitional state, the situation can be stable for a long period, provided that pressures do not trespass the boundaries, that is, the threshold opening/closing pressures. The *red color* illustrates an alveolar condition producing low pulmonary shunt (perfusion of alveoli in an open condition), whereas the *blue line* illustrates a condition associated with high pulmonary shunt (perfusion of closed alveoli).

as a careful match of subsequent total PEEP application, is a prerequisite for any fair comparison. The same principles must be applied today in our understanding about the effects of recruiting maneuvers and external PEEP.[15,184,185]

Conversely, if hysteresis is small, and by using the same rationale, it is also possible to explain why changes in $\overline{P}_{aw}$ (as achieved through prolongation of inspiratory time) are linearly related to oxygenation in particular settings. In fact, a small hysteresis favors the occurrence of tidal recruitment, because it is easier for alveolar pressures to exceed *opening pressures* during inspiration and, similarly, to reach *closing pressures* during exhalation (in the absence of hysteresis, *opening* pressures would equal *closing* pressures). Under this circumstance, any prolongation of inspiration would prolong blood flow through open lung units, decreasing shunt fraction. Using ultrafast intraarterial partial pressure of oxygen (Po_2) sensors, Baumgardner et al[186] showed that arterial Po_2 can oscillate by more than 400 mm Hg along the respiratory cycle, demonstrating the importance of the intricate relationships between *opening and closing* pressures and its direct influence on oxygenation.

Nonetheless, as explained in Figure 9-10, it is often possible to achieve the same oxygenation with conventional I:E ratios, while generating a much lower $\overline{P}_{aw}$ and, consequently, milder hemodynamic consequences.[72,73,176,181,182,187] The latter observation means that IRV represents a waste of $\overline{P}_{aw}$ application: it is always possible to achieve the some oxygenation benefits at a lower hemodynamic cost while using a shorter inspiratory time. More than a waste of airway pressures, some experimental reports have shown greater lung injury and edema linked with longer distending stress during inspiration.[101,187]

The lower peak inspiratory pressures achieved during IRV[177–179] were never proved to be consistent. Many studies show a decrease in peak airway pressures,[72,76,176,181–183,187] but not in peak alveolar pressures. In the few studies in which a true reduction in plateau inspiratory pressures was achieved by IRV (associated with lower levels of total PEEP), the oxygenation benefits could no longer be demonstrated.[177–180]

Finally, the better CO_2 removal by IRV[72,76,176,177,179–183] was shown to be of minor importance and related to the decelerating flow pattern, which increases the *mean distribution time* of the inspired gas.[41,42] As explained in the section The Controversy on Optimal Distribution of Ventilation, however, most of this effect is already observed when T_I slightly exceeds the point of zero flow (see Fig. 9-6), which means that prolonging inspiration beyond this point is of questionable benefit.

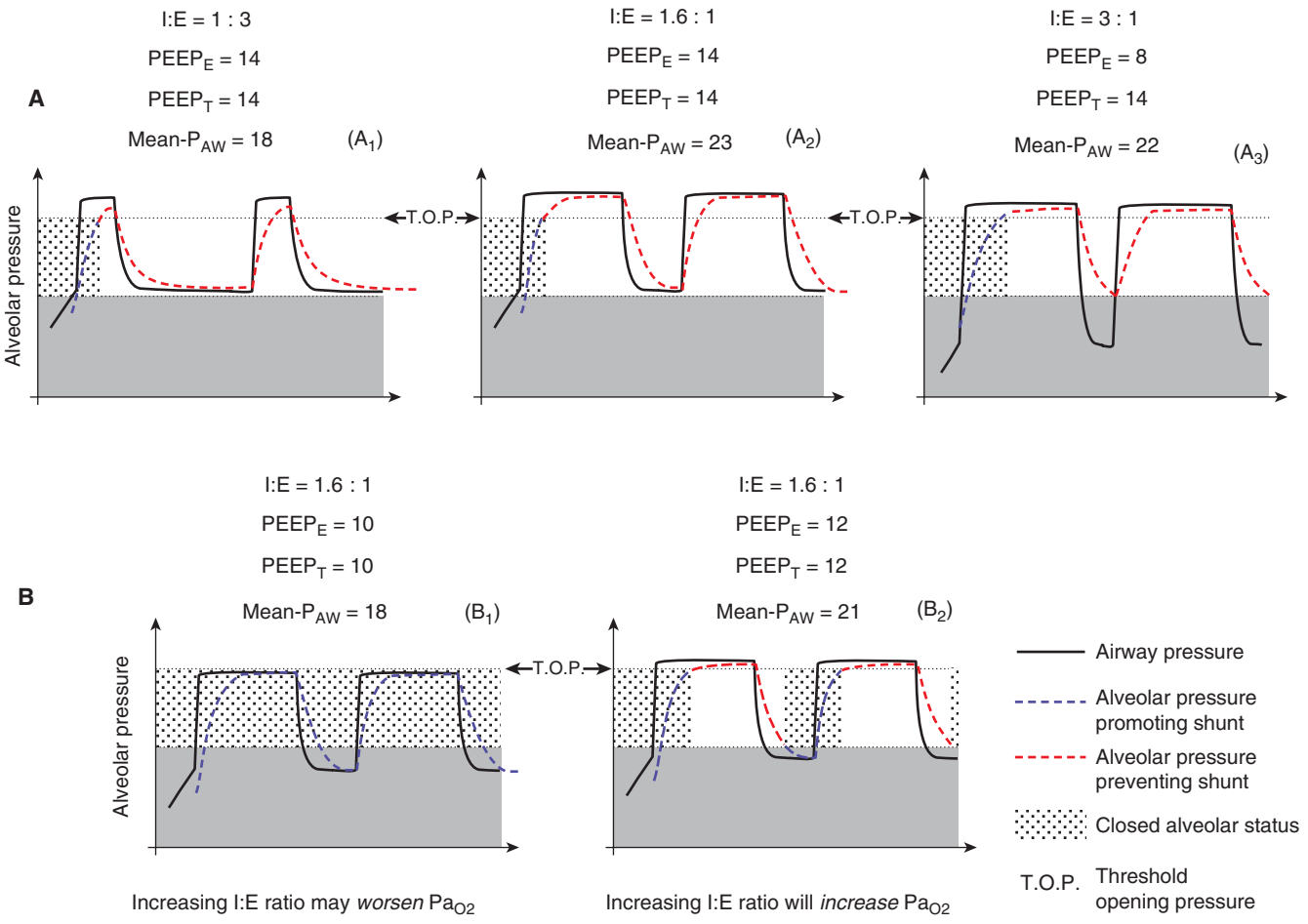

FIGURE 9-10 **A.** Low-shunt situations. Three ventilator settings producing the same effect on Pa_{O2}. In each, alveolar pressures exceeded the threshold opening pressure after the first breath *and* were kept above the threshold closing pressures (defined by the *gray zone*) for the rest of cycles. Provided that a major part of lung units is adequately represented by the boundaries of threshold pressures indicated, the three settings will result in very low and equivalent shunt levels. Under such conditions, increments in mean airway pressure (produced by increased I:E ratios, as in the examples A_2 and A_3) will only put hemodynamics at risk. **B.** High-shunt situations. Because *end-expiratory* alveolar pressures are now trespassing on the closing pressures, the situation changes dramatically. The effect of increased mean airway pressure differs according to *end-inspiratory* pressures developed. In B_1, because P_{SET} is below the threshold-opening pressures, prolongation of inspiratory time can only impair hemodynamics, but the lung stays closed and producing high shunt levels. Conversely, if P_{SET} and alveolar pressures trespass threshold opening pressures during inspiration (B_2), Pa_{O2} becomes dependent on mean airway pressure. The longer the inspiratory phase, the longer the open status and the higher the Pa_{O2}. This situation is commonly observed when lung hysteresis is low or, alternatively, when driving pressures are relatively high, producing tidal recruitment/derecruitment. Alveolar pressures are represented in *blue* or *red dashed lines*, whenever they are promoting or preventing pulmonary shunt, respectively.

Intrinsic Positive End-Expiratory Pressure versus Extrinsic Positive End-Expiratory Pressure

The research on IRV has fostered great controversy on the role of intrinsic PEEP, as opposed to extrinsic PEEP, in patients with alveolar instability. According to some initial proponents of IRV, intrinsic PEEP (intentionally promoted by IRV) should be considered as a "selective" form of PEEP that preferentially ventilates parts of the lung with short time constants, placing at rest parts with prolonged time constants.[188] In a theoretical exercise, if respiratory rate approaches infinity, alveolar pressures would remain practically constant in the *slow* units, equilibrating at an intermediate value between PEEP and P_{SET}. Because healthier units tend to have slower time constants and to be located in nondependent regions in patients with ARDS, intrinsic PEEP is expected to produce less cyclic overdistension of the nondependent parenchyma, increasing ventilation in dependent and more perfused lung regions. Consequently, such selective improvement of ventilation at low $\dot{V}/\dot{Q}$ areas would eliminate CO_2 more efficiently.[189] Another way of formulating such rationale has been to propose a strategy in which "the absolute time of the expiratory phase is so short that the stiffest parts of the lung have no time for collapse."[188] Thus, external PEEP could be reduced, with desirable benefits in terms of hemodynamics.

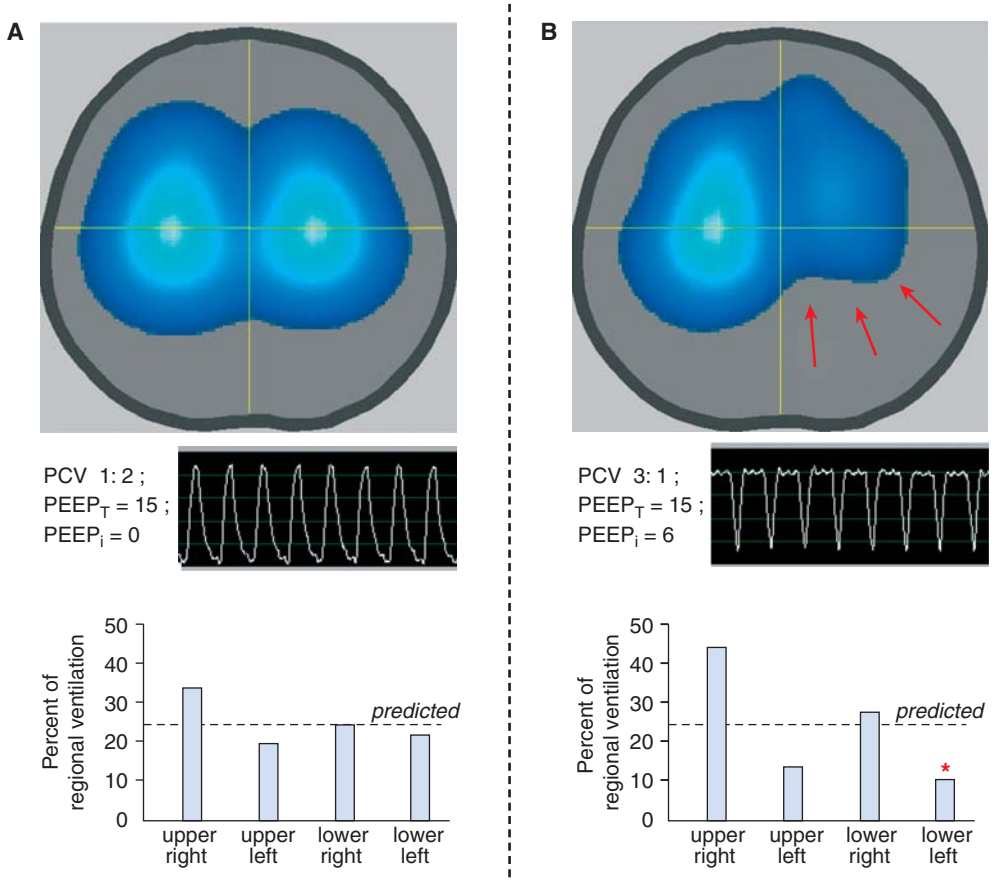

FIGURE 9-11 Regional ventilation distribution measured by electrical impedance tomography (EIT) in an animal model (pig) of acute lung injury. There was preferential injury of the left lung. The functional images display the amplitude of cyclic changes in aeration for each pixel during tidal ventilation. Bright colors represent regions with higher swings in aeration and hence higher regional ventilation. Perfusion perturbations were subtracted by temporal filtering. Although total PEEP in both conditions was the same (15 cm H_2O; checked by end-expiratory occlusion), the left image was obtained during ventilation with external PEEP equaling 15 cm H_2O and PCV with I:E ratio equaling 1:2, whereas the right image was obtained during 9 cm H_2O of external PEEP added to 6 cm H_2O of intrinsic PEEP (PCV with I:E ratio = 3:1). This latter pattern resulted in more heterogeneous ventilation, with preferential ventilation of the right lung and marked hypoventilation of the left lower lung (*red arrows* and *asterisk*). The black midpanel represents the temporal changes in total impedance of the thoracic slice monitored by EIT, which roughly illustrates the cyclic lung volume changes associated to each condition. The graph with bars at the bottom shows that external PEEP produced more even pattern of regional ventilation.

Recent evidence does not support this view but demonstrates the opposite.[54,76,190–194] Because different time constants in individual lung regions are crucial for a "selective effect" of intrinsic PEEP, intrinsic PEEP may allow the "selective collapse" of regions with short time constants, especially the edematous regions. When comparing intrinsic PEEP with matching levels of external PEEP in patients with ARDS, Zavala et al[76] demonstrated that shunt levels increased by 6% with intrinsic PEEP. There was some increase in the efficiency of CO_2 removal, but this could be ascribed to better inspiratory flow distribution during IRV rather than to intrinsic PEEP. Animal experiments in dogs[191] reproduced the same results. Other clinical studies came to similar conclusions,[193] including studies in patients with obstructive disease,[194] suggesting that partial or complete substitution of intrinsic PEEP by external PEEP improves gas exchange without any impairment in CO_2 removal.

The original perspective of considering absolute time for collapse[188]—instead of end-expiratory pressures—also carries some problems. Computed tomographic studies demonstrate that the time window to prevent end-expiratory lung collapse without external PEEP is extremely short (<0.6 second) and might not be feasible during mechanical ventilation of many patients with ARDS.[54,192] To avoid unnecessary confusion, it is also important to prove that time per se, independent of local alveolar pressure, is an important variable affecting lung collapse. To our knowledge, this has never been demonstrated.

After reviewing available evidence, we conclude that there is no rationale supporting the preferential use of intrinsic PEEP. In terms of oxygenation, it seems inferior to external PEEP, slightly increasing the risk of collapse in unstable units.[195] In lung models with different time constants, it is clear that fast (more disease) units are at a disadvantage during intrinsic PEEP generation.[190] Figure 9-11 provides further insight: regional ventilation becomes more

heterogeneous with intrinsic PEEP, with evident collapse in the left lower lung, and ventilation is increased in nondependent regions. A computed tomographic study revealed more hyperinflation with intrinsic PEEP than with equivalent external PEEP.[74]

In terms of CO_2 removal, it is impossible to draw any conclusion because the concomitant use of IRV and decelerating flow in most studies precludes any estimation of the isolated impact of intrinsic PEEP. In clinical practice, one also has to consider that a combination of IRV plus intrinsic PEEP usually results in a higher $\bar{P}_{aw}$ than conventional I:E ratios plus external PEEP and thus greater hemodynamic compromise. Another major drawback of the intrinsic PEEP approach is its complexity. Much closer monitoring and more frequent adjustments of ventilator settings are required, even with a computerized protocol.[196] Consequently, external PEEP in association with conventional I:E ratio is preferable.

If CO_2 removal is a clinical problem, an increased frequency—even if associated with low tidal volumes—may solve the problem, especially when using high PEEP levels. By increasing functional residual capacity, external PEEP usually causes a decrease in airway resistance and lung compliance, both factors contributing to a very short time constant. Under such conditions, respiratory rates up to 40 to 50 cycles per minute could increase minute ventilation considerably (see Fig. 9-3), improving CO_2 removal.

THE FUTURE OF PRESSURE-CONTROLLED VENTILATION

During controlled ventilation, there is little doubt that PCV is advantageous in terms of lung protection, helping physicians better define the targets for lung protection. This is especially true during recruitment maneuvers or in any situation where lung tissue is close to its limits of rupture. In this context, we believe that the growing acceptance of PCV over VCV represents a consistent trend. In the presence of spontaneous efforts, however, the future of assisted PCV is still uncertain and we need more studies to solve important physiologic questions. For instance, during protective, low tidal-volume ventilation, the assisted-PCV option commonly result in higher transpulmonary pressures and higher work of breathing than occurs with optimally adjusted assisted VCV.[25] This is not a limitation of the mode per se, but a problem in the way we employ it. This is also true when we have to choose between assisted PCV and PSV to improve synchrony. Research that addresses deeper questions about priorities in such situations will help us to better define the future of assisted-PCV.

SUMMARY AND CONCLUSION

Contrasted with the growing acceptance of PCV, use of IRV is almost extinct. Safer, more predictable, and more efficient ventilator solutions can be implemented at the bedside. Physicians were initially enthusiastic about IRV because internal PEEP and peak pressures were hidden. Later, physicians realized that total PEEP and peak alveolar pressures were not that different, yet IRV necessarily imposed higher levels of $\bar{P}_{aw}$ and greater hemodynamic consequences for similar clinical benefits. Whereas concepts such as VILI and permissive hypercapnia have boosted the use of PCV, the better understanding of the dynamics of alveolar collapse have dampened enthusiasm for use of IRV.

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10

POSITIVE END-EXPIRATORY PRESSURE

Paolo Navalesi
Salvatore Maurizio Maggiore

Positive end-expiratory pressure (PEEP) is not a ventilator mode itself, but rather an adjunctive treatment that can be combined with all forms of mechanical ventilation, both controlled and assisted,[1–7] or applied to spontaneous breathing throughout the entire respiratory cycle, so-called continuous positive airway pressure (CPAP).[8–10] Following the pioneering work of Poulton and Oxon[11] and Barach and associates[12] who demonstrated in the mid-1930s that application of positive pressure to the airway can effectively treat patients with pulmonary edema, several pathological conditions were proved to benefit from PEEP, which is today considered by intensive care unit physicians as one of the most powerful treatments available for acute respiratory failure (ARF).[13]

Since publication of the second edition of this book in 2006, several relevant studies have been published on PEEP and CPAP, primarily concerning lung injury and cardiogenic pulmonary edema. To update the chapter with this new information, we have condensed material that was covered in greater depth in the second edition.

OVERVIEW OF PERTINENT PATHOPHYSIOLOGY

The reversal of hypoxemia caused by intrapulmonary shunt and venous admixture requires interventions that recruit more aerated lung units for ventilation. In patients with an acute reduction of lung volume secondary to lung edema and/or atelectasis, PEEP can improve arterial oxygenation[1,8] by increasing functional residual capacity (FRC),[14–19] reducing venous admixture,[20–24] shifting tidal volume (V_T) to a more compliant portion of the pressure–volume curve,[25] preventing the loss of compliance during mechanical ventilation,[5,26] reducing intratidal alveolar opening and closing[27] and the work of breathing.[28] Figure 10-1A summarizes the

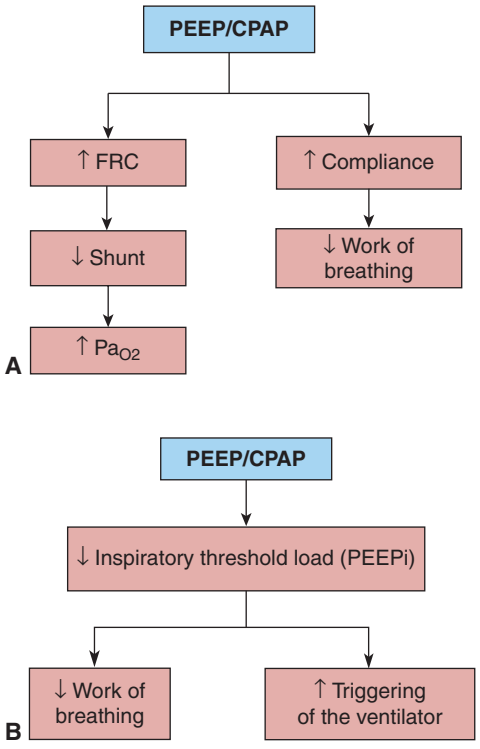

FIGURE 10-1 Respiratory effects of PEEP/CPAP in acute respiratory failure secondary to (**A**) lung volume reduction caused by edema and/or atelectasis and (**B**) airway obstruction and expiratory flow limitation. *FRC*, functional residual capacity; Pa_{O_2}, partial pressure of arterial oxygen; *PEEP*, positive end-expiratory pressure.

rationale for PEEP in patients with ARF secondary to acute lung volume reduction.

Although there is general consensus about the potential of PEEP in treating patients with hypoxemic ARF secondary to lung edema and/or atelectasis, several aspects are controversial. For many years, it has been recognized that the actions of PEEP on gas exchange and pulmonary mechanics are variable,[29,30] depending on the type and severity of lung injury, which may be sustained by different pathways[31,32] and pathophysiologic mechanisms.[31,33] As with any treatment, PEEP is not free of side effects.[34] In patients with acute respiratory distress syndrome (ARDS), PEEP may recruit nonaerated regions, but also distend normally aerated regions,[35,36] contributing to barotrauma through increase in end-inspiratory plateau pressure.[22,37–40] High levels of PEEP also have been shown to augment the physiologic dead space,[24,41,42] and worsen gas exchange[35] and tissue perfusion.[43–45] Potential extrapulmonary side effects of PEEP include decreased cardiac output,[46–51] increased intracranial pressure,[52,53] renal dysfunction,[54,55] and decreased splanchnic perfusion[56–58] and oxygenation.[43,44] Although the benefits and detriments of PEEP in patients with ARDS have been variously weighted for many years, debate as to optimal PEEP and the best method for detecting it is still ongoing.

In the presence of airflow obstruction, the lungs may fail to deflate to FRC at end-expiration and alveolar pressure remain positive to an extent that depends on the volume of trapped air, a phenomenon referred to as *auto* or *intrinsic PEEP (PEEPi)*.[59] In this setting, application of external PEEP may be beneficial. Benefit is evident during spontaneous breathing: CPAP reduces dyspnea[9,60] and work of breathing.[9,60] Benefit is also evident with any patient-triggered mode of ventilation:[2,61–63] PEEP enhances triggering function,[2,61–63] reduces patient's respiratory drive,[62] reduces inspiratory muscle effort,[2,61–63] and improves patient–ventilator interaction.[63,64] PEEP replaces the amount of pressure that must be generated by the inspiratory muscles to offset PEEPi (necessary to initiate inspiratory flow or trigger the ventilator).[2,62] Figure 10-1B summarizes the principal effects of PEEP in patients with chronic obstructive pulmonary disease (COPD).

PEEP has substantial effects on hemodynamics. When left-ventricular function is normal, an increase in intrathoracic pressure causes a fall in cardiac output, largely secondary to decrease in venous return (i.e., preload).[47,65,66] In patients with poor left-ventricular function, when filling pressure and left-ventricular diastolic volume are elevated, cardiac output is relatively insensitive to decline in venous return.[67] In this condition, the dominant effect of an increase in intrathoracic pressure is to decrease left-ventricular transmural pressure (i.e., afterload), which improves left-ventricular performance.[68–71] These effects (Fig. 10-2C) are also observed with relatively moderate levels of CPAP; the impact on afterload is likely to result primarily from a reduction in the inspiratory negative swings of intrathoracic pressure,[72] consequent to improvement in respiratory mechanics.[72] Application of CPAP in patients with severe cardiogenic pulmonary edema may accelerate the physiologic improvement and reduce the need for endotracheal intubation.[10,73–75]

Several investigators have studied the use of CPAP in the treatment of the obstructive sleep apnea syndrome, which is characterized by reduction or cessation of breathing secondary to periodic narrowing and/or collapse of the upper airway. Detailed discussion of this topic is beyond the scope of this chapter. Likewise, we do not provide detailed discussion of positive expiratory pressure, a physiotherapeutic technique aimed at clearance of secretions.

PHYSIOLOGIC RATIONALE FOR POSITIVE END-EXPIRATORY PRESSURE

Effect of Positive End-Expiratory Pressure on Gas Exchange

The role of PEEP in correcting hypoxemia in patients with pulmonary edema and ARF has long been recognized[11,12] and extensively documented.[24,42,76–79] The chief mechanism by which PEEP improves arterial oxygenation is through an increase in the amount of alveoli reached by the air. By decreasing cardiac output, however, PEEP may negatively

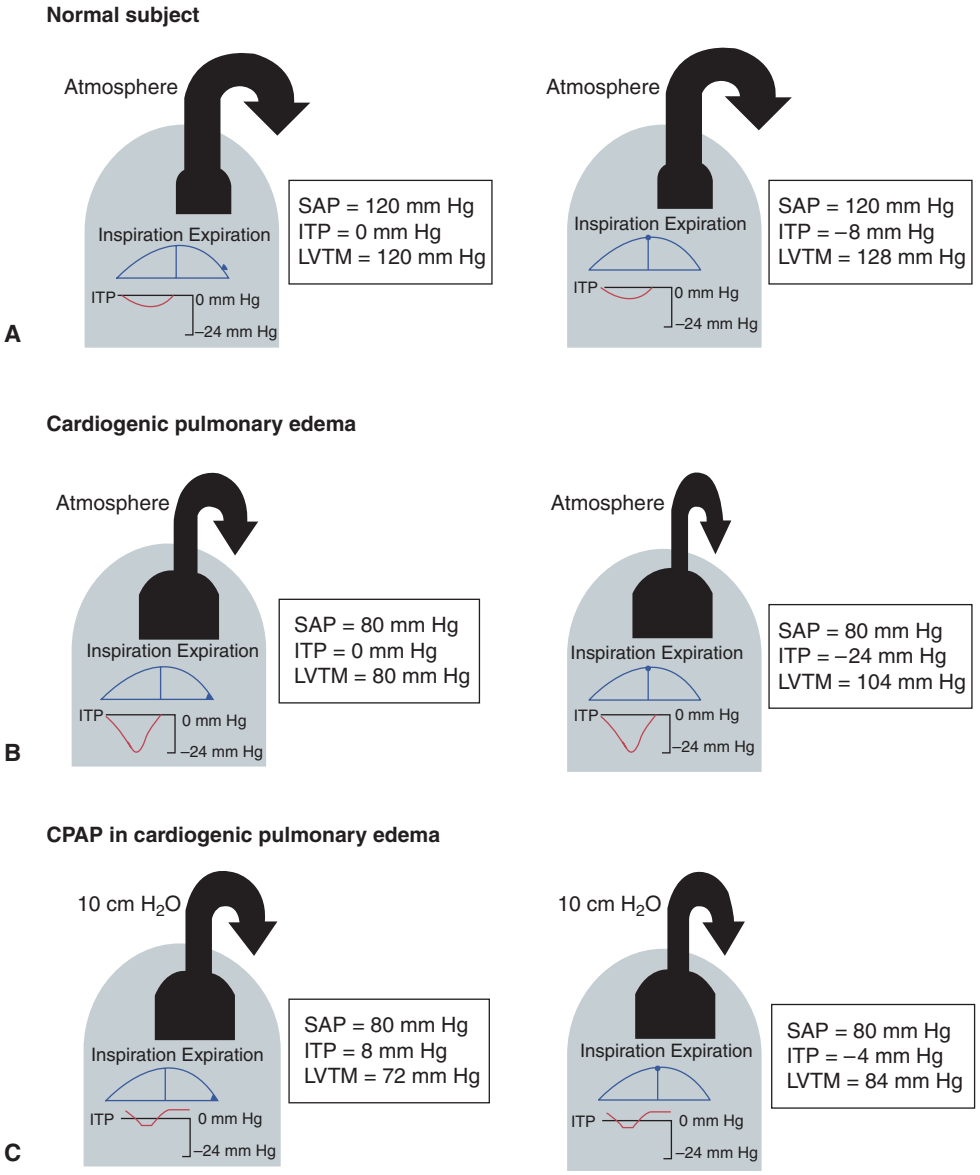

FIGURE 10-2 Heart–lung interactions during spontaneous breathing in a normal subject (**A**), and in a patient with cardiogenic pulmonary edema resulting from a low cardiac output in the absence (**B**) and presence (**C**) of CPAP. The effects of variations in intrathoracic pressure (ITP) on left-ventricular systolic function are shown at end-expiration (*left panels*) and end-inspiration (*right panels*). LVTM, left-ventricular transmural pressure (SAP – ITP); SAP, systolic arterial (intraventricular) pressure. In a normal subject (A), tidal excursions in ITP have little effect on left-ventricular systolic function. With pulmonary edema (B), more negative swings in ITP are needed to achieve the same tidal volume. As a result, LVTM (afterload) is increased independently of systemic vascular resistance. The rise in ITP produced by CPAP 10 cm H_2O (C) produces a slight reduction in LVTM during expiration. CPAP remarkably decreases LVTM during inspiration by decreasing negative swings in ITP, because of improved lung mechanics.

affect mixed venous O_2 tension, which, in turn, decreases the partial pressure of arterial oxygen (Pa_{O_2}) to an extent that depends on alveolar ventilation–perfusion ($\dot{V}_A/\dot{Q}$) mismatch.[80–83]

EFFECT IN ANESTHETIZED SUBJECTS

Arterial oxygenation is often impaired during anesthesia[84,85] as a result of the intrapulmonary shunt[86–90] caused by atelectasis, predominantly in the dependent zones.[85,91–97] Areas of collapsed parenchyma occur in 90% of all intubated anesthetized subjects, both during spontaneous breathing and muscle paralysis.[90,98–100] Other mechanisms, such as regional distribution of ventilation,[101] airway closure,[102–112] and pharmacologic inhibition of hypoxic vasoconstriction[113–116] may also contribute. Application of PEEP during anesthesia can prevent or reverse closing of peripheral airways,[105] decrease atelectasis,[90,100,117,118] and improve regional $\dot{V}_A/\dot{Q}$ ratios and oxygenation,[118–120] although shunt may only be partially improved.[90] In normal anesthetized dogs, however,

Dueck et al found that PEEP ≥10 cm H_2O produced a reduction in Pa_{O_2} and increases in dead space ventilation and partial pressure of arterial carbon dioxide (Pa_{CO_2}). This was mainly caused by a drop in cardiac output associated with an increase in alveolar ventilation of both high $\dot{V}_A/\dot{Q}$ and unperfused lung regions, suggesting overdistension of nondependent lung regions.[121] Similarly, Pelosi et al showed that PEEP values up to 10 cm H_2O decreased, although not significantly, Pa_{O_2} during general anesthesia in normal subjects.[122]

Alterations in diaphragmatic position and mechanics during anesthesia also contribute to impaired gas exchange by inducing ventilation abnormalities in the dependent and caudal zones.[123,124] This phenomenon has been elegantly studied in anesthetized rabbits by Heneghan et al who compared PEEP and phrenic nerve stimulation, adjusted to produce the same increase in lung volume. Phrenic stimulation caused a greater caudal movement of the diaphragm, particularly in the dependent regions, and produced greater improvement in gas exchange than did PEEP.[123]

Beneficial effects of PEEP on oxygenation have been reported in obese patients, who are at greater risk to develop caudal atelectasis during anesthesia, and during pneumoperitoneum induced for laparoscopic surgery causing cephalad displacement of the diaphragm.[122,125,126] Pelosi et al found that PEEP induced an increase in Pa_{O_2} in obese patients; this increase was correlated with recruitment of atelectatic lung regions.[122] Other authors found that the sole application of 10 cm H_2O PEEP was able to reduce atelectasis but not to improve oxygenation in these patients.[125,127,128] Oxygenation improved and atelectasis was further decreased, however, when PEEP application was preceded by a recruitment maneuver or associated with vertical positioning both in obese patients and healthy subjects undergoing laparoscopic surgery. In the former case, use of high airway pressures opened atelectatic lung areas subsequently kept open by PEEP, while in the latter case vertical positioning decreased the negative effect of abdominal pressure on diaphragmatic displacement. In morbidly obese patients, PEEP has also been found beneficial during induction of general anesthesia. Gander et al showed that applying 10 cm H_2O PEEP during induction of anesthesia increased the duration of apnea without hypoxia by approximately 50%.[129]

Conflicting data on the effect of PEEP have been obtained in postoperative patients who had developed respiratory failure. In two studies, PEEP up to 10 cm H_2O did not significantly modify Pa_{O_2} during the early postoperative course of patients who underwent cardiac or vascular surgery.[130,131] Conversely, other investigators found that PEEP, combined with bilevel positive airway pressure ventilation administered via a nasal mask, improved oxygenation in the vast majority of patients who exhibited respiratory distress after various types of surgery.[132–135] A recent randomized, clinical trial found that the use of noninvasive positive-pressure ventilation with low PEEP (approximately 4 cm H_2O) increased Pa_{O_2}, reduced the need for intubation, and improved survival of patients who developed ARF after lung resection.[136]

In summary, use of PEEP to improve oxygenation during and after anesthesia in normal subjects has generated contradictory results, probably because of the deleterious effects of PEEP on hemodynamics and lung overdistension. PEEP, however, can be effective in improving gas exchange in selected patients.

EFFECT IN HYPOXEMIC RESPIRATORY FAILURE

Most forms of hypoxemic respiratory failure, such as cardiogenic pulmonary edema, ARDS, and unilateral pneumonia, are characterized by a decrease in lung volume caused by atelectasis, interstitial and alveolar edema, and small airway closure. The pivotal mechanism for hypoxemia in these conditions is intrapulmonary shunt as demonstrated by the small increase in Pa_{O_2} when pure O_2 is administered,[137] and, to a lesser extent, $\dot{V}_A/\dot{Q}$ mismatch.[138,139] Moreover, the high fractional inspired oxygen concentration (FI_{O_2}) frequently used in these patients, may decrease lung volume by promoting alveolar denitrogenation and reabsorption atelectasis.[137,140,141] In ARDS, the altered blood flow distribution, resulting from widespread involvement of the pulmonary vasculature[142] and impaired hypoxic vasoconstriction, contributes to worsening of gas exchange.[140]

PEEP has long been recognized as an effective means of increasing lung volume and improving gas exchange.[1] In cardiogenic pulmonary edema, CPAP (alone or in association with an inspiratory assistance) improves gas exchange[10,73,143–154] by increasing aerated lung volume,[155] and improving cardiac output[73,143,148] and $\dot{V}_A/\dot{Q}$ distribution.[155,156] A decrease in extravascular lung water is another possible mechanism whereby PEEP reduces intrapulmonary shunt.[157] Yet, PEEP does not decrease, and sometimes increases, extravascular lung water when microvascular hydrostatic pressure is high.[158] Malo et al[156] clarified this issue. They showed that PEEP 13 cm H_2O decreased shunt and alveolar flooding without modifying extravascular lung water; indeed, perivascular cuff edema increased.[156] These findings indicate that PEEP redistributes the excess alveolar water into the compliant perivascular space, thus reinflating previously flooded and collapsed air spaces, without decreasing the overall amount of lung edema.[159]

Unilateral pneumonia and ARDS are characterized by severe impairment of gas exchange because of increased intrapulmonary shunt,[138,140] resulting mainly from flooded and/or collapsed alveoli.[160–163] This observation is corroborated by the correlation between the extent of lung densities mainly found in the dependent regions on a computed tomography (CT) scan and deterioration in arterial blood-gases.[18,78] In fact, the edema increases the total mass of the lung (up to more than twice that of normal lungs); consequently, the dependent zones progressively collapse under the weight of the superimposed lung (compression atelectasis), and aerated lung decreases ("baby lung" concept).[164–166]

Atelectasis in the lower lobes and in dependent lung regions may be caused by other mechanisms, such as

external compression by the heart[167,168] and the abdominal compartment.[93,169–172] The severity of intrapulmonary shunt may also be affected by surfactant abnormalities,[173] increased airway resistance,[174–187] hyaline membranes, and inflammatory proteins and cells accumulating within the alveoli. Interstitial edema and the deposition of cells and connective tissue in the interalveolar septa may further contribute to gas exchange impairment in ARDS. The amount of nonaerated lung volume may also be increased by the combined effects of reabsorption atelectasis[89,138,140,188] and ventilation occurring at low lung volumes.[141,189,190] Hypoxic pulmonary vasoconstriction appears greatly impaired in most patients with ARDS.[140,191] In some patients with diffuse lung injury, however, hypoxic pulmonary vasoconstriction is partially preserved, explaining a lack of hypoxemia despite diffuse loss of aeration. Conversely, hypoxic pulmonary vasoconstriction is constantly impaired in some patients with localized lung injury, explaining severe hypoxemia despite well-preserved lung aeration.[191]

Use of PEEP to correct gas exchange impairment in ARDS was initially proposed by Asbaugh et al.[1] It remains the cornerstone of ventilatory management of these patients. Extensive literature supports the use of PEEP for improving oxygenation in hypoxemic respiratory failure, alone or combined with various ventilator modes, during both invasive[5,18,42,76,78,184,192–209] and noninvasive ventilation.[210–213] Several mechanisms may explain the effect of PEEP on gas exchange. PEEP promotes alveolar recruitment and increases aerated lung volume, therefore decreasing intrapulmonary shunt.[214,215] PEEP-induced recruitment of aerated lung volume is strongly correlated with arterial oxygenation (Table 10-1).[18,197,200,215,216] Prevention of atelectasis consequent to pure O_2 breathing helps explain the beneficial effect of PEEP on oxygenation.[141] In addition, a redistribution of alveolar edema to the interstitial spaces may also explain the benefit of PEEP on gas exchange.[156] Following the pioneering work of Webb and Tierney,[217] PEEP has been shown to decrease pulmonary edema,[218–220] partly because of a concomitant reduction in cardiac output.[219] By recruiting nonaerated alveoli and stabilizing airways, PEEP also affects the regional distribution of tidal ventilation.[169,199,221,222] When the predominant effect of PEEP is recruitment, alveolar ventilation is expected to become more homogeneous, particularly in the dependent zones. Although an increase in lung volume is the main mechanism for PEEP-induced changes in oxygenation, a small decrease in cardiac output also reduces intrapulmonary shunt and improves Pa_{O_2}.[48] Finally, different pathophysiologic mechanisms of ARDS influences the response to PEEP,[31,33,198] although understanding is far from being conclusive.[223]

Improved efficiency of alveolar ventilation and an expected decrease in alveolar dead space should produce a reduction in Pa_{CO_2}. Several authors, however, have failed to find any significant relationship between Pa_{CO_2} and PEEP. The lack of response probably arises because PEEP both favors lung recruitment, which theoretically reduces Pa_{CO_2}, and promotes pulmonary overdistension, which theoretically increases Pa_{CO_2}.[33,169,224]

The benefit of PEEP on gas exchange might also be expected in unilateral pneumonia and localized lung injuries. In these conditions, however, high PEEP is more likely to produce overdistension of normally aerated regions, because of the coexistence of areas with normal, low, and very low compliances.[169,199] The net effect of PEEP on gas exchange depends on the balance between overdistension of already aerated alveolar units and recruitment of collapsed (nonaerated) alveoli, and is also influenced by the level of PEEP.[169,225] In patients with unilateral lung disease, PEEP may be detrimental whenever it hyperinflates the normal lung, thus directing the blood flow to the diseased lung and increasing intrapulmonary shunt.[226–230] To limit this risk, unilateral delivery of PEEP to the injured lung has been proposed;[231] the technical complexity of this approach greatly limits its feasibility in the clinical practice.

In summary, PEEP improves gas exchange in hypoxemic ARF, mainly through recruitment of previously nonaerated lung areas and the homogenization of regional distribution of tidal ventilation. PEEP remains the cornerstone of ventilator treatment of most forms of hypoxemic ARF. Debate continues about the optimal level of PEEP, not about its usefulness.

EFFECT IN OBSTRUCTIVE LUNG DISEASE

Impaired gas exchange in obstructive lung diseases is caused by complex disturbances of regional $\dot{V}_A/\dot{Q}$ relationships associated with alveolar hypoventilation; diffusion impairment is not a major factor.[232] During an acute exacerbation of COPD, high $\dot{V}_A/\dot{Q}$ areas predominate in patients who mostly have the emphysematous variant with loss of blood flow consequent to alveolar wall destruction.[232–234] Conversely, low $\dot{V}_A/\dot{Q}$ regions are mostly seen in patients with a predominant obstructive component.[232–234] In general, application of PEEP does not affect gas exchange.[2,235–238] Nevertheless, Rossi and coworkers reported that low PEEP (50% of PEEPi) induced a moderate increase in Pa_{O_2} and slight decrease in Pa_{CO_2} secondary to improved $\dot{V}_A/\dot{Q}$ distribution without alteration in respiratory mechanics or hemodynamics.[239] Further increases in PEEP (up to 100% of PEEPi) did not produce further improvement in gas exchange.[239] In other small studies, low to moderate PEEP (5 to 9 cm H_2O) produced similar improvements in Pa_{CO_2} and Pa_{O_2}.[240–243] Other authors, however, reported little or no change in arterial oxygenation with PEEP[2,60,237,238] unless high levels were applied;[237,238] Pa_{CO_2} did not change with up to 15 cm H_2O PEEP.[2,60,236–238]

PEEP may have some benefit on gas exchange. Unless hypoxemia is caused by a large intrapulmonary shunt, the benefit is small and of little clinical importance and PEEP may have negative hemodynamic effects that worsen oxygen delivery.[236–238] The balance between positive and negative effects depends to some extent on the level of applied

TABLE 10-1: STUDIES ASSESSING THE EFFECT OF POSITIVE END-EXPIRATORY PRESSUREON LUNG VOLUMES AND OTHER PHYSIOLOGIC VARIABLES

Reference	Technique	PEEP cm H_2O	FRC mL	ΔEELV mL	Vrec mL	Vrec/ΔEELV	Voverdist ml	ΔPa_{O2} mm Hg
Ranieri 1991 (200)	P-V curve	15	–	720	230	0.32	–	50
Ranieri 1994 (201)	P-V curve	15	–	690	248	0.36	–	–
Ranieri 1995 (202)	P-V curve	10	–	1274	756	0.59	–	55
Jonson 1999 (25)	P-V curve	10	–	–	205	–	–	–
Richard 2001 (204)	P-V curve	11	–	–	175	–	–	–
Maggiore 2001 (197)	P-V curve	15	–	764	304	0.40	–	79*
Mergoni 2001 (315)	P-V curve	15	–	–	379	–	–	29
Koutsoukou 2002 (184)	P-V curve	15	–	660	457	0.69	–	57
Richard 2003 (203)	P-V curve	14	–	–	384	–	–	20†
Maggiore 2003 (296)	P-V curve	15	–	650	235	0.36	–	–
Vieillard-Baron 2003 (316)	P-V curve	12	–	358	69	0.19	–	44
Thille 2007 (345)	P-V curve	11	–	–	226	–	–	–
Valta 1993 (208)	Static compliance	14	–	500	126	0.25	–	–
Gattinoni 1998 (282)	Static compliance	15	576	721	131	0.18	–	–
Chelucci 2000 (314)	Static compliance	13	–	446	102	0.23	–	–
Vieira 1998 (36)	CT scan	13	–	–	320	–	238	117
Vieira 1999 (225)	CT scan	16	–	–	332	–	13	113
Puybasset 2000 (199)	CT scan	10	1621	659	187	0.28	41	45
Malbouisson 2001 (18)	CT scan	15	1553	820	499	0.61	24	99
Nieszkowska 2004 (311)	CT scan	15	1105	1115	369	0.33	63	80
MEAN		**13**	**1214**	**721**	**287**	**0.37**	**76**	**66**
SD		2	483	249	161	0.16	93	32

Abbreviations: *CT*, computed tomography; Δ*EELV*, change in end-expiratory lung volume; *FRC*, functional residual capacity; ΔPa_{O_2}, change in arterial oxygen tension compared to PEEP 0 cm H_2O; *P-V*, pressure-volume; *SD*, standard deviation; *Voverdist*, volume of lung overdistension; *Vrec*, recruited volume.

* Compared to PEEP 5 cm H_2O; † compared to PEEP 10 cm H_2O.

PEEP; nevertheless, the chief reason for using PEEP in COPD is not to improve gas exchange.

Effect of Positive End-Expiratory Pressure on Respiratory Mechanics

ASSESSMENT OF RESPIRATORY MECHANICS

The static behavior of the respiratory system is described by the pressure–volume curve.[244–246] In healthy subjects, the pressure–volume curve, from residual volume to total lung capacity, has a sigmoidal shape.[246] Above FRC, however, the curve is linear. Thus, the tangential slope of the curve (i.e., the linear or chord compliance, reflecting the elasticity of the respiratory system) is constant over the range of tidal ventilation. FRC is the volume of gas in the lungs at the end of a passive expiration. It corresponds to the point of equilibrium between lung and chest-wall elastic recoil.

The shape of the pressure–volume curve reveals two important features: stiffening of the lungs at high lung volumes, and closure of peripheral airways and lung units at low lung volumes.[247] At volumes above 75% to 80% of total lung capacity, the slope of the pressure–volume curve varies, with a sharp decrease in compliance, indicating that the lungs are close to their maximum stretch limit, although the chest wall is normally not stiffer. Further increases in pressure beyond this point, the so-called *upper inflection point* (UIP), have progressively less effect on lung volume. When lung volume falls below FRC and approaches residual volume, the smallest airways tend to collapse under the influence of surface tension of alveolar lining fluid.[248–251] During the subsequent inflation, these structures remain closed until a much higher pressure is applied. From this point on, compliance rapidly increases during inflation, as the closed lung units progressively pop open. This action produces a knee on the pressure–volume curve, termed the *lower inflection point* (LIP).

During constant-flow controlled ventilation, the elastic and resistive properties of the respiratory system can be assessed using the occlusion technique, which consists of occluding the airway at end-inspiration for 3 to 5 seconds.[252–258] As soon as flow is interrupted, there is a rapid drop in airway pressure from the peak (P_{PEAK}) to a lower value (P_1), followed by a gradual decay to an apparent pressure plateau (P_{PLAT}) (Fig. 10-3). Ohmic (flow-dependent) resistance (R_{max}) is calculated as the initial drop in airway pressure ($P_{PEAK} - P_1$) divided by inspiratory flow. The slower pressure change ($P_1 - P_{PLAT}$) divided by the inspiratory flow preceding the occlusion yields the additional tissue resistance (ΔR). The sum of airflow and tissue resistances provides the total respiratory resistance ($R_{TOT} = (P_{PEAK} - P_{PLAT})/\dot{V}$). By occluding the airway at end-expiration, it is possible to determine the total PEEP ($PEEP_{TOT}$), which is the sum of the externally applied PEEP and PEEPi (Fig. 10-4). The difference between P_{PLAT} and $PEEP_{TOT}$ is the recoil pressure. It is then possible to compute the static compliance (Cst) of the respiratory system according to the equation $Cst = V_T/(P_{PLAT} - PEEP_{TOT})$. The failure to take into account PEEPi may result in a substantial underestimation of Cst, especially when low or no PEEP is used.[259,260]

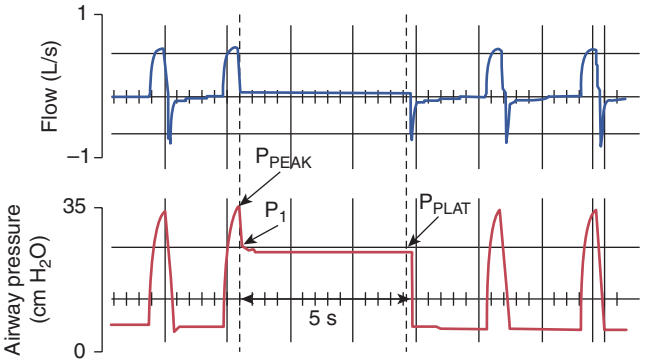

FIGURE 10-3 End-inspiratory occlusion during constant flow controlled ventilation. As soon as the airway is occluded, flow suddenly falls to zero and airway pressure drops from a peak (P_{PEAK}) to a lower value (P_1), and then slowly declines to an apparent plateau (P_{PLAT}).

EFFECTS OF POSITIVE END-EXPIRATORY PRESSURE IN ANESTHETIZED SUBJECTS

Anesthetized healthy subjects may have decreased aerated lung volume, consequent to the decline in FRC associated with the supine posture[93,127,128,261,262] and the potential for airway closure and atelectasis.[85,96,100,127,128,190] Both anesthesia and paralysis affect the mechanical characteristics of the respiratory system,[85,263,264] which can be also impaired by abdominal and thoracic surgical procedures.[125,128,265–267]

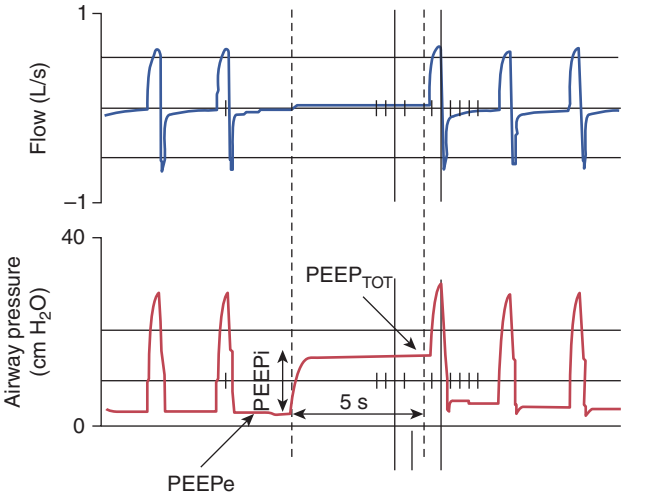

FIGURE 10-4 End-expiratory occlusion. Airway pressure rises following an end-expiratory occlusion and reaches a plateau, which corresponds to total PEEP ($PEEP_{TOT}$). Auto or intrinsic PEEP (PEEPi) is the difference between $PEEP_{TOT}$ and the externally applied preset PEEP (PEEPe). PEEPi measured by an end-expiratory occlusion is termed static.

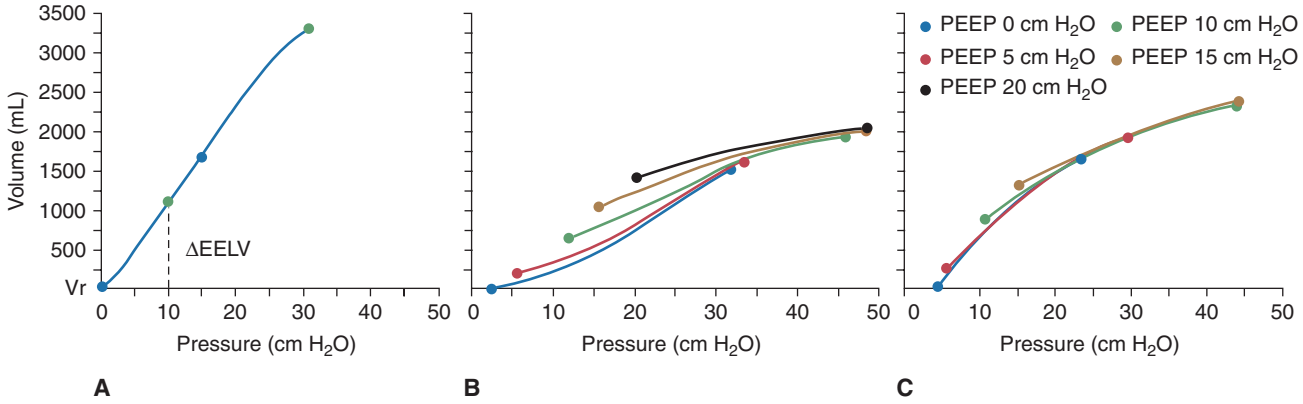

FIGURE 10-5 Pressure–volume (P-V) curves recorded from different PEEP levels in a healthy subject (**A**), a patient with ARDS (**B**), and a patient with an acute exacerbation of COPD (**C**). All curves are related to the relaxation volume of the respiratory system. For each curve, end-expiratory and end-inspiratory points are indicated by *circles*. In the healthy subject, PEEP 10 cm H_2O generates an increase in end-expiratory lung volume and a rightward shift of the P-V curve. The new curve is superimposed on the curve acquired without PEEP, indicating the absence of recruitment. In the patient with ARDS, increasing PEEP produces increases in end-expiratory lung volume and significant lung recruitment, as indicated by the upward shift of the P-V curves. In the patient with COPD, the application of PEEP results in end-expiratory lung volume increase with worsening of hyperinflation, as indicated by the superposition of P-V curves and the progressive decrease in the slope (compliance) of the curves. The reduction in aerated volume in ARDS produces a lower inflection point and flattening of the P-V curve at PEEP 0 cm H_2O. The presence of PEEPi during ventilation without PEEP in ARDS, and more so in COPD, induces a rightward shift of the initial P-V curve. In the healthy subject (*left panel*), the PEEP-induced increase in end-expiratory lung volume is indicated by the *dotted line*. *Vr*, Relaxation volume of the respiratory system.

It is thought that anesthesia primarily alters the elastic properties of the chest wall, causing a fall in FRC, whereas the changes in lung compliance may result from breathing at low lung volumes.[128,263,268,269] Application of PEEP in anesthetized and paralyzed subjects produces an increase in end-expiratory lung volume[125,128,270–272] and upward displacement of respiratory system, lung and chest wall pressure–volume relationships (Fig. 10-5A).[272–274] Several authors, however, report little or no increase in static respiratory compliance with PEEP.[272,275,276] In some studies, PEEP increased both chest wall and lung compliance.[272] In other studies, chest wall compliance increased and lung compliance decreased,[276] or no effect was observed.[275]

The effect of PEEP on the elastic properties of the respiratory system varies with the amount of applied PEEP[273] and preexisting derangement in respiratory mechanics. Compared with zero end-expiratory pressure (ZEEP), D'Angelo et al[273] found that PEEP of 9 cm H_2O increased both respiratory system and lung static compliance; the compliances, however, decreased when PEEP was raised above 20 cm H_2O, indicating lung overdistension. Dechman et al[277] also observed an increase in lung compliance at PEEP 10 cm H_2O in patients undergoing closed-chest surgery, but not in patients undergoing open-chest surgery, who exhibited a progressive decrease in dynamic lung compliance. The mechanical characteristics of the chest wall may influence the effect of PEEP in subjects with normal lungs during anesthesia.[263] In patients undergoing abdominal surgery, Pelosi et al[122] reported that 10 cm H_2O PEEP did not improve respiratory function in normal subjects, although it increased end-expiratory lung volume and lung and chest wall compliance in morbidly obese patients. Others reported similar improvements in end-expiratory lung volume and/or in respiratory system compliance both in obese patients[125,127,128] and in healthy subjects with impaired chest wall compliance caused by pneumoperitoneum during laparoscopic surgery.[125,267]

In general, PEEP decreases airway resistance.[122,267,272,273] The decrease in airway resistance is generally small and mainly related to increase in lung volume,[272] although other mechanisms, such as a PEEP-induced modification of basal vagal tone,[278] might also play a role.

EFFECT OF POSITIVE END-EXPIRATORY PRESSURE ON LUNG VOLUME IN ACUTE RESPIRATORY DISTRESS SYNDROME

Since the first description by Asbaugh et al,[1] ARDS has been recognized as a condition characterized by reduction in aerated lung and respiratory system mechanical derangements.[76,79,279,280] In ARDS, massive lung edema, atelectasis, and tissue consolidation cause a marked decrease in FRC.[76,79] This fall in normally ventilated lung volume is the main cause of the impaired respiratory mechanics.[165] Conversely, an increase in aerated lung volume is long recognized as the main cause of the benefit of PEEP on lung function.[42,76] The increase in lung volume may result from two different mechanisms: recruitment of terminal lung units not accessible to ventilation because of collapse or flooding, and distension or overdistension of already open lung units.

Several authors reported an increase in end-expiratory lung volume and FRC following the application of PEEP in patients with ARDS (see Fig. 10-5B).[14,18,36,42,76,199,214,281,282] In absence of PEEPi, the increase in lung volume above FRC at end-expiration, or change in end-expiratory lung volume

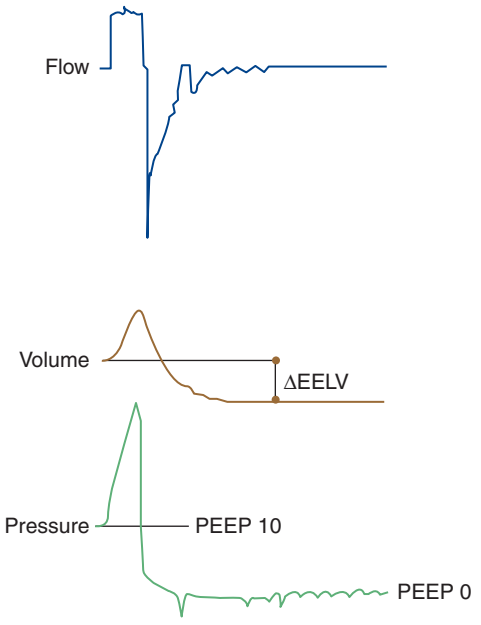

FIGURE 10-6 Measurement of PEEP-induced change in end-expiratory lung volume (ΔEELV). PEEP 10 cm H_2O is abruptly brought to zero. A prolonged expiration ensues, and relaxation volume is achieved. The difference between the volume exhaled during this expiration and the tidal volume delivered by the ventilator equals the increase in EELV induced by PEEP.

(ΔEELV), depends on the amount of applied PEEP and the compliance of the respiratory system. Different techniques can be used to measure FRC and EELV, such as helium dilution,[283–288] nitrogen[285,288–290] and sulphur hexafluoride[288,291–294] washout, positron emission tomography,[295] and CT scan.[36,78,199] These measurements are not routinely obtained in the clinical setting because of technical limitations and/or logistic complexities.

A surrogate approach has been used for assessing PEEP-induced ΔEELV; this involves measuring the volume exhaled between PEEP and elastic equilibrium volume of the respiratory system (Fig. 10-6).[25,197,200–204,266,296,297] While the ventilator is delivering V_T, the preset PEEP is rapidly brought to zero. During the following expiration, sufficient time (5 to 10 seconds) is provided to enable complete exhalation; thus the elastic equilibrium, relaxation volume, will be reached.[25,176,197,200,202] The difference between the volume exhaled during this prolonged expiration and the volume insufflated during the preceding inspiration represents the ΔEELV produced by $PEEP_{TOT}$. The excess volume caused by PEEPi should be separately assessed, and accounted for, to avoid overestimation of PEEP-induced ΔEELV. PEEP-induced variations in EELV can also be measured by inductive[208,296,298–301] or optoelectronic plethysmography.[19,302]

An increase in EELV may also occur when PEEP distends or overdistends already aerated lung regions (Fig. 10-7 and see Table 10-1). Hence, measurement of ΔEELV, without quantification of lung recruitment, may be misleading. *Lung recruitment* refers to re-aeration of collapsed or fluid-filled terminal airways and alveoli. These areas become accessible to ventilation (anatomic recruitment) and may participate in gas exchange if local perfusion is preserved (functional recruitment). Lung recruitment can be quantified by using pressure–volume curves, traced from different levels of PEEP, or by CT scan analysis (see Table 10-1). Other techniques have been proposed, but their application in clinical practice is at present very limited.[295,303–306]

Measurement of PEEP-induced lung recruitment using pressure–volume curve stems from the pioneering

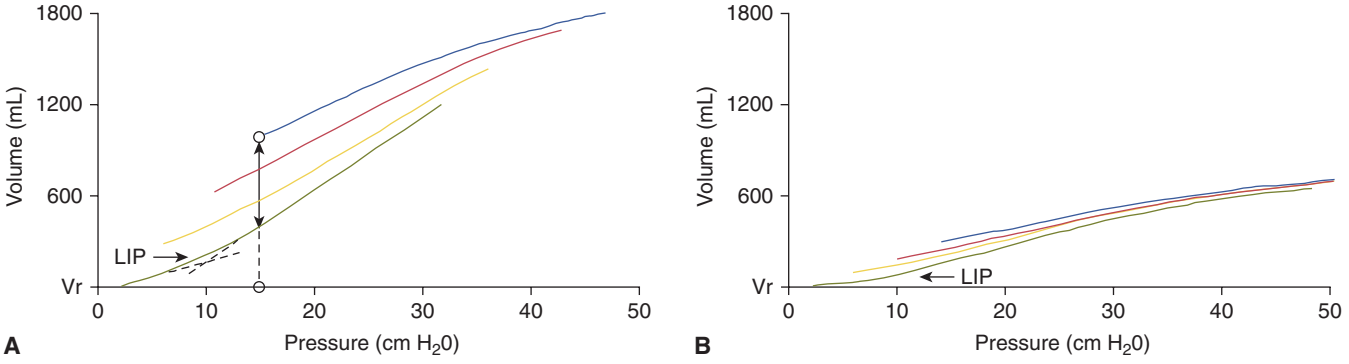

FIGURE 10-7 Pressure-volume (P-V) curves at different levels of PEEP (0, 5, 10, and 15 cm H_2O), related to relaxation volume (*Vr*) of the respiratory system, in two patients with ARDS. In the left panel (**A**), PEEP induces progressive upward shifts of P-V curves, indicating recruitment. At PEEP 15 cm H_2O, PEEP-induced increase in end-expiratory lung volume above Vr is indicated by the *dotted line* between the two *open circles*. Alveolar recruitment induced by PEEP 15 cm H_2O, compared to PEEP 0 cm H_2O, and measured at a pressure of 15 cm H_2O is shown by the *double-arrow solid line*. In the right panel (**B**), P-V curves are particularly flattened, suggesting a marked decrease in aerated lung volume. Increasing PEEP results in minimal recruitment: P-V curves are almost totally superimposed and progressively shifted to right. In both panels, all P-V curves tend to converge at high lung volumes, suggesting that total lung capacity is approached. PEEP-induced recruitment is greater when the slope of the linear segment above the lower inflection point (*LIP*)—that is, linear compliance—of curve recorded from 0 cm H_2O (the lowest curve) is high (A). When the curve at 0 cm H_2O has a very low linear compliance, PEEP-induced recruitment is trivial (B). PEEP-induced recruitment also proceeds far above LIP (up to pressures greater than 40 cm H_2O), suggesting that lung reopening is a pan-inspiratory phenomenon (A).

observations of Katz et al[14] on the time course of PEEP-mediated increase in lung volume. After applying PEEP, these authors observed that end-expiratory lung volume increased to approximately 66% of its total change within the first breath; it reached 90% in approximately five breaths, and was fully complete only after several minutes, suggesting time-dependence for lung recruitment.[14] For a given pressure, lung volume measured during ventilation with 13 cm H_2O PEEP was larger than the volume predicted for that pressure by the static compliance computed at 3 cm H_2O PEEP. This observation suggests that some lung units were not ventilated at the lower PEEP, but were recruited by the higher PEEP.[14] Quantification of lung recruitment induced by PEEP was not attempted until Ranieri et al[200–202] proposed a simple method using pressure–volume curve analysis. This approach consists of aligning on the same pressure–volume diagram curves obtained at ZEEP and varying PEEP levels. With this technique, which assumes that FRC (i.e., the relaxation volume at ZEEP) remains constant,[14,200,201] the ΔEELV induced by PEEP is added to the volume insufflated during the maneuver for recording pressure–volume curve at the corresponding PEEP level.[197,247,297] Lung recruitment is then computed as the difference in volume between pressure–volume curves obtained at different PEEP levels at a given value of elastic recoil pressure (generally 20 cm H_2O). Anatomic recruitment is reflected by an upward shift of the pressure–volume curve (see Fig. 10-7). If PEEP fails to recruit new regions, no volume gain at a given pressure will be observed; the resulting pressure–volume curve will be shifted rightward and superposed on the curve acquired at ZEEP.[197,201]

The CT scan is used to measure recruitment.[215,307,308] PEEP-induced lung recruitment is computed as the decrease in volume of nonaerated lung parenchyma[78,164,216,221,307] or, as recently proposed, the increase in volume of gas penetrating nonaerated and poorly aerated lung regions.[18,308–311] With this technique, however, recruitment is assessed by comparing scans taken at different pressures (ZEEP and PEEP), and not at the same pressure as is done with the pressure–volume curve technique. Consequently, no matter how it is computed, recruitment at a given PEEP will include also a certain volume of gas corresponding to lung units that inflate normally from end-expiration at ZEEP up to the pressure corresponding to that PEEP. This helps explain some of the differences in the amounts of recruitment with the CT and pressure–volume techniques.[312] Conversely, the CT scan offers a unique opportunity to estimate the amount of PEEP-induced hyperinflation (see Table 10-1),[18,36,78,199,225,311,313] computed as the increase in gas volume within normally aerated lung regions; hyperinflation, however, does not necessarily mean overstretching.[307]

Bedside lung ultrasound has been proposed as a mean to estimate PEEP-induced recruitment. In forty patients with ARDS, Bouhemad et al compared the pressure–volume curve method and lung ultrasound to assess recruitment with PEEP 15 cm H_2O.[303] Significant correlations were found between an ultrasound re-aeration score and recruitment measured by pressure–volume curve, and between ultrasound score and oxygenation. This new technique did not, however, allow assessment of lung hyperinflation. Further studies are needed to evaluate the usefulness of this technique.

In patients with ARDS, PEEP increases end-expiratory lung volume and produces varying recruitment (see Table 10-1).[18,25,76,78,169,197,199–204,208,216,221,225,275,282,296,311,313–317] Recent work[197] shows that PEEP achieves progressive recruitment, from 84 mL at PEEP 5 cm H_2O (range: 41 to 156 mL) to 304 mL at 15 cm H_2O (range: 114 to 545 mL). The large interindividual differences suggest that, in certain patients, PEEP increases lung volume without achieving significant recruitment, likely reflecting overdistension of previously aerated lung regions. Indeed, PEEP-induced overdistension has been shown in several studies.[200–202] [18,36,199,225,311] In most cases, recruitment and overdistension occur concomitantly, rather than sequentially, in different regions of the lung following PEEP application.[199,225,308,309,311,313] Vieira et al[36] found that applying PEEP 10 and 15 cm H_2O in patients with ARDS who did not have a clear LIP on the pressure–volume curve produced progressive recruitment of nonaerated lung areas and overdistension of aerated lung zones. The interplay between these two phenomena depends on several factors, such as lung and chest wall mechanics,[266,318] stage of disease,[319,320] lung morphology,[199,225,309] and amount of PEEP.[225]

Recent studies highlight the importance of assessing lung recruitability for an individually tailored optimization of PEEP. By using CT scan in sixty-eight patients with ARDS, Gattinoni et al. assessed the percentage of potentially recruitable lung, as defined by the proportion of lung tissue in which re-aeration was restored at airway pressure between 5 and 45 cm H_2O, and the effects of PEEP.[33] Lung recruitability was 13% ± 11% of the lung weight, varied widely across the studied population (from 0% to more than 50%), and was highly correlated with lung recruitment induced by an increase in PEEP from 5 to 15 cm H_2O. Patients with higher lung recruitability had more severe disease (lower oxygenation and respiratory system compliance) and a higher mortality rate.

Assessment of lung recruitability is important for setting PEEP: the use of high PEEP in patients with a low percentage of potentially recruitable lung provides little, if any, benefit and may actually be harmful if it produces overdistension.[321] Lung recruitability may influence the effects of PEEP on alveolar strain (the ratio between the amount of gas delivered during a tidal breath and the amount of aerated lung available for ventilation) and alveolar opening and closing.

Caironi et al reported that an increase in PEEP from 5 to 15 cm H_2O in patients with a lower percentage of potentially recruitable lung did not significantly affect the amount of opening and closing lung tissue, which was already negligible at lower PEEP.[27] Conversely, in

patients with a higher recruitability, opening and closing was dramatically reduced (approximately equal to 50%) by increase in PEEP. Interestingly, increases in PEEP led to an identical increase in alveolar strain in the two groups of patients. In patients with higher recruitability, the lung volume available for ventilation conceivably increases during inspiration as recruitment of nonaerated lung regions at end-expiration progressively occurs. These findings further suggest a relationship between the amount of intratidal lung recruitment and the effective end-inspiratory alveolar strain, such that the larger the amount of potentially recruitable lung, the lower the risk of PEEP-induced overdistension. In addition, opening and closing lung tissue turned out to be an independent risk factor for death (odds ratio 1.10 for each 10 g increase), while alveolar strain did not.[27] This suggests that in patients with higher lung recruitability, the beneficial impact of reducing intratidal opening and closing by increasing PEEP prevails over the effects of increasing alveolar strain. In this regard, lung imaging morphology (chest radiograph or CT scan) may help in assessing lung recruitability: patients with a lower percentage of potentially recruitable lung generally show a "lobar" pattern of lung consolidation, whereas patients with greater lung recruitability often present diffuse lung collapse.[27,199,225,321]

The integrated analysis of respiratory mechanics, lung volumes, and lung imaging enhances recognition of the effects of PEEP on recruitment and overdistension, and hence facilitates to set optimal PEEP at the bedside.

EFFECT OF POSITIVE END-EXPIRATORY PRESSURE ON RESPIRATORY MECHANICS IN ACUTE RESPIRATORY DISTRESS SYNDROME

Contrasted with normal subjects, the rate of change per unit of pressure is smaller, and linear compliance of the pressure–volume curve falls to very low values in patients with ARDS (because of the decrease in normally ventilated alveolar units); the whole curve is also flattened and shifted downward, and the inflection knees, normally seen at low (LIP) and high (UIP) lung volumes, may appear in the range of tidal ventilation[247] (see Figs. 10-5B and 10-7). The presence of LIP and UIP in the V_T range suggest considerable susceptibility of the ARDS lung to detrimental mechanical shear forces, generated by cyclic end-expiratory alveolar opening and collapse[78,165,322] and end-inspiratory overstretching.[201,323] These forces are considered the main mechanism of ventilator-induced lung injury.[324,325] Recent evidence suggests that airspace reopening can occur along the entire pressure–volume curve.[197,216,307,326–329] Moreover, the shape and characteristics of the pressure–volume curve can be greatly influenced by several factors including pathophysiologic mechanisms, stage of disease,[282,322] chest wall mechanics,[198,266] breathing pattern, and differences in measurement technique.[330]

As already mentioned, one typical feature of ARDS is the fall in respiratory system compliance (see Figs. 10-5B and 10-7), described both in experimental[331–334] and clinical settings.[42,76,176,322,335] Decreased compliance was initially attributed to increased lung stiffness.[280] Subsequent studies have demonstrated that the decreased compliance in ARDS has different pathophysiologic mechanisms.[333,334] In an animal model, Grossman et al[333] showed that the loss of aerated lung units, secondary to alveolar flooding, accounted for virtually all of the decreased static lung compliance. With CT scan analysis, Gattinoni et al[165] found that several parameters of the pressure–volume curve, including linear compliance, were correlated with the amount of aerated areas (mainly distributed in the nondependent, ventral lung regions) but not with nonaerated areas (preferentially distributed in the dependent, dorsal lung regions). Indeed, compliance was in the normal range when normalized to FRC (so-called specific compliance), suggesting that the aerated areas had normal intrinsic elasticity.[165] According to this concept, respiratory system compliance provides an indirect estimate of the amount of aerated lung (see Figs. 10-5B and 10-7).

Through recruitment, PEEP prevents the fall in static compliance,[5] and restores the normal pressure–volume pattern, by suppressing small airway closure and collapse of unstable lung units.[281,336–339] Data suggest that the effects of PEEP on recruitment and overdistension can be predicted by the shape of the pressure–volume curve at ZEEP.[197,200,201,225,326,328,340] Three distinct patterns of pressure–volume curve have been described in patients with ARDS.[200,201,225] A concave shape, with a clear LIP, indicates that compliance is progressively increasing above this point, suggesting ongoing recruitment during inflation (see Fig. 10-7).[200,201,340] A convex shape, showing an UIP, denotes progressive decrease in compliance, and likely overstretching (see Fig. 10-7).[200,201] A linear pressure–volume curve, with absent or very low LIP, may be observed in localized lung injury.[225]

Rouby et al[191,309,310] hypothesized that a linear pressure–volume curve results from two separate regional curves: a concave curve, related to normally aerated lung regions, and a convex curve, related to nonaerated areas. PEEP may have different effects on lung volumes and respiratory mechanics according to these patterns. When a concave shape is observed at ZEEP, PEEP results in lung recruitment, as documented by an upward shift of the pressure–volume curve and disappearance of LIP (see Fig. 10-7).[197,200,201,225] With a convex profile and low linear compliance at ZEEP, PEEP-induced recruitment is minimal or zero: the pressure–volume curve is superimposed on that obtained at ZEEP, with a further decrease in compliance (see Fig. 10-7).[197,200,201,225]

A linear compliance on the pressure–volume curve at ZEEP may be a useful indicator of lung recruitability (see Fig. 10-7). A tight correlation between linear compliance at ZEEP and amount of PEEP-induced recruitment has been suggested.[197] Because compliance, as assessed on the pressure–volume curve, is a function of normally aerated lung regions,[165] two different situations can be imagined: (a) the

lung is principally characterized by unstable lung regions, which are collapsed at the end expiration but progressively pop open during tidal inflation, and (b) the lung is predominantly consolidated, with no large areas expanding during inflation (compliance is very low). Application of PEEP results in significant recruitment in the former case; in the latter case, PEEP may overstretch already ventilated areas without producing significant recruitment.[200,201] Independently of its effect on recruitment and overdistension, PEEP constantly and significantly decreases the linear compliance of the pressure–volume curve.[25,197,201,326,328] This contrasts with the classical notion that compliance increases with recruitment and decreases with overdistension.[42] Lung units that pop open at a certain pressure have an infinitely high compliance and contribute to the higher compliance observed at ZEEP, as opposed to that observed when the lung is fully recruited at PEEP. A corollary is that UIP may indicate the end of tidal recruitment and/or the beginning of alveolar overdistension, although both mechanisms may coexist at high pressure (see Fig. 10-7).[25,326] Therefore, PEEP-related decrease in pressure–volume linear compliance may predominantly reflect recruitment below UIP; a decrease in compliance above this point may reflect overdistension.

LIP has long been considered the pressure at which collapsed lung units open during inflation, it is therefore considered the ideal pressure at which to set PEEP.[322] No relationship between LIP and either opening or closing alveolar pressures, however, was subsequently found,[197] indicating that LIP is not useful for optimizing PEEP setting. Other studies confirmed that recruitment and derecruitment are continuous processes unrelated to LIP (see Fig. 10-7).[25,204,215,216,326,328,329] Nevertheless, the presence of a clear LIP followed by a high inflation compliance on the pressure–volume curve recorded from ZEEP may predict the effect of PEEP on recruitment (see Fig. 10-7).[165,197,225,328] Vieira et al[225] showed that patients with a diffuse loss of aeration had a marked LIP at ZEEP, whereas LIP was absent or blunted in patients with a focal loss of aeration. High PEEP induced progressive recruitment without overdistension in the former group, whereas it caused a significant overdistension of normally aerated regions in the latter group.[225] Some think that LIP is caused by time-constant inequalities within the lung and/or reopening of compressed peripheral airway associated with expiratory flow limitation.[183,184,341,342] Accordingly, the disappearance of LIP following application of low or moderate PEEP might indicate that PEEP can prevent small airway closure and make the distribution of tidal ventilation more homogeneous.[184,342] This could also explain the difference between the reported values of LIP, 5 to 15 cm H_2O, and the substantially higher pressures required to reverse atelectasis.[216,245,343]

Some studies suggest that the point of maximum curvature of the deflation limb of the pressure–volume curve may be used to set PEEP so as to optimize lung recruitment, but the feasibility of this approach is limited.[215,344]

The mechanical properties of the chest wall may influence the effects of PEEP.[198,266,282] Mergoni et al[198] found that in some patients the LIP on the pressure–volume curve of the respiratory system at ZEEP reflected the chest wall, rather than the lung. Application of PEEP abolished LIP in all instances, but oxygenation significantly improved, suggesting recruitment, only in patients exhibiting a LIP on the lung pressure–volume curve.[198] Gattinoni et al[282] found that increasing levels of PEEP decreased respiratory and lung static compliance, without any recruitment, in patients with primary pulmonary ARDS; in patients with secondary extrapulmonary ARDS, PEEP induced significant recruitment and increased respiratory, lung, and chest wall compliance.[282] These findings have been confuted by other studies, even by the same group.[25,33,197,199,225,345]

The change in static compliance produced by PEEP has been proposed as a guide for optimizing PEEP[42] and as a prognostic factor for predicting mortality in patients with ARDS.[346] Because of nonlinearity of the pressure–volume relationship in ARDS, however, and the aforementioned complex effect of recruitment on the pressure–volume relationship,[326–328] static compliance (calculated as the pressure-to-volume differences between two points) may not describe adequately the changes in respiratory mechanics produced by PEEP.[247,297] Indeed, as previously shown[347] and recently outlined,[182,327,345] static compliance may vary for different V_Ts. A mathematical model suggests that the highest static compliance computed at a low V_T during a decremental, but not incremental, PEEP trial may help to identify the level of PEEP needed to prevent end-expiratory alveolar collapse.[327] These theoretical findings are supported by data in animals,[348,349] but have not been sufficiently tested in humans.

Some authors recommend the monitoring of dynamic compliance as a means of assessing the mechanical properties of the respiratory system under dynamic condition (ongoing ventilation) and to identify the level of PEEP that prevents alveolar derecruitment.[350,351] Data on this issue, however, are far from conclusive.

Several studies[179,182,185,314,352] reveal that PEEP increases additional resistance through increased viscoelastic dissipation[180] that is consequent to a PEEP-mediated increase in end-expiratory lung volume, as suggested by the correlation between changes in tissue resistance and end-expiratory lung volume.[352] Other studies,[275,353] although confirming the rise in tissue resistance, also report a decrease in airway resistance, especially at high PEEP. Normalizing resistances for lung volume (i.e., specific resistance) caused these changes to disappear.[275] Partitioning resistance into lung and chest wall components, Pelosi et al[275] found that the increase in total and tissue respiratory system resistance, consequent to PEEP, could be mainly ascribed to the lung rather than the chest wall. Gattinoni et al[282] found that total respiratory resistance increased with PEEP in pulmonary ARDS, mainly because of a marked increase in lung additional resistance.[282] In contrast, patients with extrapulmonary ARDS, characterized by higher chest wall tissue

resistance and lower lung tissue resistance than pulmonary ARDS, did not show any change in total respiratory resistance with PEEP.[282]

EFFECT OF POSITIVE END-EXPIRATORY PRESSURE ON RESPIRATORY MECHANICS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

In COPD patients, lung and chest-wall static compliance are reported to be similar to those of normal subjects,[354] unless expiratory flow limitation and dynamic hyperinflation causes lung overdistension. Depending on the level of PEEP, static compliance may decrease (if overdistension occurs),[238,294,355,356] stay unchanged,[357] or even slightly increase (if recruitment of new lung units occurs)[252] (see Fig. 10-5C).

Total end-expiratory alveolar pressure ($PEEP_{TOT}$) may markedly exceed preset PEEP when PEEPi is present (see Fig. 10-4). Rossi et al[260] demonstrated that failure to take PEEPi into account caused static compliance to be underestimated by up to 48%. During volume-targeted controlled ventilation, an increase in inspiratory flow resulting in a prolonged expiratory time causes PEEPi to decrease. Thus, the value of static compliance calculated without correcting for PEEPi will falsely (and paradoxically) increase.[260,252] The presence of a LIP on the pressure–volume curve at ZEEP may be partly caused by PEEPi, at least in patients with expiratory flow limitation.[358]

Patients with COPD have a high resistance to air flow.[59,238,357,359,360] In patients with expiratory flow limitation, PEEP should have little influence on expiratory flow until PEEP exceeds PEEPi.[260] Other studies, however, suggest that PEEP 5 to 10 cm H_2O might partly decrease expiratory resistance, particularly at the end-expiration, and result in faster and more uniform lung emptying.[294,357,361,362]

EFFECTS OF POSITIVE END-EXPIRATORY PRESSURE ON DIAPHRAGMATIC ACTIVATION

Recent studies provide novel information about the effects produced by PEEP application on diaphragmatic electrical activity, assessed by transesophageal electromyography. Allo et al[363] induced ARDS in rabbits by intratracheal instillation of hydrochloric acid: eleven animals, five of which had been previously vagotomized, underwent a short-term protocol where PEEP and inspiratory assistance delivered by neurally adjusted ventilatory assist (NAVA) were varied over a few minutes. After hydrochloric acid instillation in the nonvagotomized rabbits, tonic (i.e., continuous throughout the respiratory cycle) diaphragmatic electrical activity increased without PEEP, while phasic (i.e., timed with inspiration) diaphragmatic electrical activity became smaller and irregular. A stepwise increase in PEEP progressively attenuated tonic diaphragmatic electrical activity and increased phasic diaphragmatic electrical activity; when PEEP was subsequently reduced, tonic and phasic diaphragmatic electrical activity returned back to the initial values. In the group of vagotomized rabbits, conversely, tonic diaphragmatic electrical activity did not rise after lung injury and was consequently unaffected by PEEP, while phasic diaphragmatic electrical activity and V_T were on average much higher than in the nonvagotomized animals. These data may suggest that tonic diaphragmatic electrical activity could result from vagally mediated reflexes acting to conserve end-expiratory lung volume and PEEP might decrease tonic diaphragmatic electrical activity by recruiting lung volume.

Using the same animal model, Beck et al[364] applied the same level of inspiratory assistance by NAVA through an endotracheal tube in the presence of PEEP (8.5 ± 3.3 cm H_2O) and in the absence of PEEP. An instantaneous increase in tonic diaphragmatic electrical activity was observed upon PEEP removal. Following extubation and initiation of NAVA without PEEP via a mask, however, tonic diaphragmatic electrical activity returned to the previous values. The authors considered the increase in tonic diaphragmatic electrical activity during invasive ventilation without PEEP as a mechanism through which the diaphragm assumes the role of conserving end-expiratory lung volume, replacing the activity of the glottal muscles that is lost when the endotracheal tube is in place.

In twenty adult patients with ARF of varied etiology undergoing NAVA, Passath et al[365] evaluated the effects of different levels of PEEP. A stepwise reduction of PEEP from 20 to 1 cm H_2O increased inspiratory diaphragmatic electrical activity by 34%, while V_T and breathing rate did not significantly change. The ratio of V_T to diaphragmatic electrical activity, an approximation of neuroventilatory efficiency, showed broad individual variability at different PEEP levels and may help in identifying the level of PEEP at which tidal breathing occurs at minimal diaphragmatic electrical activity cost.

Effect of Positive End-Expiratory Pressure on Ventilator-Induced Lung Injury

VENTILATOR-INDUCED LUNG INJURY

Recent decades have brought the recognition that mechanical ventilation per se, in ARDS, may damage the lung and/or aggravate preexisting lung injury.[325] This so-called ventilator-induced lung injury (VILI)[325,366,367] is now widely recognized and supported by a large number of animal experimental studies[220,368] and recent data in patients.[6,369,370] Attempts to prevent VILI have modified the ventilator approach to patients with ARDS.[324] Two main mechanisms for VILI are: (a) alveolar[220,368] and bronchial overdistension[371,372] occurring at high volume and transpulmonary pressure, and (b) repeated alveolar and small airways collapse and reopening at low end-expiratory volume.[217,371,373] The common pathway for these two mechanisms is mechanical stress on the terminal units (including

bronchiolar and alveolar walls).[374–376] Other factors, including elevated FI_{O_2}, high blood flow, high inspiratory flow, and intensity of local inflammation, may play a role in aggravating or inducing lung injury.

EFFECT OF POSITIVE END-EXPIRATORY PRESSURE ON VENTILATOR-INDUCED LUNG INJURY

PEEP may have opposing consequences, depending on its effects on the two aforementioned mechanisms of VILI (alveolar overdistension and cyclic alveolar collapse and reopening) (Fig. 10-8).[225,313] In one study, PEEP (13 cm H_2O) caused recruitment of nonaerated regions, and induced overdistension of already aerated lung areas in three patients.[36]

Since the 1970s, high ventilator pressures have been known to rupture alveoli and cause air leaks.[377] By increasing airway pressure, PEEP may promote alveolar overstretching,[39,201,202,225,311] ultrastructural damage,[372] worsening of pulmonary edema,[157] and triggering of local and systemic inflammation.[378] Some early studies suggest that end-inspiratory lung volume, rather than high intrathoracic pressure, may be the major determinant of ventilator-induced lung edema ("volutrauma"), at least in normal lungs.[220,379,380] PEEP, however, may also protect against edema accumulation during ventilation at high end-inspiratory pressure and

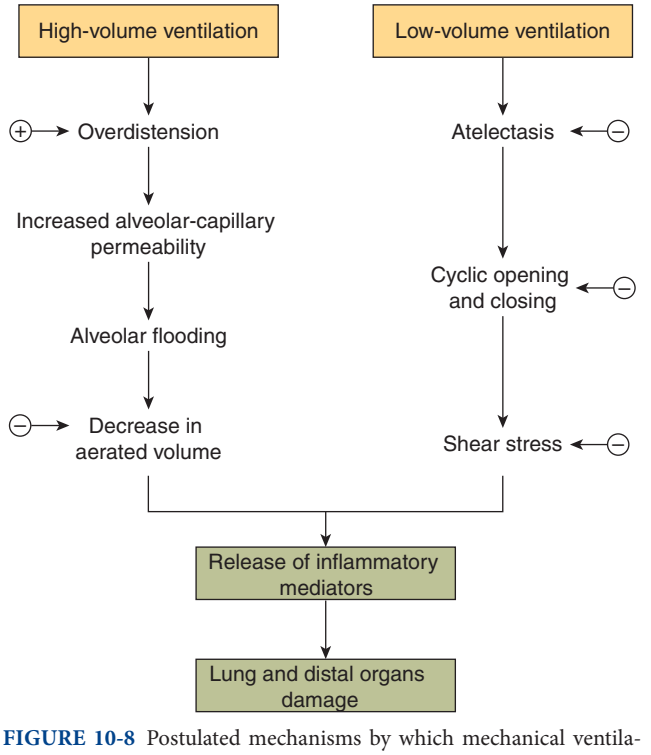

FIGURE 10-8 Postulated mechanisms by which mechanical ventilation may lead to ventilator-associated lung injury and organ injury. Beneficial (*minus sign*) and detrimental (*plus sign*) effects of PEEP on these mechanisms are shown.

end-inspiratory lung volume,[217–220,381] although alteration in microvascular permeability may not be prevented.[219,220] Several factors may explain these apparent contradictions: (a) differences in experimental setup (isolated lung vs. intact animals), (b) levels of PEEP and inspiratory airway pressure, and (c) driving pressure (difference between end-inspiratory and end-expiratory alveolar pressures, which, for a given pulmonary elastance, depends on V_T size).[325] In isolated lung with constant perfusion, PEEP augments edema formation probably because of increased filtration across extraalveolar vessels associated with lung overdistension.[382,383] Conversely, in intact animals, PEEP does not affect edema formation, probably because of balancing between the PEEP-induced increase in end-inspiratory lung volume (which increases fluid filtration), and concomitant reduction in cardiac output and blood pressure (which reduce filtration pressure).[384–386]

The role of PEEP-induced changes in hemodynamics on edema accumulation has been suggested by several authors.[219,387] In an animal model, Dreyfuss and Saumon[219] showed that lung edema was reduced during ventilation with PEEP 10 cm H_2O, as opposed to ZEEP, despite identical end-inspiratory pressures. When the drop in arterial pressure produced by PEEP was corrected by dopamine infusion, pulmonary edema increased in direct proportion to systemic blood pressure. The increase in permeability edema was, however, less than that observed during ventilation at ZEEP, suggesting that hemodynamic modification is not the only factor explaining the effect of PEEP on edema formation.[219,388] Indeed, reduction in driving pressure while keeping end-inspiratory lung volume and pressure constant (as obtained by increasing PEEP while reducing V_T) may reduce edema and the severity of cellular damage; these findings suggest that a decrease in tissue stress may explain this protective effect of PEEP.[217–220,389] The greater amount of alveoli available to clear edema, consequent to PEEP-induced alveolar recruitment, might also contribute.[388]

PEEP may also exert beneficial effects in localized lung injury. De Prost et al assessed the dispersion of localized alveolar flooding and alveolar protein permeability in rats undergoing local instillation of albumin solution followed by different ventilator strategies with varying levels of V_T and PEEP.[390] High V_T ventilation caused alveolar liquid dispersion, which PEEP had prevented; this occurred even when V_T was kept constant, thus producing higher end-inspiratory pressures that did not exceed the safe limit of 30 cm H_2O. PEEP also reduced the increase in alveolar protein permeability caused by high V_T. In an animal model of unilateral lung injury, Schreiber et al reported that stepwise increases in PEEP, from zero up to a relatively moderate level of 13 cm H_2O, reduced the inflammatory response in the injured lung, did not result in detrimental effects on inflammation in the healthy lung, and preserved oxygenation.[391]

PEEP-associated preservation of surfactant may further explain the benefit of PEEP on high-volume mediated

VILI.[217] Thus, severity of overinflation is one major determinant of VILI.[321,378,392] When ventilator-induced lung edema is produced by high V_T, the combination of PEEP and V_T reduction decreases the severity of injury at the same end-inspiratory pressure. When PEEP, however, is not accompanied by V_T reduction, excessive inspiratory pressures and additional overstretching occur, further increasing the rate of edema formation and tissue injury[219] and triggering systemic inflammation.[378]

In a mechanically heterogeneous lung, noninflating collapsed tissue is surrounded by open airspaces. Mead et al[374] suggested that recruitment of nonaerated lung units induces a local stress to alveoli and bronchioles, which is substantially higher than the average transpulmonary or transbronchial pressure, respectively, because of alveolar and small airways interdependence.[371,375] If this process recurs cyclically, high shear forces may damage the alveolar and airway epithelium, overstretch fragile microvessels, deplete surfactant, and initiate or worsen inflammation. By recruiting nonaerated portions, and stabilizing airways and lung units prone to repetitive opening and collapse, PEEP plays a key role in protecting the lung from the mechanical shear stress and tissue injury produced by ventilation at low end-expiratory lung volume ("atelectrauma").[373,374,393–398]

A large body of animal data supports the protective effect of PEEP on low-volume mediated VILI.[217,218,338,373,389,393,395,398–402] By minimizing shear stress associated with cyclic opening and collapse, PEEP may attenuate inequalities in the regional distribution of tidal ventilation, thus avoiding or limiting overdistension in the less-injured lung zones.[374,375] By increasing end-expiratory lung volume, PEEP can also prevent surfactant loss and preserve surfactant function.[400,403–406] By minimizing mechanical stress, PEEP may also ease the intensity of ventilator-induced lung inflammation[393,396,407] and remodeling,[397] and reduce the decompartmentalization of a number of inflammatory mediators[408] and bacteria from the lung into the circulation ("biotrauma").[409–411] These aforementioned mechanisms may play a role in initiating or propagating the systemic inflammatory response, which contributes to the multiple organ failure often observed in the terminal stage of ARDS.[412–414] The local and systemic beneficial effects of PEEP are, however, dependent on the level of applied PEEP. Several authors, in fact, have suggested that higher-than-optimal levels of PEEP, defined as the PEEP required for maximum oxygenation and/or minimum elastance, may worsen lung mechanics, increase the amount of atelectasis and the lung-tissue expression of type III procollagen messenger RNA (an early marker of lung parenchyma remodeling), and also promote bacterial translocation.[415,416]

Recent clinical trials show that protective ventilator strategies, reduced V_T (to limit the end-inspiratory stretch),[6,369,370] and high PEEP (to avoid cyclic opening and closing)[6,369] are associated with decreased pulmonary and systemic cytokine response,[369,370] less organ dysfunction,[417] and reduced mortality in patients with ARDS,[6,370] compared to conventional, injurious mechanical ventilation. Although the mechanisms whereby VILI causes organ dysfunction are not completely understood, a recent study suggests that cell apoptosis may be involved.[414] Rabbits ventilated with a low V_T and high PEEP showed less epithelial apoptosis in the kidney and small intestine than did rabbits ventilated with a high V_T and low PEEP.[414] The former rabbits had more apoptotic cells in the lung, whereas the latter rabbits had less lung apoptosis and necrosis of alveolar epithelial type III cells.[414] Analysis of plasma samples from a previous clinical trial[369] revealed higher levels of soluble Fas ligand (a proapoptotic factor) in patients who received conventional ventilation than in patients who received protective ventilation; changes in soluble Fas ligand were correlated with changes in plasma creatinine.[417]

Effects of Positive End-Expiratory Pressure on the Cardiovascular System

The lungs and heart are subject to variations in intrathoracic pressure. How alterations in intrathoracic pressure affect the heart and intrathoracic vessels varies substantially and depends on several factors, such as mechanical properties of the lung and chest wall, type of ventilation (spontaneous vs. mechanical), blood volume, and left-ventricular function. The complex interplay of these factors and the effects of PEEP on heart–lung interactions have been extensively reviewed.[418–426]

EFFECT ON VENOUS RETURN

Positive airway pressure causes a drop in cardiac output secondary to a decrease in cardiac filling (preload); this was initially attributed to a reduction in the pressure gradient for venous return, determined by the rise in right-atrial pressure consequent to increased intrathoracic pressure.[50,66,427–430] The PEEP-mediated decrease in the gradient for venous return, however, is less than expected because PEEP produces a concomitant rise in mean systemic pressure[431] (the circulatory filling pressure representing the upstream pressure for venous return). In patients without lung disease undergoing implantation of defibrillator devices under general anesthesia, Jellinek et al[432] measured right-atrial pressure and mean systemic pressure at airway pressure zero and 15 cm H_2O during 15-second periods of apnea when ventricular fibrillation was induced to test the defibrillator. Rising airway pressure produced a drop in left-ventricular stroke volume.[432] Right-atrial and mean systemic pressure, however, increased equally, showing that the reduction in venous return was not determined by a decrease in pressure gradient.[432] The rise in mean systemic pressure may result from a reduction in vascular capacitance determined by neurovascular reflexes,[433] displacement of blood from the pulmonary to the systemic circulation,[434] and descent of the diaphragm, which increases the upstream pressure for venous return by augmenting intraabdominal pressure.[435] These homeostatic

adaptations, however, may be counteracted by a concomitant increase in venous resistance,[431,436] suggesting that PEEP may alter venous return by affecting the peripheral venous circulation.

The effects of PEEP on hemodynamics strongly depend on intravascular volume. Cardiac output can be restored by increasing the ventricular filling through volume infusion.[47,437–440] PEEP discontinuation produces a rise in cardiac filling, proportional to the pressure withdrawn and the circulating blood volume.[47,441] In hypervolemic and hemodynamically stable patients who underwent cardiac surgery, van der Berg et al found that maintaining airway pressure up to 20 cm H_2O for 25 seconds produced minimal variations in right ventricular output despite a concomitant rise in right atrial pressure.[435]

In summary, PEEP reduces cardiac output through a decrease in venous return that is not a primary consequence of a decrease in its pressure gradient. Regardless of the cause, the drop in cardiac output can be counteracted by blood volume expansion.

EFFECT ON RIGHT-VENTRICULAR AFTERLOAD AND VENTRICULAR INTERDEPENDENCE

PEEP alters both left- and right-ventricular configurations and reduces left-ventricular diastolic compliance by augmenting right-ventricular afterload.[49,442–444] An increase in lung volume causes a rise in pulmonary vascular resistance by directly compressing the alveolar vessels.[445] The interconnections between lung volume and pulmonary blood flow are not straightforward, because blood expelled from the alveolar vessels can be retained in the extraalveolar vessels.[446,447] When airway pressure is augmented, right-ventricular outflow impedance (i.e., afterload) is also increased.[426,448] In patients with ARDS, high levels of PEEP can cause or worsen tricuspid regurgitation.[449]

The fall in cardiac output with PEEP has been also attributed to the stress exerted by the right ventricle on the interventricular septum,[443] which is displaced leftward and restricts left-ventricular filling.[49] Culver et al[450] altered right-ventricular afterload, through a partial occlusion of the main pulmonary arteries, and found that this did not produce the same hemodynamic changes induced by increases in lung volume; these findings suggest that ventricular interdependence (caused by an increased right-ventricular afterload) was unlikely to be the main mechanism for PEEP-mediated fall in cardiac output. Wise et al[69] evaluated the impact of PEEP 15 cm H_2O on left-ventricular compliance in a study where they bypassed the right heart to exclude the effects of interventricular interdependence; they concluded that the elevation in left-ventricular filling pressure was mainly consequent to pericardial compression. In patients with ARDS, Dhainaut et al[440] did not find any changes in ventricular diastolic compliance and ejection fraction when PEEP was increased up to 20 cm H_2O during controlled ventilation; they attributed the reduction in cardiac output mainly to the preload effect.

More recently, Gernoth et al reported that an open-lung strategy with high PEEP (20 cm H_2O), which improved oxygenation without significantly affecting Pa_{CO_2}, caused no major hemodynamic alteration, while right- and left-ventricular function, respectively, were improved and unchanged.[451] An impairment in right-ventricular function and hemodynamics, however, has been reported when PEEP is increased at constant plateau pressure, with significant worsening of respiratory acidosis despite improvement in oxygenation.[452]

In summary, PEEP increases pulmonary vascular resistance and right-ventricular afterload and may therefore increase the stress exerted by the right ventricle, which has to maintain an adequate output to guarantee left-ventricular filling. Right-ventricular systolic overload may result in leftward displacement of the interventricular septum; the effect on left-ventricular function seems to be adjunctive, rather than a major determinant of the PEEP-mediated reduction in cardiac output.

IMPACT OF RESPIRATORY MECHANICS ON THE HEMODYNAMIC EFFECT OF POSITIVE END-EXPIRATORY PRESSURE

A reduction in lung compliance reduces the transmission of airway pressure to the pericardial space,[453,454] and to the pleural space. The transmission of PEEP to the pleural space increases when chest wall compliance is reduced[455] and decreases when chest wall compliance is increased.[454] Venus et al[456] found that the fraction of PEEP transmitted to the pleura was reduced from 62% to 34% and to the pericardium from 54% to 36%, in intact and acutely injured lungs, respectively. V_T was kept constant throughout the study and the reduction in cardiac output produced by PEEP did not differ before and after inducing lung injury, because absolute pericardial pressure at end-expiration did not differ.[456]

EFFECT ON AFTERLOAD

Left-ventricular afterload is the force opposing contraction. It corresponds to the tension developed by the contracting cardiac muscle. It is determined by both the systemic arterial resistance and the transmural pressure exerted on the left-ventricular wall; that is, the difference between the systolic pressure and the pressure surrounding the heart (i.e., intrathoracic pressure). A reduction in left-ventricular afterload is achieved either by decreasing systemic arterial resistance (through vasodilator administration) [457]or increasing intrathoracic pressure.[69–71] In healthy subjects with normal cardiac function the dominant action of increase in intrathoracic pressure is reduction in venous return; the consequences of the lowered transmural pressure are rather small (see Fig. 10-2A). In patients with poor left-ventricular function and congestive heart failure, cardiac output is relatively insensitive to reduction in venous return because left-ventricular filling pressure and diastolic volume are elevated.[67] Thus, the net effect of a rise in intrathoracic pressure is a reduction in

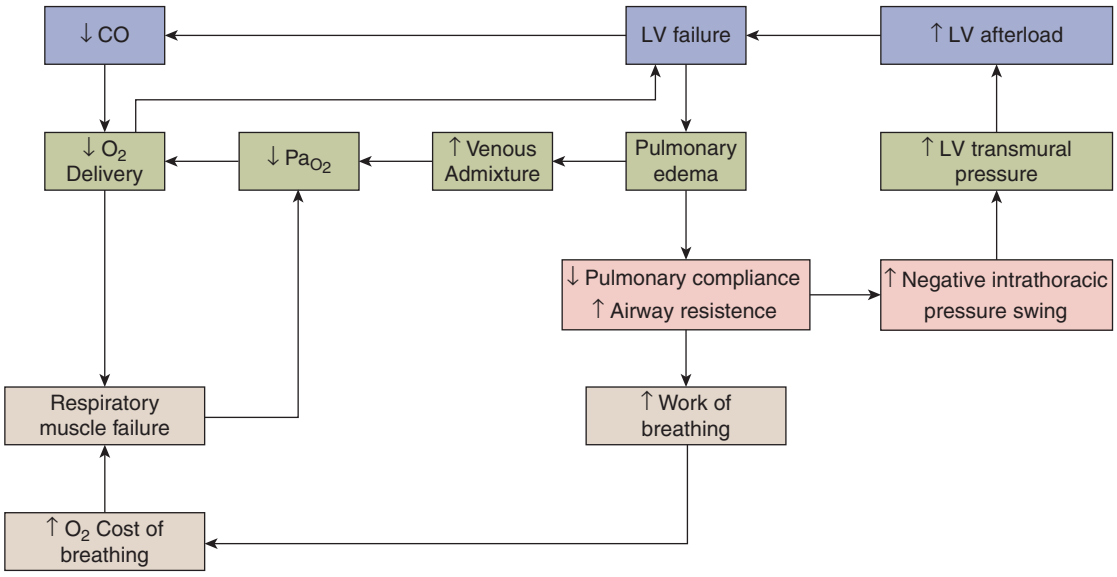

FIGURE 10-9 Pathophysiologic mechanisms and pathways of cardiogenic pulmonary edema. Worsening in pulmonary mechanics increases negative swings in intrathoracic pressure and left-ventricular afterload. Worsening in gas exchange decreases oxygen delivery to the heart and the respiratory muscle. See text for further explanation. *CO*, Cardiac output; *LV*, left ventricle; O_2, oxygen; Pa_{O_2}, partial pressure of arterial oxygen.

left-ventricular transmural pressure (see Fig. 10-2B).[68,458,459] Conversely, a decrease in intrathoracic pressure raises afterload by augmenting left-ventricular transmural pressure (see Fig. 10-2B).[332,460]

When afterload exceeds the capacity of the left ventricle, pulmonary edema ensues, establishing a vicious circle (Fig. 10-9). Because of worsening pulmonary compliance[332,460,461] and resistance,[460,462–464] the inspiratory muscles must exert a stronger effort to achieve adequate alveolar ventilation. Thus, inspiratory intrathoracic pressure becomes more negative, and afterload increases. The combination of reduced O_2 delivery[465] and increased metabolic cost of breathing[464–466] may precipitate respiratory muscle failure,[466] which further worsens gas exchange.

The impact on left-ventricular transmural pressure of the increase in intrathoracic pressure produced by CPAP 10 cm H_2O during expiration is rather small (see Fig. 10-2C). Conversely, the improvement in pulmonary mechanics[466] generated by the same CPAP may minimize the swings in intrathoracic pressure[466,467] and hence decrease afterload,[467,468] thereby improving left-ventricular function (see Figs. 10-2C and 10-10).[72,468] CPAP may simultaneously improve gas exchange[72,73,146] by reducing venous admixture[10,146] and avert failure of the respiratory muscles by improving their O_2 balance[10] (Fig. 10-10).

EFFECT ON OXYGEN DELIVERY

The effect of PEEP on O_2 delivery depends on its relative effects on cardiac output and arterial oxygen content: in other words, on the balance between the pulmonary and hemodynamic consequences of PEEP. PEEP-induced increase in Pa_{O_2} and arterial oxygen content may be accompanied by a decrease in O_2 delivery, because of concomitant decrease in cardiac output.[46] The impact of PEEP on O_2 delivery depends primarily on its hemodynamic effect. By decreasing cardiac output and consequently O_2 delivery, PEEP may worsen O_2 balance and promote pathologic supply-dependency of O_2 delivery.[430,469–472]

The effect of protective ventilation on O_2 delivery was evaluated in patients with ARDS.[473–475] In forty-eight patients with severe ARDS, Carvalho et al[474] found that PEEP up to 24 cm H_2O (average: 16 cm H_2O) produced an increase in cardiac output, heart rate, and O_2 delivery, and decreased systemic vascular resistance and plasma lactate. The authors speculated that the good tolerance of high PEEP may have been a consequence of the acute hemodynamic effects of hypercapnia and the observed very low lung compliance.[474] No correlation was found between changes in PEEP and cardiac output. A strong inverse correlation existed between changes in plateau pressure and cardiac output. These findings suggest, in line with other reports,[202,318] that the negative hemodynamic effect classically attributed to PEEP may depend more on the associated high inspiratory pressure (if V_T is not concomitantly reduced).[474]

Noncardiorespiratory Effects of Positive End-Expiratory Pressure

RENAL AND HORMONAL EFFECTS

PEEP decreases urinary output,[47,54,55,476–500] sodium excretion,[55,476–478,480–482,484–490,493,500] and creatinine clearance.[476,480,481,484,490] Although there is general consensus about these effects of PEEP, studies investigating the mechanisms

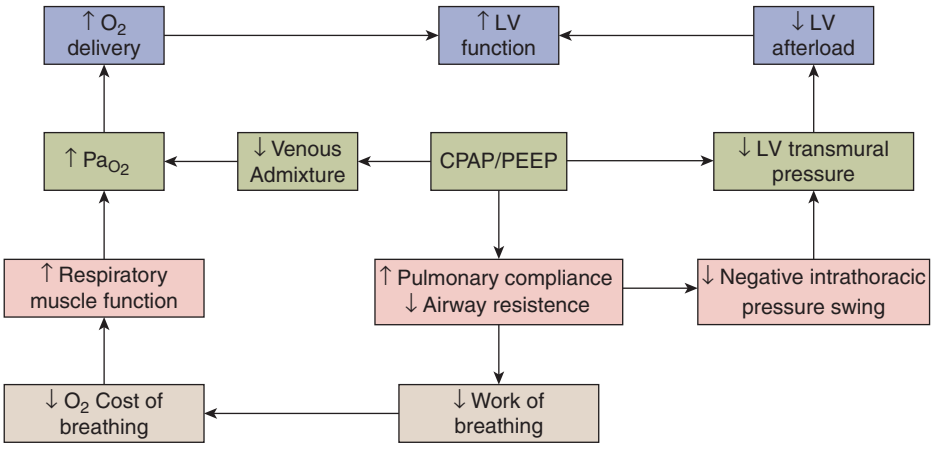

FIGURE 10-10 Cardiopulmonary effects of CPAP in cardiogenic pulmonary edema. By improving pulmonary mechanics, CPAP reduces negative swings in intrathoracic pressure and left-ventricular afterload. By improving gas exchange CPAP increases oxygen delivery to the heart and the respiratory muscle. See text for further explanation. *LV*, left ventricle; O_2, oxygen; Pa_{O_2}, partial pressure of arterial oxygen.

are conflicting. Discrepancies are related to differences in experimental design, such as diverse subjects, trial duration, type and severity of underlying disorder, volemic state, use of drugs and anesthetics (which commonly cause sympathetic depression), and level of PEEP. The decrease in urinary output caused by PEEP has been attributed to multiple factors, such as fall in cardiac output[54,477,491] and renal blood flow,[477,479,487,491,495] reduced intravascular volume,[54] reflex sympathetic nerve activation,[497] and altered release of hormones including catecholamines,[476] renin–angiotensin–aldosterone system,[476,488,498–500] antidiuretic hormone,[476,488] and atrial natriuretic factor.[485,486,488–490,493]

In dogs receiving a constant fluid infusion, Berry et al[55] observed that the time needed for urinary output to approximate the rate of fluid infusion was 20, 27, and 46 hours during spontaneous breathing, positive-pressure ventilation and positive-pressure ventilation plus PEEP 10 cm H_2O, respectively. Priebe et al[54] found that renal impairment caused by PEEP 10 cm H_2O in anesthetized dogs primarily resulted from a reduction in intravascular volume. In swine, Venus et al[476] found that the addition of PEEP to positive-pressure ventilation caused a fall in cardiac and urinary output, associated with increase in plasma antidiuretic hormone, renin, epinephrine, and norepinephrine in normovolemic animals, but not in animals that received volume expansion through crystalloids. In six neurologic patients with intact cardiopulmonary and renal function who were receiving positive-pressure ventilation plus PEEP 15 cm H_2O, an increase in lower body pressure via military antishock trousers improved systemic and renal hemodynamics and decreased plasma norepinephrine, with no change in total blood volume.[499] Urinary output and sodium excretion did not improve. The authors concluded that increased plasma renin and sympathetic activation were the main determinants of renal impairment with PEEP.[499]

Annat et al[477] evaluated the short-term effects of PEEP 10 cm H_2O in normovolemic patients without cardiac and renal abnormalities and little or no respiratory failure who were receiving positive-pressure ventilation. PEEP decreased urinary output by 34%, renal blood flow by 32%, and sodium excretion by 33%; the associated drop in cardiac output was 15%.[477] PEEP also increased urinary antidiuretic hormone and plasma renin and aldosterone.[477] In a similar setting, Payen et al[491] found that PEEP 15 cm H_2O reduced urinary output (55%) and fractional sodium excretion (39%); cardiac index fell by 21%. Plasma antidiuretic hormone did not vary, and norepinephrine increased.[491]

PEEP increases sympathetic activity.[501] Nevertheless, the observation by Fewell et al[494] that the effects of PEEP on renal function are mediated by sympathetic activity has not been confirmed.[481,492] PEEP decreases plasma atrial natriuretic factor.[478,485,486,488,493] This may contribute to the reduction in urinary output and sodium excretion, probably as a result of the reduced atrial transmural pressure consequent to the raised intrathoracic pressure.[485]

In summary, PEEP may alter renal function by reducing cardiac output and renal blood flow to an extent that depends on the volemic state and on the amount of applied pressure, although other mechanisms, including several hormones, may play a role.

EFFECTS ON SPLANCHNIC CIRCULATION AND OXYGENATION

PEEP decreases splanchnic blood flow[43,57,58,502–504] and causes hepatic congestion.[503] The reduction in splanchnic blood flow is consequent to a fall in cardiac output secondary to impaired central hemodynamic[43,57,58,502–504]; it is less pronounced when cardiac output is maintained either by expanding blood volume[57,58] or inotropic drugs.[504] In hemodynamically stable patients with ARDS, Kiefer et al[505] found that PEEP 13 cm H_2O (5 cm H_2O increment above the preset values), did not decrease cardiac index

or splanchnic blood flow and metabolism, suggesting that PEEP does not affect splanchnic blood flow. Other factors, however, such as hepatic outflow resistance, may play a role.[58,506] In swine, Brienza et al[506] found that PEEP 15 cm H_2O reduced portal vein flow through an increase in liver venous resistance; the authors postulated a direct compressive effect caused by diaphragmatic descent on the liver.

Sha et al[502] applied increasing PEEP (up to 20 cm H_2O) and found proportional decreases in hepatic blood flow. Because the rate of decrease in hepatic O_2 delivery exceeded that of cardiac output and hepatic blood flow, the authors concluded that hepatic O_2 delivery was reduced primarily because of the drop in portal venous O_2 content.[502] Aneman et al[507] evaluated the impact of PEEP 10 cm H_2O on mesenteric and hepatic blood flow in patients under general anesthesia (during elective surgery for gastric or pancreatic neoplasm). Neither arterial pressure nor arterial, portal, and hepatic venous norepinephrine were significantly affected by PEEP.[507] A decrease in portal blood flow was associated with a rise in mesenteric vascular resistance; conversely, an increase in hepatic arterial flow was associated with a drop in hepatic arterial resistance.[507] Mesenteric O_2 delivery was reduced and hepatic O_2 delivery remained unchanged.[507] Mesenteric and hepatic $\dot{V}O_2$ did not significantly vary with PEEP.[507] In similar patients, Berendes et al[43] found that hepatic venous lactate did not change with PEEP up to 15 cm H_2O, and concluded that a critical reduction in splanchnic oxygenation did not occur.

In spontaneously breathing normal subjects, Fournell et al[508] reported that CPAP levels up to 10 cm H_2O progressively altered gastric mucosal microvascular O_2 saturation, as assessed by reflectance spectrophotometry. Lehtipalo et al[44] found that PEEP 10 cm H_2O had little effect on intestinal perfusion pressure; mesenteric blood flow and oxygenation were maintained until the intestinal perfusion pressure exceeded 33 mm Hg. In patients with septic shock, Träger et al[509] increased PEEP up to 15 cm H_2O. PEEP decreased cardiac index and hepatic venous O_2 saturation.[509] Hepatic metabolic performance, assessed by glucose production, fell at each PEEP level in patients who did not survive, whereas it decreased only at the highest PEEP among survivors.[509] In 141 unselected critically ill patients, PEEP greater than 5 cm H_2O during mechanical ventilation was found to be a risk factor for liver dysfunction, as defined by serum bilirubin equal to or greater than 2 mg/dL for at least 48 hours.[510]

In sixty-five patients who underwent liver transplantation, Saner et al found in the immediate postoperative period that application of PEEP up to 10 cm H_2O did not affect venous liver outflow, portal vein and hepatic artery flow, and systemic hemodynamics.[511] In a retrospective observation study, Kocabayoglu et al reviewed the records of 50 patients who underwent mechanical ventilation for more than 7 days because of pulmonary complications following liver transplantation and found that PEEP equal to or greater than 10 cm H_2O did not harm liver-graft function.[512]

In summary, PEEP reduces hepatic and splanchnic blood flow when determining a drop in cardiac output, although other factors, such as regional outflow resistance or derangements in microcirculation consequent to sepsis, are likely to play a role.

EFFECTS ON INTRACRANIAL PRESSURE AND CEREBRAL PERFUSION

High intracranial pressure (ICP) and reduced cerebral perfusion pressure (the difference between mean arterial pressure and ICP) are common in several acute neurologic and neurosurgical intensive care unit patients, particularly those who have focal or generalized cerebral edema. Hypoxemic respiratory failure secondary to ARDS is a fearful complication in these patients leading to use of PEEP.[513]

ICP may be altered by PEEP through a rise in right-atrial pressure, which increases superior vena cava pressure and hence reduces cerebral venous return.[53,514,515] The effects of PEEP on ICP depend on the amount of intracranial compression, and are of little importance when cerebral compliance is not altered.[52] In a study evaluating twenty-five head-injured patients, Apuzzo et al[52] found that PEEP caused an increase in ICP in only twelve patients who had low cerebral compliance, and reduced cerebral perfusion pressure below 60 mm Hg in only six of the twelve patients.[52] In normal healthy volunteers, Hormann et al[516] found that alterations in ICP and cerebral perfusion pressure produced by CPAP 12 cm H_2O were slight and not of clinical relevance. Body position also affects the impact of PEEP on ICP. PEEP raises ICP through an increase in the downstream venous pressure; thus, elevating the head above the chest should lessen the transmission of intrathoracic pressure to the venous sinuses and mitigate the effects of PEEP on ICP. In supine anesthetized patients undergoing posterior fossa surgery, Lodrini et al[517] found that PEEP up to15 cm H_2O caused proportional increases in central venous pressure and ICP; in the sitting position, PEEP also increased central venous pressure, but ICP changed little in most of the patients.

Muench et al found that increases in PEEP up to 25 cm H_2O in healthy pigs did not produce any adverse effect on ICP, cerebral blood flow, or tissue oxygenation. On the contrary, in patients with subarachnoid hemorrhage, reduction in mean arterial pressure consequent to application of PEEP up to 20 cm H_2O caused a significant decrease in cerebral blood flow attributable to the altered cerebrovascular autoregulation.[518] Caricato et al studied the effects of increasing PEEP up to 12 cm H_2O in twenty-one patients with severe head injury or subarachnoid hemorrhage and who were receiving mechanical ventilation; static compliance of the respiratory system was normal in thirteen patients and reduced in the other eight.[519] The authors found that PEEP caused a decrease in mean arterial pressure and cerebral perfusion pressure in the first subgroup of thirteen patients, whereas it did not produce any significant change in the eight patients

with reduced respiratory compliance.[519] In twelve severely brain-injured patients with ARDS and high ICP, Mascia et al randomly applied 5 and 10 cm H_2O of PEEP; recruited volume and elastance were used to classify patients as recruiters ($n = 6$) and nonrecruiters ($n = 6$).[520] Pa_{CO_2}, ICP, Doppler flow velocity, and jugular saturation increased significantly with higher PEEP in the nonrecruiters, but did not change in the recruiters.[520]

Several studies in neurologic, neurosurgical, or brain-injured patients found that judicious use of PEEP was not detrimental.[521–526] As PEEP may affect cerebral circulation, adequate monitoring of cerebral and respiratory function should be used to titrate its application.[527]

EFFECTS ON BRONCHIAL CIRCULATION AND THORACIC LYMPH DRAINAGE

By increasing intrathoracic pressure, PEEP alters bronchial blood flow[528–530] and thoracic lymph drainage, which could affect the process of lung repair and edema removal.[531] Blood from the bronchial vessels is drained to the right side of the heart via the azygos and bronchial veins and to the left atrium through anastomoses between systemic and pulmonary circulation. In ventilated open chest dogs, Baile et al[528] investigated the effect of increasing PEEP on systemic to pulmonary (anastomotic) flow (Qbra) and on bronchial blood flow (Qbr), which was further partitioned into tracheal, bronchial, and parenchymal fractions. Bronchial and parenchymal, but not tracheal, fractions of Qbr decreased with PEEP.[528] Qbr and Qbra did not differ at PEEP 3 and 10 cm H_2O.[528] At PEEP 15 cm H_2O, Qbr exceeded Qbra, indicating a decrease in the anastomotic drainage.[528] In patients undergoing cardiopulmonary bypass, Agostoni et al[530] observed that an increase in alveolar pressure of approximately 10 cm H_2O decreased Qbra by 40%.

Local release of mediators, rise in pulmonary vascular resistance, and reflex bronchial vasoconstriction may explain Qbra reduction.[529] To assess the influence of vagal reflexes on PEEP-mediated reduction in Qbra, Lakshminarayan et al[532] isolated and perfused the left lower lobe in open chest dogs, and found that increasing PEEP from 5 to 15 cm H_2O halved Qbra. At PEEP 5 cm H_2O, bilateral cervical vagal cooling decreased Qbra.[532] An increase of PEEP to 15 cm H_2O did not further diminish it, suggesting that the effect of PEEP on Qbra might be partly vagally mediated.[532]

PEEP may obstruct lymph drainage from the thoracic duct into the jugular vein.[531,533] By altering thoracic lymph return, PEEP might affect edema removal from the lungs.[531]

INTRINSIC POSITIVE END-EXPIRATORY PRESSURE

During passive exhalation, airflow is driven by the difference between alveolar and airway opening pressures and opposed by expiratory resistance. In absence of expiratory muscle activity and externally applied PEEP, alveolar pressure corresponds to the elastic recoil of the respiratory system for a given V_T: alveolar pressure is thus equal to respiratory system elastance/V_T or V_T/respiratory system compliance. The product of respiratory system compliance and airway expiratory resistance is the expiratory time constant (τ). During expiration, $V = V_T\, e^{-(t/\tau)}$ where V is the amount of V_T not yet exhaled (i.e., above FRC), t is the time elapsed from the onset of expiration, and e is the base of natural logarithms (2.7189). When $t = \tau$, V is roughly 37% (1/2.7189) of V_T. It takes five τ to almost entirely (99%) exhale V_T.

In healthy adult subjects, τ is approximately 0.3 second. Therefore, the time required to exhale V_T is approximately 1.5 seconds. Assuming a respiratory rate of 12 breaths/min and an inspiratory duty cycle (T_I/T_{TOT}) of 40%, expiratory time (T_E) is 3 seconds, which considerably exceeds the time necessary for the lungs to deflate to FRC. If either breathing frequency or T_I/T_{TOT} increase, T_E diminishes. Any condition causing an increase in expiratory resistance, including an artificial airway,[534] or a loss in elastic recoil prolongs τ and thus the time required for complete V_T exhalation. When shortened T_E and/or prolonged τ impede a complete exhalation to FRC, dynamic hyperinflation occurs. End-expiratory relaxation volume will exceed FRC to an extent that is proportional to τ and V_T and inversely related to T_E (Fig. 10-11).

Expiratory flow may also be limited in the course of V_T exhalation because the airways collapse at a choke point where intrathoracic pressure equals intrabronchial pressure (so-called equal pressure point). The airways located downstream of the equal pressure point are then compressed because intrathoracic pressure exceeds the

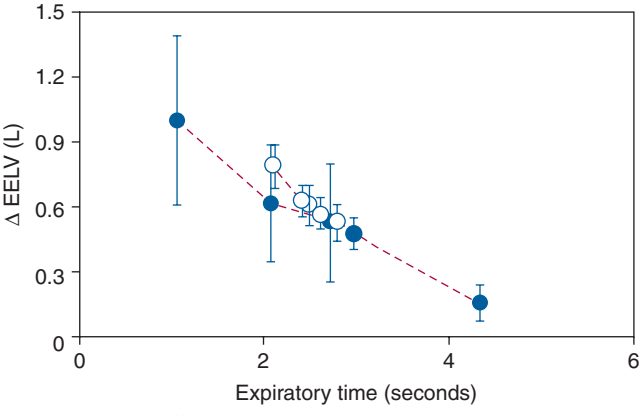

FIGURE 10-11 Effects of varying expiratory time on end-expiratory trapped volume in patient with airway obstruction. ΔEELV indicates end-expiratory lung volume above functional residual capacity. The shorter the expiratory time, the greater the amount of end-expiratory trapped volume. Data are expressed as mean ± standard deviation (*closed circles*) and mean ± standard error (*open circles*), and taken from references 237 and 359, respectively. Tidal volume was always 1 L in reference 237, and averaged 0.576 L (± 0.026) in reference 359. In reference 359, changes in expiratory time were obtained by manipulating the ventilator preset inspiratory time, while leaving respiratory rate (and hence minute ventilation) unmodified. In reference 237, inspiratory duty cycle remained unchanged and expiratory time was changed by modifying respiratory rate; accordingly minute ventilation also varied.

intrabronchial pressure. Thus, alveolar pressure–airway opening pressure no longer represents the pressure driving expiratory flow. Expiratory flow limitation is very common in patients with an acute exacerbation of COPD.[238,535–538] It has also been reported in patients with asthma,[539,540] obesity,[271,541] and ARDS.[183,184,535,542]

Regardless the underlying mechanism, after a few breaths a steady state is achieved that depends on the variations in the different components of respiratory mechanics. For a certain trapped volume, the amount of PEEPi is determined by the corresponding respiratory system compliance.

Measurement of Intrinsic Positive End-Expiratory Pressure

PEEPi can be detected qualitatively by observing the flow-time curve, available on most ventilators. In absence of PEEPi, expiratory flow is zero before the onset of the subsequent inspiration (Fig. 10-12A). The persistence of expiratory flow at end-expiration indicates the presence of PEEPi, during either mechanical ventilation (Fig. 10-12 B) or spontaneous breathing (Fig. 10-12C).

Because the ventilator built-in pressure gauge is open to atmosphere, PEEPi cannot be detected by simply inspecting airway pressure. During controlled ventilation, PEEPi can be measured by occluding the airway opening at end-expiration for a few seconds[59,543] (see Fig. 10-4), the end-expiratory occlusion maneuver. This value is static PEEPi (PEEPi,stat). Unless some alveolar units are not at all communicating with the central airways (because the corresponding peripheral airways are completely occluded),[544] PEEPi,stat represents the average pressure in the different lung regions.[9,238,545–547] A second approach is to measure the difference between preset PEEP and airway pressure at the onset of inspiratory flow[260,546,547]; this value is dynamic PEEPi (PEEPi,dyn). PEEPi,dyn can be considered as the lowest regional end-expiratory alveolar pressure that has to be overcome to begin inspiratory flow.[9,238,545–547] PEEPi,dyn and PEEPi,stat approximate each other, in animals[546] and in human subjects[547] in the absence of severe airway disorders, when PEEPi is consequent to T_E shortening and/or increasing minute ventilation (V_E). In animals receiving high doses of aerosolized methacoline[546] and patients affected by severe airway obstruction,[547] PEEPi,dyn is considerably lower than PEEPi,stat. A low ratio of PEEPi,dyn to PEEPi,stat suggests time constant inequalities within the lung and high lung tissue viscoelastic pressure losses.[183,546–549]

When the inspiratory muscles are contracting, assessing PEEPi is more complex. When inspiration is active and expiration relaxed, PEEPi,dyn can be measured with a balloon-tipped esophageal catheter.[2,545,550,551] PEEPi,dyn equals the difference in esophageal (pleural) pressure between the onset of negative deflection (indicating the start of the inspiratory effort), and the pressure at the transition between expiratory and inspiratory flow

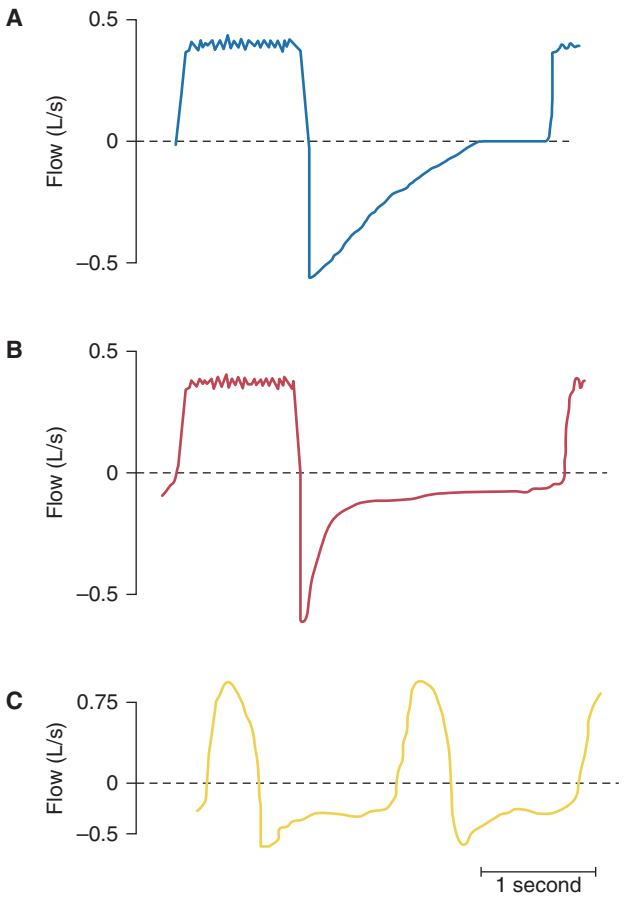

FIGURE 10-12 Flow-time tracings during controlled ventilation in a normal anesthetized subject (**A**), in a patient with severe COPD during controlled ventilation (**B**) and during spontaneous breathing (**C**). In the normal subject (A), expiratory flow reaches zero before expiration ends. In the patient with COPD, expiratory flow remains below zero value before the subsequent inspiration, denoting dynamic hyperinflation, during both controlled ventilation and spontaneous breathing.

(Fig. 10-13).[2,545,551] When the expiratory muscles are contracting, which is common in flow-limited patients,[552–555] especially during partial ventilator support,[2,554,556,557] the pressure developed in the abdomen is transmitted through the relaxed diaphragm and raises intrathoracic pressure. Consequently, assessing PEEPi via esophageal pressure will overestimate the true end-expiratory elastic recoil pressure.[2,552–558] With a second balloon-tipped catheter in the stomach, it is possible to measure, and correct for, the amount of intrathoracic pressure rise caused by expiratory muscles contraction[2,554,556]; briefly, the expiratory rise in gastric pressure is subtracted from the esophageal pressure at the onset of the subsequent inspiration (Fig. 10-14).[554,556] Another method is to subtract the rise in gastric pressure, during an end-expiratory occlusion, from airway pressure.[559] Partitioning the rise in intrathoracic pressure from recording of airway, esophageal and gastric pressures is complex, and infrequently performed in the clinical setting.

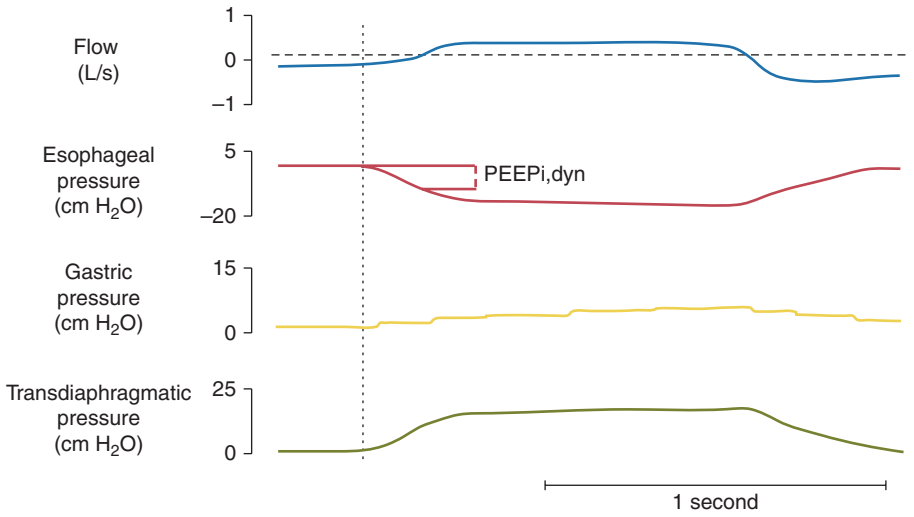

FIGURE 10-13 Measurement of dynamic intrinsic PEEP (PEEPi,dyn) in a spontaneously breathing patient without expiratory muscle activity. The *dashed horizontal line* indicates zero flow. The *dotted vertical line* indicates the onset of the inspiratory effort. The *solid vertical line* indicates the start of inspiratory flow. Gastric pressure rises during inspiration and descends during expiration, indicating that expiratory muscles were not active. PEEPi,dyn is the difference in esophageal pressure between onset of inspiratory effort and start of inspiratory flow.

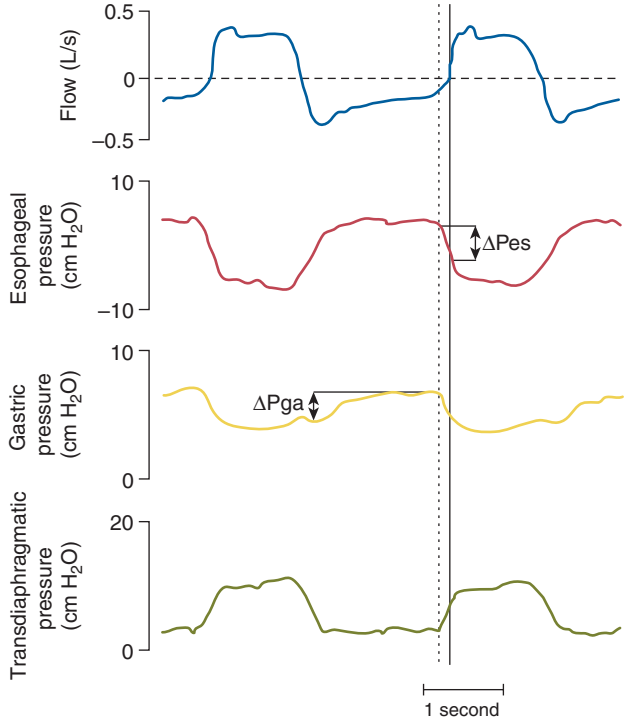

FIGURE 10-14 Measurement of dynamic intrinsic PEEP (PEEPi,dyn) in a spontaneously breathing patient with expiratory muscle activity. The *dashed horizontal line* indicates zero flow. The *dotted vertical line* indicates onset of inspiratory effort. The *solid vertical line* indicates the start of inspiratory flow. Unlike in Figure 10-13, gastric pressure rises during expiration (ΔPga) and descends at the following inspiration, indicating expiratory muscle recruitment. ΔPga must be subtracted from the difference in esophageal pressure between onset of inspiratory effort and start of inspiratory flow (ΔPes) to determine PEEPi,dyn.

Physiologic Effects of Intrinsic Positive End-Expiratory Pressure

During volume-targeted controlled ventilation PEEPi does not affect V_T, whereas it elevates peak airway pressure, which is a dependent variable (i.e., it varies depending on the impedance of the respiratory system) (Fig. 10-15A). Conversely, during pressure-targeted controlled ventilation, the independent variable is the preset positive pressure applied to the airway during inspiration, the presence of PEEPi decreases the actual lung distending pressure and therefore V_T (Fig. 10-15B).

PEEPi resembles in several respects external PEEP. In patients with hypoxemic ARF consequent to ARDS or cardiogenic pulmonary edema, an increase in end-expiratory lung volume, produced by T_E shortening, secondary to tachypnea or inverse-ratio ventilation, can decrease intrapulmonary shunt as much as can external PEEP.[560] In patients without COPD, Brandolese et al[192] found that external PEEP produced more consistent increases in Pa_{O_2} than did an equivalent level of PEEPi. The authors attributed the less-favorable impact of PEEPi on Pa_{O_2} to less-homogeneous gas distribution between different lung units.[192] PEEPi decreases cardiac output[59,192,238,560] and blood pressure[59,238] to an extent similar to that produced by external PEEP for the same increase in lung volume.[560] Connery et al[561] reported fatal cardiac arrest and life-threatening hypotension during manual ventilation with large V_T and high respiratory frequencies in two patients with severe COPD. By increasing alveolar pressure, PEEPi may also cause barotrauma.[562]

In spontaneously breathing patients, PEEPi poses a threshold load that has to be overcome before inspiratory flow can be initiated;[9,545,550,563] this load is perceived as inspiratory difficulty.[564] With any mode of partial ventilator

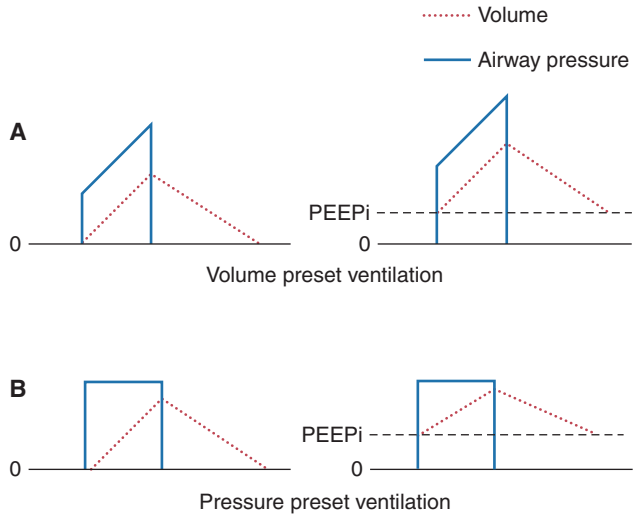

FIGURE 10-15 Simulation of the effects of PEEPi on volume-targeted (**A**) and pressure-targeted (**B**) controlled ventilation. Volume and airway pressure are indicated by *dotted* and *solid lines*, respectively. In the *left panels*, when PEEPi is absent, tidal volume is the same for both modes. In the *upper* (A) *right panel*, during volume-targeted ventilation, PEEPi cause a rise in airway pressure, while preset tidal volume is unchanged. During pressure-targeted ventilation, *lower* (B) *right panel*, preset pressure does not vary, and, consequently, tidal volume falls.

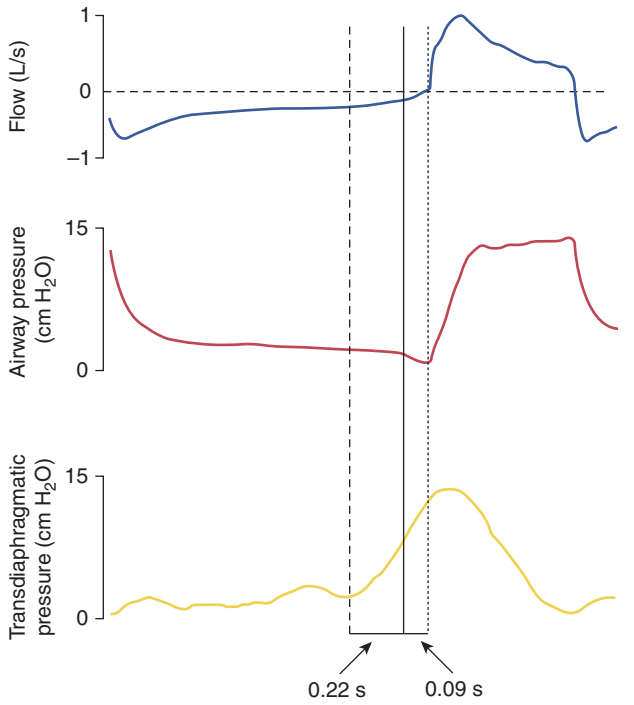

FIGURE 10-16 Effect of intrinsic PEEP (PEEPi) on ventilator triggering. The *dashed horizontal line* indicates zero flow. The *dashed vertical line* on the left indicates the onset of the inspiratory effort. The *dotted vertical line* on the right corresponds to the start of inspiratory flow. The *solid vertical line* indicates the point at which the ventilator is triggered and the mechanical assistance initiated. The amount of effort spent in overcoming PEEPi corresponds to the difference in transdiaphragmatic pressure between the points crossed by the *dashed* and *solid lines*. PEEPi increases the magnitude of the inspiratory effort and remarkably lengthens the effort-to-assist delay.

support, this threshold must be overcome before the ventilator can be triggered (Fig. 10-16).[2,61,63,551,565–568] Inspiratory efforts that are not intense enough to overcome PEEPi fail to trigger the ventilator,[63,64,569–571] a phenomenon referred to as *wasted* or *ineffective inspiratory efforts* (Fig. 10-17). Wasted efforts occur with all triggered modes,[570] and are more frequent at higher ventilator assistance[63,64,570] because of higher PEEPi, consequent to increased lung volume,[63,64,570] and diminished respiratory drive.[570]

Acute hyperinflation impairs the force-generating capacity of the diaphragm by moving the diaphragm to an inefficient part of its force-length relationship[572–574] and increasing the O_2 cost of breathing.[575] In healthy volunteers, Beck at al[576] showed that greater diaphragmatic activation to generate a certain amount of pressure increased with increasing lung volume, and pressure generated by maximal diaphragmatic activation decreased with increasing lung volume. In spontaneously breathing dogs, Kawagoe et al[577] found that a threshold load associated with PEEPi produced pulmonary artery hypertension and decreases in cardiac output and blood flow to the liver, pancreas, sternomastoid and parasternal muscles, while little change in blood flow to the diaphragm.[577] An equivalent resistive load increased diaphragmatic blood flow, without changes in cardiac output or regional blood flow.[577] Both loads produced noncompensated respiratory acidosis, but the severity was greater for the threshold load.[577] An acute inspiratory threshold load causes a greater diaphragmatic sarcomere disruption in patients with COPD than in patients without lung disease[578]; hyperinflation explains approximately 40% of the injury.[578]

The complex interactions of dynamic hyperinflation and PEEPi on preload were reviewed by Ranieri et al.[579] During spontaneous breathing or triggered ventilation, venous return is decreased by the higher end-expiratory lung volume and intrathoracic pressure or increased by the larger negative inspiratory swings in intrathoracic pressure, with latter dominating.[579]

Clinical Consequences of Intrinsic Positive End-Expiratory Pressure

The extra load imposed on the respiratory muscles by PEEPi may be large (Fig. 10-18) and have relevant clinical consequences. In patients with COPD in ARF, Coussa et al[580] found that work of breathing was increased because of increased resistance and PEEPi. PEEPi accounted for more than 30% of the overall workload (Fig. 10-18A). In a ventilator-dependent patients with COPD, Appendini et al[64] found that the effort to overcome PEEPi accounted for more than 40% of overall inspiratory effort[64] (Fig. 10-18B).

Jubran and Tobin[581] studied thirty-one patients with COPD undergoing a T-tube trial, seventeen of whom

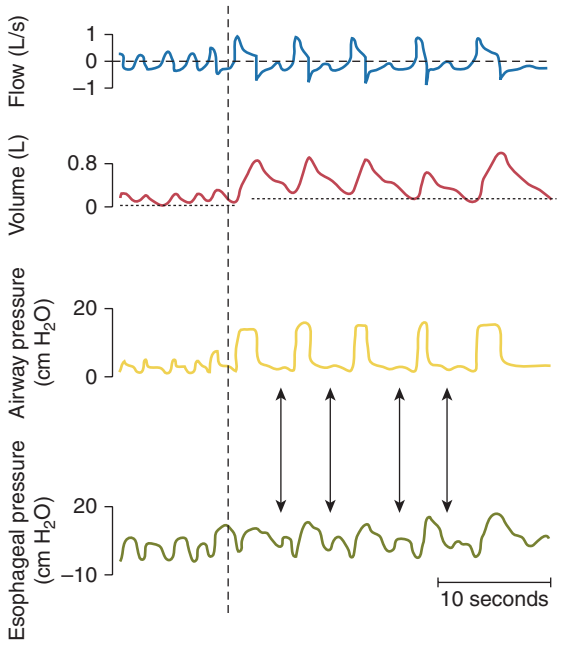

FIGURE 10-17 Ineffective or wasted inspiratory efforts. The *dashed horizontal line* on the flow tracing indicates zero. The *dashed vertical line* indicates the onset of the ventilator assistance. To the left of the dashed line, the patient is spontaneously breathing with the ventilator set in CPAP mode. The breathing pattern is rapid and shallow. Initiation of pressure support increases tidal volume and decreases respiratory rate, as assessed on the flow and airway pressure tracings. The respiratory rate, assessed by swings in esophageal pressure is higher. The *arrows* show that half the inspiratory efforts fails to trigger the ventilator. The *dotted horizontal lines* on the volume tracing indicate that end-expiratory lung volume increased after institution of pressure support (dynamic hyperinflation).

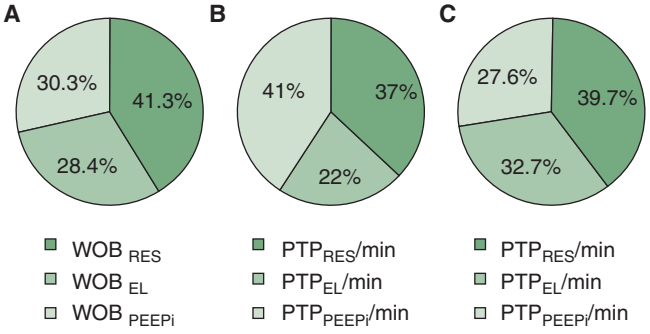

FIGURE 10-18 Fractions of the respiratory load in ventilator-dependent patients with COPD. **A.** Elastic (*EL*), resistive (*RES*), and *PEEPi* fractions of work of breathing (*WOB*) in sedated and paralyzed patients with COPD in acute respiratory failure while receiving controlled ventilation. **B.** Elastic (*EL*), resistive (*RES*), and *PEEPi* components of inspiratory effort, assessed as esophageal pressure-time product (*PTP*), during a brief period of spontaneous breathing in patients with COPD who could not be weaned. **C.** Same measurement as in *B* in patients with COPD who failed a T-tube trial. Despite the different settings, PEEPi accounted for a considerable fraction of inspiratory load.

failed and fourteen were successfully extubated. At the onset of the trial, PEEPi was higher in the failure group than in the success group.[581] Between the start and end of the trial, the fraction of inspiratory effort caused by PEEPi more than doubled in the failure group, while it did not change in the success group.[581]

In thirty patients who failed an initial weaning trial but who later succeeded, Vassilakopoulos et al[582] found that dynamic hyperinflation and PEEPi were higher at the time of weaning failure.

Impact of External Positive End-Expiratory Pressure on Dynamic Hyperinflation and Intrinsic Positive End-Expiratory Pressure

Depending on the mechanisms of dynamic hyperinflation and PEEPi, external PEEP can have different effects, as elegantly pointed out by Marini (Fig. 10-19).[583] When PEEPi is not caused by flow limitation, external PEEP is entirely transmitted to the distal airway, producing a concomitant rise in alveolar pressure (Fig. 10-19B). In six patients with acute asthma or a COPD exacerbation, Tuxen et al[237] increased dynamic hyperinflation and PEEPi by increasing

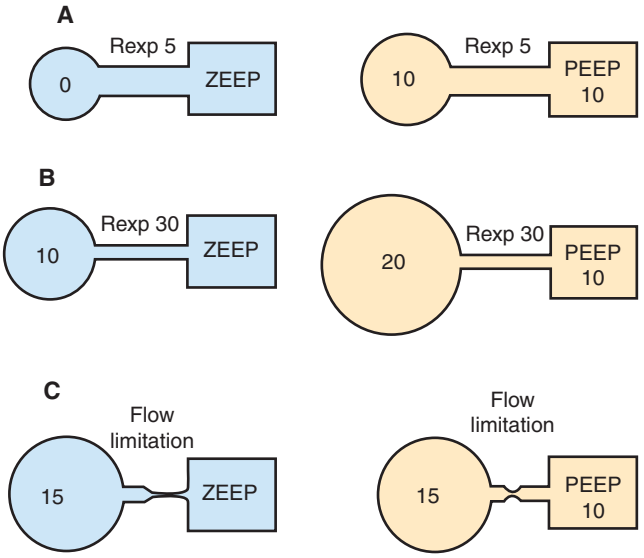

FIGURE 10-19 Schematic of the effects of PEEP on alveolar pressure in normal conditions (A), high airway resistance but no expiratory flow limitation (B), and expiratory flow limitation and dynamic airway compression (C). The *circles* represent the alveoli, the *rectangles* represent the ventilator, and the *tubes* represent the bronchi. *PEEP*, Positive end-expiratory pressure expressed in cm H_2O; *Rexp*, expiratory resistance expressed in cm H_2O/L/s; *ZEEP*, zero positive end-expiratory pressure. **A.** At ZEEP (*left panel*), the alveolar pressure falls to zero. Applied PEEP (*right panel*) is entirely transmitted to the alveoli. **B.** At ZEEP (*left panel*), the high expiratory resistance causes alveolar pressure to remain positive at end-expiration. Applied PEEP (*right panel*) is entirely transmitted to the alveoli. **C.** At ZEEP (*left panel*), the alveolar pressure is positive. Applied PEEP does not exceed the critical pressure at the choke point and does not affect alveolar pressure.

V_E from 10 L/min to 16 L/min and 22 L/min. Increasing levels of PEEP up to 15 cm H_2O produced increases in end-expiratory lung volume and intrathoracic pressure, accompanied by a parallel hemodynamic deterioration.[237] At the lowest V_E, trapped volume was small, suggesting little if any flow limitation.[237]

When flow limitation and dynamic airway compression are present, PEEP is not transmitted to the distal airway and does not increase alveolar pressure as long as it does not exceed the critical pressure corresponding to the choke point (see Fig. 10-19C).[583] The waterfall analogy helps in understanding this concept. The equal-pressure point is viewed as the crest of a waterfall, and the airway segment between the choke point and the airway opening as the downstream water.[584,585] Increasing the level of downstream water (external PEEP) does not alter upstream water flow (air flow), as long as it does not exceed the crest (critical pressure at the choke point).[585] In flow-limited patients with COPD who had PEEPi 10 cm H_2O and trapped volume of 1 L, Ranieri et al[238] applied PEEP 5, 10, and 15 cm H_2O. Up to PEEP 10 cm H_2O, changes in peak and plateau airway pressure, end-expiratory lung volume, and total PEEP (i.e., PEEPi + external PEEP) were minimal; hemodynamic impairment was absent. PEEP 15 cm H_2O increased peak and plateau airway pressure, trapped volume and total PEEP, with worsening of hemodynamics.[238] Changes in end-expiratory lung volume and cardiac index started to occur when external PEEP matched approximately 85% of PEEPi,stat.[238] In eight patients with severe airway obstruction undergoing controlled mechanical ventilation, Caramez et al evaluated the application of a PEEP level that exceeded by 50% the PEEPi value; in five patients, such PEEP levels produced a reduction in airway plateau pressure and total PEEP.[586] In flow-limited patients with COPD receiving a triggered ventilation, Appendini et al found that PEEP slightly lower than PEEPi,dyn did not cause further hyperinflation.[2]

Flow limitation associated with small airway closure and PEEPi may be present in ventilated patients with ARDS.[183] In patients with ARDS who have flow limitation and PEEPi, Koutsoukou et al[184] found that PEEP 10 cm H_2O, produced a small increase in total PEEP and alveolar recruitment, but a significant increase in Pa_{O_2}; the latter was attributed to improved regional PEEPi in homogeneity. In another group of patients who did not exhibit flow limitation and had little PEEPi, PEEP 10 cm H_2O increased total PEEP and produced greater alveolar recruitment, which was the chief reason for an increase in Pa_{O_2}.[184] Analogous results were reported by Vieillard-Baron et al,[342] who found flow limitation and PEEPi in 73% of patients with ARDS receiving volume-controlled ventilation.

An increase in respiratory rate is commonly used during lung-protective ventilation in patients with ARDS to limit the hypercapnia consequent to V_T reduction. de Durante et al reported the occurrence PEEPi when patients with ARDS were ventilated with the low-V_T protocol of the ARDS Network (6 mL/kg) as opposed to a traditional V_T (12 mL/kg); respiratory rate was adjusted to achieve a V_E that maintained arterial pH between 7.30 and 7.45 (rate: 34 ± 1 breaths/min) during the low-V_T protocol, and rate was decreased to maintain the same V_E (rate: 14 ± 1 breaths/min) during the traditional-V_T protocol.[587] PEEPi averaged 5.8 cm H_2O with low V_T and 1.4 cm H_2O with a traditional V_T.[587] Analogous results were obtained by Richard et al[588] and, though to a lesser extent, by Hough et al.[589] Preliminary data indicate that PEEPi is reduced when higher PEEP levels are applied, confirming that flow limitation occurs also in ARDS patients.[590]

In actively breathing patients, the threshold load imposed by PEEPi may be offset by applying CPAP[9,60,591,592] or external PEEP.[2,61,63,566] If excessive or improperly applied,[583] external PEEP can worsen hyperinflation[238,593,594] placing the diaphragm at an additional disadvantage[573,574,576] and causing further hemodynamic impairment.[238,593]

USE OF POSITIVE END-EXPIRATORY PRESSURE IN THE CLINICAL SETTING

Acute Respiratory Distress Syndrome

The rationale for PEEP in patients with ARDS is to increase the amount of aerated lung volume,[197,200,221] improve respiratory mechanics,[197,200,338] reduce intrapulmonary shunt[140,595] and ameliorate gas exchange,[1,18,76,197,200] stabilize unsteady lung units,[596] and reduce the risk of VILI.[338,393] From its introduction almost fifty years ago,[1] PEEP remains a cornerstone in management of patients with ARDS.[597] It is easy to see no randomized trial evaluated ventilator strategies without PEEP in patients with ARDS, except in the very early phase.[151,598] A few studies have assessed the effect of PEEP on clinical outcome of patients with ARDS (Table 10-2).[6,599–604] One early study reported that high PEEP levels did not improve survival and caused more adverse events, when compared to patients treated with low PEEP.[599]

In the last decade, research has focused on ventilator strategies that protect the lung from VILI. These investigations have shown that ventilator settings may per se affect outcome.[605]

Three randomized, controlled trials suggest that high levels of PEEP (15 to 20 cm H_2O), used in the context of a lung-protective strategy, may improve both the physiologic[369] and clinical[6,604] outcome in patients with ARDS. Amato et al[6] found that low V_T combined with PEEP set 2 cm H_2O above the LIP (average: 16 cm H_2O) reduced mortality compared to a conventional approach where PEEP was titrated to optimize oxygenation (see Table 10-2). Ranieri et al[369] compared a strategy of high PEEP and low V_T, respectively based on LIP and UIP, against a conventional approach, where lower PEEP and higher V_T were targeted to normalize gas exchange (see Table 10-2). The control group exhibited more inflammatory mediators than the lung-protective group.[369] The control group also had a higher rate of organ failure and mortality and fewer ventilator-free days.[369,417] The occurrence

TABLE 10-2: RANDOMIZED CONTROLLED TRIALS EVALUATING THE EFFECT OF POSITIVE END-EXPIRATORY PRESSUREON CLINICAL AND PHYSIOLOGIC OUTCOMES

Reference	Population	Arm	No. of patients	Associated settings	PEEP setting	Mean PEEP (cm H_2O)	Outcomes
Carroll 1988 (599)	Surgical	Intervention	22	VT = 12 mL/kg PIP unlimited	Titrated to reduce shunt or to reach an oxygenation target	15	ICU mortality: 27%
		Control	28	VT = 12 mL/kg PIP unlimited	Minimal PEEP to reach an oxygenation target	4	ICU mortality: 4%
Amato 1998 (6)	Medical	Intervention	29	VT <6 mL/kg PIP <40 cm H_2O CPAP recruiting	2 cm H_2O > LIP (minimum 5 cm H_2O)	16	Mortality: 45% Barotrauma: 7%
		Control	24	VT = 12 mL/kg PIP unlimited	Titrated to P/F ratio (minimum 5 cm H_2O)	7	Mortality: 71% Barotrauma: 42%
Ranieri 1999 (369)	Medical-surgical	Intervention	18	VT for Pplat < UIP (or VT = 5 to 8 mL/kg)	2-3 cm H_2O > LIP (minimum 15 cm H_2O)	15	BAL/systemic levels of inflammatory mediators: ↓ Ventilator-free days: 12* Mortality: 38%* Organ failure score: unchanged
		Control	19	VT for Pa_{CO_2} 35 to 40 mm Hg Pplat < 35 cm H_2O	Titrated to SaO_2 (minimum 5 cm H_2O)	7	BAL/systemic levels of inflammatory mediators: ↑ Ventilator-free days: 4* Mortality: 58%* Organ failure score: increased (mainly renal)
Brower (ARDS Network) 2004 (601)	Medical-surgical	Intervention	276	VT = 6 mL/kg Pplat < 30 cm H_2O	Titrated to oxygenation (minimum 12 cm H_2O)	13†	Mortality: 25%‡ Unassisted breathing: 72% Barotrauma: 11% Days without organ failure: 16
		Control	273	VT = 6 mL/kg Pplat < 30 cm H2O	Titrated to oxygenation (minimum 5 cm H_2O)	8	Mortality: 28%‡ Unassisted breathing: 73% Barotrauma: 10% Days without organ failure: 16

Villar 2006 (604)	Medical-surgical	Intervention	50	VT = 5 to 8 mL/kg FI_{O_2} according to oxygenation	2 cm H_2O > LIP	14	ICU mortality: 32% Ventilator-free days: 11 Barotrauma: 2% New organ failures: 0.3
		Control	45	VT = 9 to 11mL/kg FI_{O_2} according to oxygenation	Titrated to oxygenation (minimum 5 cm H_2O)	9	ICU mortality: 53% Ventilator-free days: 6 Barotrauma: 4% New organ failures: 1.2
Meade (LOVS) 2008 (602)	Medical-surgical	Intervention	475	VT = 6 mL/kg Pplat <30 cm H_2O	Titrated to oxygenation (minimum 5 to 10 cm H_2O)	14†	Mortality: 36% Days of mechanical ventilation: 10 Barotrauma: 11% Refractory hypoxemia: 5%
		Control	508	VT = 6 mL/kg Pplat <30 cm H2O	Titrated to oxygenation (minimum 5 cm H_2O)	9	Mortality: 40% Days of mechanical ventilation: 10 Barotrauma: 9% Refractory hypoxemia: 10%
Mercat (ExPress) 2008 (603)	Medical-surgical	Intervention (increased recruitment)	385	VT = 6 mL/kg Pplat = 28 to 30 cm H_2O	Titrated to reach the plateau pressure target	14	Mortality: 35% Ventilator-free days: 7 Pneumothorax: 7% Organ failure-free days: 6 Rescue therapies: 19%
		Control (minimal distension)	382	VT = 6 mL/kg Pplat <30 cm H_2O	Titrated to oxygenation (5 to 9 cm H_2O)	7	Mortality: 39% Ventilator-free days: 3 Pneumothorax: 6% Organ failure-free days: 2 Rescue therapies: 35%

Abbreviations: *BAL*, Bronchoalveolar lavage; *CPAP*, continuous positive airway pressure; *LIP*, lower inflection point on the pressure-volume curve; *P/F*, ratio between arterial oxygen tension and fractional inspired oxygen; *PIP*, peak inspiratory pressure; *Pplat*, plateau pressure; SaO_2, arterial oxygen saturation; *VT*, tidal volume.

* Post hoc analysis; † after protocol amendment; ‡ after adjustment for differences in baseline covariates.

of PEEPi, consequent to high respiratory rate in the low V_T group, may have contributed[587,588] to the positive results in the ARDS Network trial that compared low and high V_T in patients with ARDS.[370] Villar et al compared a protective strategy, with PEEP set 2 cm H_2O above LIP (average: 14 cm H_2O) and low V_T (average: 7 mL/kg) to a conventional approach with PEEP set according to oxygenation (average: 9 cm H_2O) and higher V_T (average: 10 mL/kg).[604] Intensive care unit mortality, hospital mortality, and number of organ failures after randomization were lower, while the number of ventilator-free days at day 28 was greater in the protective-strategy group than in the conventional-strategy group. Of note, patients included in this study had more severe disease ($Pa_{O_2}/FI_{O_2} \leq 200$ with PEEP ≥5 cm H_2O) and persistent ARDS (criteria lasting 24 hours with standardized settings), than in previous studies (see Table 10-2).

Three randomized trials have compared the impact of different PEEP levels on clinical end points (see Table 10-2).[601–603] These trials randomized patients with ARDS to high or low PEEP levels to determine whether high PEEP, by enhancing lung recruitment, reduces VILI and improves outcome (see Table 10-2).[601–603] In the two arms of each trial, V_T was 6 mL/kg of predicted body weight and plateau pressure was less than 30 cm H_2O. In two studies, PEEP was titrated according to predefined combinations of PEEP and FI_{O_2}, to achieve an identical oxygenation goal (Pa_{O_2} 55 to 88 mm Hg or arterial oxyhemoglobin saturation [SpO_2] 88% to 95% and Pa_{O_2} 55 to 80 mm Hg or SpO_2 88% to 93%).[601,602] In the third trial, PEEP (and, consequently, plateau pressure) was set as low as possible (total PEEP between 5 and 9 cm H_2O), without falling below oxygenation targets (Pa_{O_2} 55 to 80 mm Hg or SpO_2 88% to 95%), in the low-PEEP group (minimal distension strategy); in the high-PEEP group (increased recruitment strategy), PEEP was kept as high as possible without increasing plateau pressure above 28 to 30 cm H_2O, regardless of its effect on oxygenation. The ARDS Network study Assessment of Low Tidal Volume and Elevated End-Expiratory Volume to Obviate Lung Injury (ALVEOLI) was interrupted after enrolment of 549 patients because no difference was detected in any predefined clinical outcome variable between the two groups (see Table 10-2).[601] Several methodological biases cast doubt on the conclusions.[606,607]

In the Lung Open Ventilation to Decrease Mortality in the Acute Respiratory Distress Syndrome (LOVS) trial, hospital mortality was not different between groups (36% and 40%, in the experimental and control groups, respectively). The higher PEEP group had better secondary end points related to hypoxemia, such as lower rates of refractory hypoxemia (5% vs. 10%), death with refractory hypoxemia (4% vs. 9%), and use of rescue therapies (5% vs. 9%).[602] The Comparison of Two Strategies for Setting Positive End-Expiratory Pressure in Acute Respiratory Distress Syndrome (ExPress Study) trial reported similar 28-day and hospital mortality in the two PEEP groups; ventilator-free days and organ failure-free days were higher, while the use of rescue therapy for severe hypoxemia was lower in the high-PEEP group as opposed to the low-PEEP group.[603] Interestingly, improvments in these secondary end points were more pronounced in the sicker ARDS patients than in the milder ones. Patients with more severe ARDS also showed a trend toward a reduced mortality ($p = 0.08$) in the high-PEEP group. Several meta-analyses have been subsequently performed to assess the effect on clinical outcomes of low versus high PEEP,[608–611] and these suggest that higher PEEP may improve survival, particularly in patients with more severe ARDS.

In summary, current evidence support the use of high PEEP, especially in the sickest patients with ARDS; in fact, high PEEP is safe, decreases the number of patients with severe hypoxemia and at high risk of death, and is associated with greater numbers of ventilator-free days and organ failure-free days. Nevertheless, it is uncertain how best to select the right patients and the optimal level of PEEP. The first issue is directly related to the current definitions of ARDS.[612] Villar et al report that severity of lung injury and outcomes vary widely in patients meeting the current definition of ARDS, and proposed the adoption of standardized ventilator settings so as to identify patients with similar severity of lung injury and mortality.[613] Several approaches have been proposed to optimize PEEP in ARDS, but none has proven effective in improving clinical outcome (Table 10-3).[6,22,42,164,171,201,215,303,309,322,327,344,351,599,601,614–623]

Optimal PEEP in ARDS should recruit as much nonaerated lung as possible, while avoiding lung overdistension, hemodynamic impairment, and global and regional disturbances of O_2 balance (Fig. 10-20). In the ALVEOLI and LOVS studies, PEEP was set according to preset PEEP/FI_{O_2} tables and PEEP-induced recruitment was estimated by improvement in oxygenation.[601,602] It is well known that changes in oxygenation depend not only on recruitment, but also on cardiac output.[48,138,140,191] Thus, oxygenation may have improved without any lung recruitment. Grasso et al[318,321] analyzed the physiologic effects of the ALVEOLI protocol. They demonstrated that the protocol has unpredictable effects on lung recruitment. Indeed, the protocol may increase the risk of overdistension when high PEEP is applied in patients with a low potential for recruitment, such as those with a focal distribution of lung atelectasis.[27,225,321] As recently suggested,[27,33,624] assessment of lung recruitability can be important when attempting to optimize PEEP on an individual basis. Results from the ExPress study support this reasoning and suggest that setting PEEP at the highest level compatible with a plateau pressure of 28 to 30 cm H_2O and a VT of approximately 6 mL/kg of predicted body weight is an acceptable approach (Fig. 10-20).

In ARDS, lung units are unstable and have a strong tendency to collapse. Thus, any ventilator circuit disconnection or leakage, leading to a complete or partial drop in pressure, can cause harmful falls in lung volume and oxygenation.[296]

Another approach to setting PEEP based on real-time, continuous analysis of the dynamic airway pressure-time profile ("stress index") has been proposed for optimizing ventilator settings in ARDS.[201,340,625] In animal studies and in a single study in patients, this approach was able to predict a ventilator strategy that minimizes VILI.[321,340,625] The

TABLE 10-3: METHODS FOR SELECTING OPTIMAL POSITIVE END-EXPIRATORY PRESSURE

Reference	Year	PEEP target	Proposed method
Suter (42)	1975	Maximal oxygen delivery	Maximal static compliance during stepwise incremental PEEP
Kirby (22)	1975	Intrapulmonary shunt < 15%	Stepwise incremental PEEP to reach the target, while supporting cardiac output with fluids and vasopressors
Hurewitz (617)	1981	Drop of mixed venous oxygen tension	Stepwise incremental PEEP to reach the target
Weisman (618)	1982	Adequate Pa_{O_2} with minimal FI_{O_2}	Stepwise incremental PEEP to reach the target
Murray (619)	1984	Minimal arterial end-tidal CO_2 gradient	Stepwise incremental PEEP to reach the target
Matamis (322)	1984	Best improvement in gas exchange, intrapulmonary shunt, and respiratory mechanics	PEEP set at the lower inflection point on inspiratory P-V curve
Albert (620)	1985	Adequate Pa_{O_2} with $FI_{O_2} < 0.6$	Lowest PEEP to reach the target
Hartman (616)	1992	Maximal peripheral tissue perfusion	Maximal subcutaneous oxygen tension during stepwise incremental PEEP
Gattinoni (164)	1993	Prevention of compression atelectasis	Maximal PEEP (equal to superimposed hydrostatic pressure) corresponds to 70% of the dorsal-ventral height of thorax (in cm)
Ranieri (201)	1994	Linear airway pressure-time profile	PEEP variations to reach the target
Amato (6)	1998	Maximal recruitment	PEEP set 2 cm H_2O above the lower inflection point on the inspiratory P-V curve
Hickling (327)	2001	Maximal static compliance	Stepwise decremental PEEP trial
Rouby (309)	2002	Best oxygenation with the lowest FI_{O_2} (>0.6)	Lung morphology, slope and inflection points of the P-V curve, PEEP trial
Brower (601)	2004	Oxygenation (Pa_{O_2} 55 to 80 mm Hg, SpO_2 88% to 95%)	PEEP-FI_{O_2} combination table
Albaiceta (215)	2005	Expiratory point of maximum curvature	Deflation limb of the P-V curve
Suarez-Sipmann (351)	2007	Maximum dynamic compliance	Stepwise decremental PEEP trial
Talmor (626)	2008	Transpulmonary pressure between 0 and 10 cm H_2O	Esophageal pressure measurement

Abbreviations: CO_2, carbon dioxide; FIo_2, fractional inspired oxygen; Pa_{O_2}, arterial oxygen tension; *P-V*, pressure-volume; SpO_2, percutaneous oxygen saturation.

implementation of automatic tools that facilitate standardized assessment and continuous monitoring of respiratory mechanics might allow this approach to be incorporated into clinical practice. Another approach for choosing PEEP is based on the estimation of trans-pulmonary pressure with the placement of an esophageal-balloon catheter. Talmor et al compared a level of PEEP, where transpulmonary pressure at end-expiration was maintained between 0 and 10 cm H_2O, against standard strategy, where PEEP was set according to PEEP/FI_{O_2} tables.[626] Compared to the standard approach, the transpulmonary pressure-guided strategy resulted in a higher level of PEEP (17 vs. 10 cm H_2O), and better oxygenation and respiratory system compliance. This interesting approach may prove useful in the future.

Postoperative State

Postoperative hypoxemia is mainly caused by atelectasis.[85,96,627] After various surgical procedures, atelectasis develops in 30% to 50% of cases,[628] and leads to ARF requiring intubation and mechanical ventilation in 8% to 10% of patients.[628–631] The application of CPAP (5 to 10 cm H_2O) via a face mask, alone or combined with pressure support, reduces atelectasis and improves oxygenation after both cardiac[134,632] and noncardiac surgery,[633–637] without increasing surgical complications, such as anastomotic leaks.[638] By reducing atelectasis, CPAP may decrease bacterial growth in the lung, mitigating bacterial translocation into the bloodstream, and normalizing alveolocapillary permeability.[411,639]

Onset and duration of CPAP seem to be critical for avoiding or reversing atelectasis. Studies that failed to demonstrate benefit used CPAP several hours after surgery[640] or for a relatively short time.[641–643] Despite well-recognized physiologic benefits, only recently have randomized trials assessed the effects of CPAP on outcome variables.[644,645] In seventy patients, Fagevik Olsen et al[644] reported that, compared to breathing exercises, use of CPAP after thoracoabdominal resection of esophageal cancer resulted in a lower intubation rate. Squadrone et al[645] randomized patients who developed hypoxemia following major abdominal surgery to either O_2 alone (FI_{O_2} 50%) or O_2 plus CPAP 7.5 cm H_2O. The study was interrupted after 209 patients were enrolled, because the intubation rate was lower in the CPAP group than in the O_2 group (1% vs. 10%).[645] The patients who received CPAP at the end of treatment had higher oxygenation and lower rates of pneumonia, infection, and sepsis than the O_2 group.[645] Although limited to selected patients undergoing elective abdominal surgery, these data show that improvement in physiologic parameters achieved with

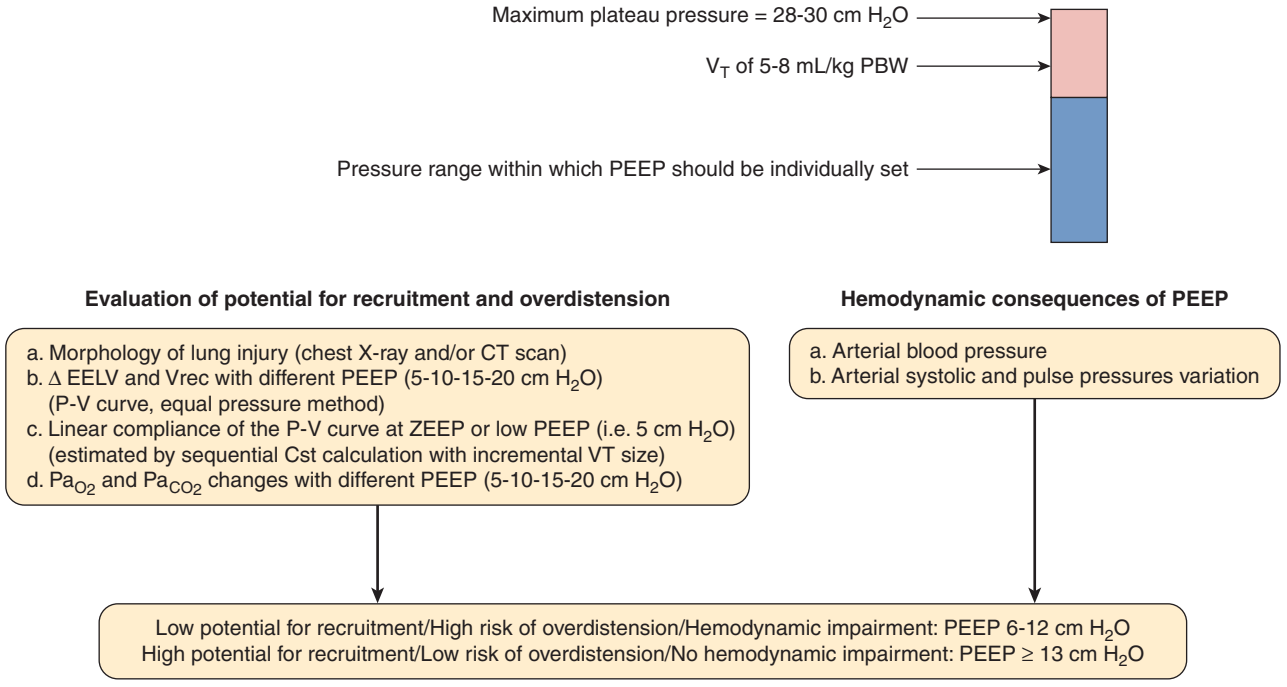

FIGURE 10-20 Proposed algorithm for setting PEEP in ARDS. First, a safe plateau pressure limit of 28 to 30 cm H_2O is recommended; it should not be exceeded except when chest wall compliance is very low (30 to 35 cm H_2O). Second, V_T is preset, which corresponds to a certain pressure oscillation. Third, PEEP should not exceed the pressure difference between plateau pressure and the tidal pressure oscillation. After hemodynamic stabilization, the potential for recruitment, the risk of overdistension, and the hemodynamic consequences are individually assessed for different levels of PEEP. Potential for recruitment is greater when: (a) lung injury is diffuse; (b) alveolar recruitment is large (i.e., >100 mL); (c) the ratio between alveolar recruitment and change in end-expiratory lung volume is high (greater than 15% to 20%); (d) linear compliance of the pressure-volume curve at 0 cm H_2O is high (>40 mL/cm H_2O); (e) static compliance measured at low or no PEEP progressively increases with increasing V_T; and (f) Pa_{O2} increases and Pa_{CO2} concomitantly decreases. By contrast, the risk for overdistension is greater when changes in the above parameters go in the opposite direction. PEEP-induced hemodynamic impairment may be considered clinically relevant when arterial systolic pressure falls more than 20 mm Hg and/or variations in both arterial systolic pressure or pulse pressure appear or increase. The use of standardized ventilator settings (particularly PEEP) to assess oxygenation and severity of lung injury may be useful for identifying the more severe patients who are likely to have a better response to PEEP. *Cst*, static compliance; *CT*, computed tomography; *ΔEELV*, change in end-expiratory lung volume; *P-V*, pressure-volume; *PBW*, predicted body weight; *PEEP*, positive end-expiratory pressure; *Vrec*, recruited volume; V_T, tidal volume; *ZEEP*, zero end-expiratory pressure.

CPAP can translate into a better clinical outcome. Of note, CPAP was applied almost continuously for a prolonged time (19 ± 22 hours).[645] One recent meta-analysis, based on more than nine randomized controlled trials that included a total of 654 patients undergoing abdominal surgery, suggested that CPAP decreases the risk of postoperative pulmonary complications, including atelectasis, pneumonia, and endotracheal intubation.[646]

In summary, CPAP is a simple, practical and safe technique for managing postoperative hypoxemia. It may improve outcome in selected patients, provided it is applied for a sufficient time.

Chronic Obstructive Pulmonary Disease

ARF in patients with COPD is characterized by high airway resistance and PEEPi,[176,545,550,580,647] which increase respiratory muscle load.[2,61,64,550,569] Hyperinflation simultaneously reduces the force-generating capacity of the diaphragm.[574,576] When the force-load balance is altered to a level that severe respiratory acidosis ensues, mechanical ventilation becomes necessary. The ventilator acts as an accessory pump that helps reversing the unfavorable force-load balance. By reducing O_2 cost of breathing and correcting arterial blood gases, mechanical ventilation can improve respiratory muscle function (force). Inspiratory assistance by the ventilator, however, does not reduce the inspiratory resistive load consequent to airway resistance or the threshold load consequent to PEEPi.

Pharmacotherapy can have favorable effects on both load reduction and force restoration.[648] Agents act on bronchial smooth muscle (β_2-agonists, anticholinergic)[649–652] or inflammatory process (glucocorticoids and antibiotics).[649,650,652,653] These agents decrease airway resistance, dynamic hyperinflation and PEEPi in ventilated patients.[654–659] Glucocorticoids and antibiotics are commonly administered parenterally. In ventilated patients, bronchodilators are more effectively and safely given via a small volume nebulizer or a metered-dose inhaler connected to an appropriate spacer.[660]

External PEEP reduces the threshold load imposed on the inspiratory muscles. PEEP, however, does not reduce

hyperinflation and its effects on diaphragmatic force-generating capacity. Application of PEEP in patients with COPD may cause a decrease in expiratory resistance and promote a faster and more uniform lung emptying,[357] although the clinical relevance of these findings remains to be determined. CPAP is effective in reducing dyspnea,[9,60,592] decreasing work of breathing,[9,60,591,592] and improving cardiac function.[579] During triggered ventilation, PEEP reduces inspiratory effort[2,61,63,566] and ventilatory drive,[566] and facilitates triggering of the ventilator[2,61,63,566] by reducing both inspiratory effort and the delay between onset of inspiratory effort and initiation of assistance, improving patient–ventilator interaction, and reducing ineffective inspiratory efforts.[63,64]

Despite a large body of physiologic data, no randomized trial has evaluated the effectiveness of PEEP with CPAP in improving outcome in ventilated patients with COPD. Most trials that evaluated the effectiveness of noninvasive ventilation in patients with acute hypercapnia secondary to COPD exacerbation used PEEP 4 to 5 cm H_2O in addition to pressure support.[661–663]

NAVA is a novel mode of ventilation that utilizes diaphragmatic electrical activity, measured with an electrode array in the lower esophagus, to trigger and drive the ventilator.[664] The ventilator is triggered, irrespective of PEEPi, as soon as the diaphragm contracts.[664] By reducing the delay between onset of inspiratory effort and initiation of machine support,[665] NAVA markedly enhances patient–ventilator coordination without the need for external PEEP, thereby eliminating the difficulties in selecting the appropriate PEEP level and avoiding the risk of further hyperinflation.[664]

Acute Severe Asthma

Patients with acute severe asthma have high airway resistance, dynamic hyperinflation, and PEEPi, which increase respiratory muscles load and decrease force-generation capacity.[666] These patients are generally less responsive to external PEEP.[237] Although some flow limitation may be present,[539] the main cause of dynamic hyperinflation and PEEPi is the prolonged time constant, secondary to the high expiratory resistance. In the absence of flow limitation, PEEP increases hyperinflation and alveolar pressure.[583,667] Some alveolar units may be entirely occluded by mucus plugs and thus completely disconnected from the central airway.[544]

Low levels of CPAP may decrease breathlessness.[668–670] Lin et al[671] reported that CPAP reduced the bronchial reactivity. In patients with asthma exposed to aerosolized histamine, Martin et al[672] found that CPAP 12 cm H_2O decreased both esophageal and transdiaphragmatic pressure swings. V_E increased and thus inspiratory work did not fall.[672] Meduri et al,[673] in a series that included seventeen patients with acute asthma, reported CPAP 3 to 5 cm H_2O combined with pressure support via a face mask improved gas exchange. Only two patients failed and required endotracheal intubation.[673] In a randomized trial of thirty patients treated in an emergency department for acute asthma, Sorosky et al[674] found that noninvasive ventilation with low CPAP produced greater and faster improvements in lung function and lower rate of hospitalization than did standard therapy.[674]

In summary, use of PEEP in patients receiving mechanical ventilation for acute severe asthma is often detrimental and is thus not advisable. Very few data suggest that low levels of noninvasive CPAP combined with pressure support in less severe and selected patients might be beneficial, although further evaluation is required.

Cardiogenic Pulmonary Edema

The benefit of CPAP on the failing left ventricle has already been discussed (see Fig. 10-10). Although most patients will positively respond to standard medical treatment, some do not and require endotracheal intubation and ventilator assistance.

Over the last three decades there has been growing interest in the delivery of CPAP via a noninvasive interface, as a means of avoiding endotracheal intubation and invasive mechanical ventilation. In patients with cardiogenic pulmonary edema, several randomized controlled trials have compared CPAP versus standard medical therapy,[10,73,146,153,675] bilevel positive airway pressure (BiPAP) (i.e., PEEP plus inspiratory pressure support),[154,676–681] or both.[679,682,683] That is eight trials have compared CPAP versus standard treatment[10,73,146,153,675,679,682,683] and nine trials have compared CPAP versus BiPAP.[154,676–683] Nine studies[153,154,676–681,683] had been powered a priori, according to their primary end points; three were prematurely interrupted after interim analysis.

The eight studies comparing CPAP versus standard treatment[10,73,146,153,675,679,682,683] included a total of 537 patients receiving CPAP and 564 control patients; of note, one single study included 346 and 367 patients in the CPAP and standard treatment groups, respectively.[679] CPAP was 10 cm H_2O in four studies,[10,73,675,682,683] 7.5 cm H_2O in one study,[153] varied between 2.5 and 12.5 cm H_2O in one study,[146] and between 5 and 15 cm H_2O in another one.[679] CPAP produced a greater and more rapid physiologic improvement in all studies but one.[682] Five studies[10,73,146,153,675] reported a prompter and greater improvement in oxygenation with CPAP, although in only three studies[10,153,675] was Pa_{O_2}/FI_{O_2} assessed. Bersten et al[10] and Gray et al[679] observed improvement in pH and Pa_{CO_2} with CPAP. Dyspnea was reduced by CPAP in three studies,[153,679,683] but not in a fourth study.[682] CPAP produced a lower rate of therapeutic failure and intubation in four studies[10,146,153,683] and decreased hospital mortality in only one study.[682] None of the eight studies revealed differences in the length of hospital stay.

The nine studies comparing CPAP with BiPAP[154,676–683] included a total of 652 CPAP and 657 BiPAP patients. Six studies used CPAP 10 cm H_2O. The setting of BiPAP varied. Park et al[683] added a small level of inspiratory positive airway pressure to expiratory positive airway pressure 10 cm H_2O. Mehta et al[154] and Crane et al[682] decreased expiratory positive

airway pressure from 10 to 5 cm H_2O and raised inspiratory positive airway pressure to 15 cm H_2O, in order to achieve a mean pressure of 10 cm H_2O throughout the entire breath in both groups. Bellone et al[676] also used PEEP 5 cm H_2O and an initial pressure support of 15 cm H_2O (i.e., inspiratory positive airway pressure 20 cm H_2O). In the remaining studies PEEP varied from 5 to 10 cm H_2O, while the inspiratory assistance was regulated to achieve a given V_T.[677–681]

Mehta et al[154] found a more rapid improvement in Pa_{CO_2} and other physiologic variables with BiPAP than with CPAP. The other studies[676–683] did not find differences in early physiologic variables. Eight studies[154,676–681,683] did not reveal differences in any clinical outcome variable. Crane et al[682] found hospital survival higher in the CPAP than BiPAP group. Metha et al[154] interrupted their study because myocardial infarction was increased in their BiPAP group; eight following randomized trials, however, did not confirm this finding.[676–683]

Three meta-analyses, not including the most recent studies,[677–681] conclude that CPAP and BiPAP are equally effective in decreasing rate of intubation and mortality as compared to the sole standard medical treatment.[684–686]

In summary, CPAP improves and expedites physiologic improvement, whereas the effects on rate of endotracheal intubation and mortality remain controversial. Several factors such as equipment, timing of intervention, underlying disease and comorbidities may explain the differences in outcome among studies. Early use of CPAP (10 cm H_2O) in addition to the medical therapy is advisable in patients with ARF secondary to cardiogenic pulmonary edema.

Prehospital Setting

Very recently, some investigators proposed early out-of-hospital application of noninvasive CPAP for treatment of hypoxemic ARF, predominantly, although not exclusively, secondary to cardiogenic pulmonary edema.

Hubble et al first reported, in a nonrandomized control trial, on the application of CPAP 10 cm H_2O via face mask in addition to standard treatment in 120 patients with presumed cardiogenic pulmonary edema presenting to an emergency service. This group of patients was compared with a group of ninety-five patients with equivalent characteristics transported by a second emergency medical service who received standard treatment only. The diagnosis was confirmed in ninety and sixty-five patients in the treatment and control groups, respectively. When considering patients with confirmed diagnosis, the treatment group had a lower rate of endotracheal intubation and mortality compared to the controls; in addition, they showed a better improvement in respiratory rate, dyspnea, and pulse heart rate.[687] Subsequently, the same research group undertook a theoretical analysis in which they modeled the cost-effectiveness of prehospital CPAP.[688]

In an observational study, Foti et al applied prehospital noninvasive CPAP via helmet to 121 patients with suspected cardiogenic pulmonary edema; sixty-two patients were treated by physicians with CPAP (approximately equal to 10 cm H_2O) in addition to medical treatment, while the remaining fifty-nine patients were treated by nurses with CPAP (approximately equal to 7.5 cm H_2O) only. The diagnosis was confirmed in fifty-four and fifty patients in the former and latter group, respectively. In both groups, oxygen saturation, breathing frequency, and hemodynamics equally improved; rate of intubation and mortality were not different between the groups.[689] These positive results were drawn into question by Frontin et al who carried out a randomized controlled trial where 124 out-of-hospital patients with presumed cardiogenic pulmonary edema received either standard treatment plus CPAP or standard treatment only. Success of treatment, as defined by a respiratory rate less than 25 breaths/min and oxygen saturation greater than 90%, was no different between the groups; rate of intubation and mortality at 5 and 30 days were also unaffected by CPAP. CPAP 10 cm H_2O was applied through a face mask fitted with a valve and controlled with a portable-flow generator. The amount of generated flow, however, was not defined; failure to control for this variable opens the possibility of overestimating the positive pressure actually applied.[690]

Thompson et al[691] performed a randomized controlled trial on patients with ARF of varied etiologies where seventy-one patients received either medical therapy plus CPAP 10 cm H_2O (intervention group) or medical therapy plus oxygen or bag-valve-mask ventilation or intubation, according to local usual care (control group). The incidence of tracheal intubation was lower in the intervention group, a result that could be strongly biased by the fact that intubation was allowed as initial treatment in the control group. Mortality was reduced in the intervention group, as opposed to controls. As in the previous study, CPAP was applied through a face mask fitted with a valve and controlled with a portable flow generator, but the generated flow was maybe not controlled.

In summary, despite a strong rationale,[692] the available data do not permit one to make definite recommendations about the appropriateness of using noninvasive CPAP in the prehospital setting.

Prophylactic Positive End-Expiratory Pressure

The term *prophylactic PEEP* was used in early studies of using PEEP in high-risk patients with the aim of reducing the incidence of ARDS.[598,693–698] Both experimental[386,404,699–701] and clinical studies[693–695,702] suggest that PEEP might favorably influence the course of lung injury in patients at risk for ARDS. The hypothesis, however, was refuted by Pepe et al[598] who randomized ninety-two ventilated patients at risk for ARDS to receive no PEEP or PEEP 8 cm H_2O. Early use of PEEP improved oxygenation, but it did not avert the development of ARDS[598] (Table 10-4). Of note, the V_T in the study of Pepe et al was high (12 mL/kg).[598] Such a high V_T might have recruited[202,204]

TABLE 10-4: RANDOMIZED CONTROLLED TRIALS EVALUATING THE EFFICACY OF PROPHYLACTIC POSITIVE END-EXPIRATORY PRESSURE

Reference	Population	Arm	No. of patients	Associated settings	PEEP setting	Mean PEEP (cm H_2O)	Outcomes
Pepe 1984 (598)	Medical-Surgical At risk for ARDS	Intervention	44	V_T = 12 mL/kg	Predetermined	8	Incidence of ARDS: 25% Mortality: 30% Barotrauma: 43%
		Control	48	V_T = 12 mL/kg	-	0	Incidence of ARDS: 27% Mortality: 38% Barotrauma: 50%
Delclaux 2000 (151)	Medical ARDS	Intervention	40*	O_2 with CPAP for SaO_2 >90%	Clinical response Tolerance	5-10	Endotracheal intubation: 38% ICU length of stay (days): 9 ICU mortality: 23% Hospital mortality: 30%
		Control	41*	O_2 alone for SaO_2 > 90%	–	0	Endotracheal intubation: 44% ICU length of stay (days): 9 ICU mortality: 22% Hospital mortality: 27%
Maitre 2000 (708)	Medical ARDS Undergoing FOB	Intervention	15	O_2 with CPAP for SaO_2 > 90%	Predetermined	7.5	Oxygenation: unchanged Ventilatory assistance after FOB: 0%
		Control	15	O_2 alone for SaO_2 > 90%	–	0	Oxygenation: ↓ Ventilatory assistance after FOB: 33%
Manzano 2008 (703)	Patients without ARDS	Intervention	64	V_T = 8 to 9 mL/kg	Predetermined According to the degree of abdominal distension	5-8	Hospital mortality: 30% Ventilator-associated pneumonia: 9% Incidence of ARDS: 5% Barotrauma: 2%
		Control	63	V_T = 8 to 9 mL/kg	–	0	Hospital mortality: 25% Ventilator-associated pneumonia: 25% Incidence of ARDS: 14% Barotrauma: 8%

Abbreviations: *ARDS*, acute respiratory distress syndrome; *CPAP*, continuous positive airway pressure; *FOB*, fiberoptic bronchoscopy; *ICU*, intensive care unit; O_2, oxygen; SaO_2, arterial oxygen saturation; V_T, tidal volume.

*subgroup of patients with early ARDS.

and overdistended the lung, masking any benefit of prophylactic PEEP. This concern is supported by barotrauma rate of around 50% in that study.[598]

A more recent randomized controlled trial compared PEEP (8 cm H_2O) with no PEEP in 131 nonhypoxemic patients who had received mechanical ventilation for less than 24 hours.[703] In this study, interrupted because of low patient recruitment, PEEP did not affect hospital mortality (30% vs. 25%), but decreased the rate of ventilator-associated pneumonia (9% vs. 25%) and the number of patients who developed hypoxemia (19% vs. 54%). There was a nonsignificant trend toward a reduction in the rate of ARDS (5% vs. 14%) (see Table 10-4). Three studies clarified the mechanisms through which PEEP may protect against ventilator-associated pneumonia, suggesting that fluid leakage across the cuff of the endotracheal tube is affected by PEEP.[704–706] Two in vitro studies showed that fluid leakage, constantly present when PEEP was not applied, progressively decreased with increasing PEEP and was abolished at 15 cm H_2O.[705,706] In intensive care unit patients, Lucangelo et al found that the minimum PEEP able to avoid fluid leakage around the cuff was 5 cm H_2O.[704]

PEEP equal to or less than 5 cm H_2O is sometimes used in intubated patients to counteract the fall in lung volume secondary to intubation, supine positioning, and/or muscle paralysis. A retrospective analysis of a large multinational cohort study conducted in 13,322 patients to evaluate current practice and outcomes of mechanical ventilation in the intensive care unit found that patients invasively ventilated without PEEP had significantly higher hospital mortality than those ventilated with PEEP.[707]

Intraoperative PEEP may have beneficial effects on the occurrence of pulmonary complications after surgery. A recent meta-analysis, including eight randomized controlled trials for a total of 330 patients, assessed the effects of intraoperative application of PEEP to mechanical ventilation on postoperative mortality and pulmonary outcomes.[118] Mechanical ventilation with PEEP had no significant effect on mortality, compared to mechanical ventilation without PEEP, although PEEP was associated with improved oxygenation and decreased rate of postoperative atelectasis.

Use of CPAP in the very early stage of ARDS was evaluated in spontaneously breathing patients and during fiberoptic bronchoscopy. The investigators tested whether CPAP prevents the severe hypoxemia and respiratory failure requiring intubation.[151,708] CPAP by face mask improved oxygenation, but did not improve the need for endotracheal intubation, length of hospital stay, or mortality (see Table 10-4).[151] Early use of noninvasive CPAP, with or without pressure support, may benefit specific high-risk patients, such as immunocompromised patients.[211,709–711] In obese patients undergoing gastroplasty, Joris et al[712] found that prophylactic nasal CPAP, with pressure support, immediately after surgery reduced pulmonary dysfunction and accelerated recovery, compared with O_2 alone. CPAP is also useful during fiberoptic bronchoscopy,[708] a procedure that can worsen oxygenation and respiratory mechanics.[713–715] In a double-blind trial, Maitre et al[708] compared mask CPAP to O_2 therapy alone during bronchoscopy in severe hypoxemic spontaneously breathing patients (see Table 10-4). During and immediately after the procedure oxygenation was well preserved in the CPAP group, whereas it fell in the O_2 group. CPAP prevented subsequent respiratory failure necessitating ventilator support.[708]

It has been suggested that PEEP may prevent VILI.[716] Despite robust physiologic rationale, no clinical evidence shows that PEEP protects against VILI. In a retrospective cohort study, Gajic et al[717] reported that approximately 25% of patients ventilated for more than 48 hours developed ARDS. V_T size was the only ventilator setting that independently identified risk for ARDS.[717] No relationship was found between PEEP and the risk of ARDS, possibly because the scatter in the data was insufficient to detect such an effect.[717]

In anesthetized patients with healthy lung, Wolthius et al compared the effects on pulmonary and plasma inflammatory mediators of two ventilatory strategies, high V_T (12 mL/kg) without PEEP and low V_T (6 mL/kg) with PEEP (10 cm H_2O).[718] The latter strategy resulted in lower interleukin-8, myeloperoxidase, and elastase in the lung, as compared to the former approach, suggesting that ventilation with PEEP and low VT may limit VILI even in patients without preexisting lung injury. Another study, performed in animals with healthy lungs, however, showed contrasting results.[719]

COMPLICATIONS AND CONTRAINDICATIONS

Table 10-5 summarizes the complications and side effects of PEEP. Complications are directly related to level of PEEP. Table 10-6 lists contraindications to the use of PEEP. In our opinion, there are only two absolute contraindications: life-threatening hypovolemic shock and undrained high-pressure pneumothorax. For all other conditions, there is little risk in using a low level of PEEP (up to 5 cm

TABLE 10-5: COMPLICATIONS OF POSITIVE END-EXPIRATORY PRESSURE

Pulmonary overdistension
Barotrauma
VILI
Increased dead space
Impaired CO_2 elimination
Reduced diaphragm force-generation capacity
Reduced cardiac output and oxygen delivery
Impaired renal function
Reduced splanchnic blood flow
Hepatic congestion
Decreased lymph drainage

TABLE 10-6: CONTRAINDICATIONS TO POSITIVE END-EXPIRATORY PRESSURE

Absolute contraindications
Life-threatening hypovolemic shock
Undrained high-pressure pneumothorax
Relative contraindications
Unresolved bronchopleural fistula
Intracranial hypertension and low cerebral compliance
Chronic chest wall restrictive disorders
Dynamic hyperinflation without expiratory flow limitation

H_2O), but benefits and drawbacks of higher levels of PEEP need to be carefully weighed in each patient.

CONCLUSIONS

PEEP is widely used in the clinical setting.[13] It is an essential component of ventilatory management of patients with both hypoxemic ARF, resulting from lung edema caused by increased microvascular permeability or hydrostatic pressure, and hypercapnic ARF, secondary to respiratory muscle failure.

Seventy-five years after the pioneering work of Poulton and Oxon[11] and Barach et al,[12] a large body of data has produced a general consensus on the usefulness of PEEP in the treatment of patients with acute respiratory failure. Although a few recent trials have assessed the effect of varied levels of PEEP on clinical outcomes, such as survival, complications, length of stay, and intensive care unit costs, doubts continue as to the optimal level of PEEP in the different clinical situations and on the best manner to determine it. Knowledge of pathophysiologic mechanisms and physiologic consequences of PEEP remains indispensable prerequisites for any decisions made at the bedside and must be the foundation for designing meaningful randomized, controlled trials.

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V

ALTERNATIVE METHODS OF VENTILATOR SUPPORT

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11

AIRWAY PRESSURE RELEASE VENTILATION

Christian Putensen

Controlled mechanical ventilation (CMV) is traditionally provided via an artificial airway to completely unload a patient's work of breathing and assure adequate gas exchange during the acute phase of respiratory insufficiency, until the underlying respiratory function has resolved.[1] The criteria used to determine when to terminate mechanical ventilation are essentially based on the clinical, and often, subjective assessment of the intensive care physician or on standardized weaning methods.[2,3] The actual process of weaning the patient from CMV is carried out by allowing spontaneous breathing attempts with a T piece or continuous positive airway pressure (CPAP) or by gradually reducing mechanical assistance.[4,5] Not surprisingly, gradual reduction of partial ventilator support benefits only patients who have difficulty in sustaining unassisted breathing.[4] Although introduced as weaning techniques, partial support modes have become standard methods of providing primary mechanical ventilatory support in critically ill patients.

BASIC PRINCIPLES OF AIRWAY PRESSURE RELEASE VENTILATION

Airway pressure release ventilation (APRV)[6] ventilates by time-cycled switching between two pressure levels in a high-flow (or demand-valve) CPAP circuit, permitting unrestricted spontaneous breathing in any phase of the mechanical ventilator cycle (Fig. 11-1). The degree of ventilator support with APRV is determined by the duration of the two CPAP levels and the mechanically delivered tidal volume (V_T).[6,7] V_T depends mainly on respiratory compliance and the difference between the CPAP levels. By design, changes in ventilatory demand do not alter the level of mechanical support during APRV. When spontaneous breathing is absent, APRV is not different from conventional pressure-controlled, time-cycled mechanical ventilation.[6,7]

Synonyms used for APRV are biphasic positive airway pressure[7] (BIPAP) and bilevel airway pressure (Bilevel). Biphasic positive airway pressure is identical to APRV

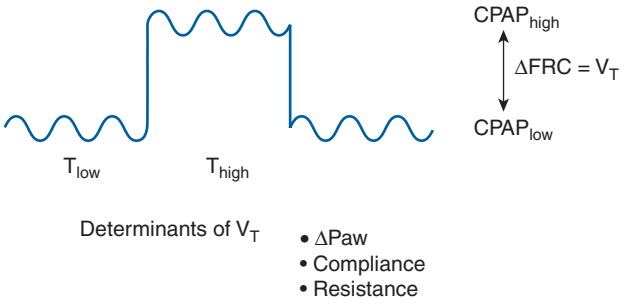

FIGURE 11-1 Airway pressure release ventilation ventilates by time-cycled switching between a high and low continuous positive airway pressure (CPAP) level in the circuit. Consequently, unrestricted spontaneous breathing is permitted in any phase of the mechanical ventilator cycle. Change between the two CPAP levels results in a change in functional residual capacity (ΔFRC), which equals the mechanical delivered tidal volume (V_T). V_T depends mainly on respiratory compliance and resistance and the airway pressure difference (ΔPaw) between the CPAP levels. Setting the time for the low (T_{low}) and the high (T_{high}) CPAP enables the adjustment of ventilator rate.

except that no restriction is imposed on the duration of the low-CPAP level (release pressure).[6,7] Based on the initial description, APRV keeps the duration of the low-CPAP level (release time) at 1.5 seconds or less.

PHYSIOLOGIC EFFECTS

Ventilation Distributions

Radiologic studies demonstrate that ventilation is distributed differently during pure spontaneous breathing and CMV.[8] During spontaneous breathing, the posterior muscular sections of the diaphragm move more than the anterior tendon plate.[8] Consequently, when patients are supine, the dependent lung regions tend to be better ventilated during spontaneous breathing (Fig. 11-2). If the diaphragm is relaxed, it will be moved by the weight of the abdominal cavity and intraabdominal pressure towards the cranium; mechanical V_T will be distributed more to the anterior, nondependent, and less perfused lung regions.[9] When compared with spontaneous breathing, the latter leads, both in patients with healthy lungs and patients with diseased lungs, to lung areas in the dorsal lung regions close to the diaphragm, being less ventilated (or atelectatic). Recent results demonstrate that the posterior muscular sections of the diaphragm move more than the anterior tendon plate when large breaths or sighs are present during spontaneous breathing.[10]

Computed tomography (CT) of patients with acute respiratory distress syndrome (ARDS) reveals radiographic densities corresponding to alveolar collapse localized primarily in the dependent lung regions, which correlates with intrapulmonary shunting and accounts entirely for the observed arterial hypoxemia.[11] Formation of radiographic densities is attributed to alveolar collapse caused by superimposed pressure on the lung and a cephalad shift of the diaphragm, most evident in dependent lung areas during CMV.[12] Persisting spontaneous breathing is considered to improve the distribution of ventilation to dependent lung areas and thereby improve ventilation–perfusion ($\dot{V}_A/\dot{Q}$) matching, presumably by diaphragmatic contraction that opposes alveolar compression.[13] This concept is supported by CT observations in anesthetized patients demonstrating that contractions of the diaphragm induced by phrenic nerve stimulation favor distribution of ventilation to dependent, well-perfused lung areas, decreasing atelectasis formation.[14]

Spontaneous breathing with APRV in experimentally induced lung injury is associated with less atelectasis formation on end-expiratory spiral CT of the whole lungs and on CT scans above the diaphragm (Fig. 11-3).[15–17] Although other inspiratory muscles may contribute to improvement in aeration during spontaneous breathing, the craniocaudal gradient in aeration, aeration differences, and the marked

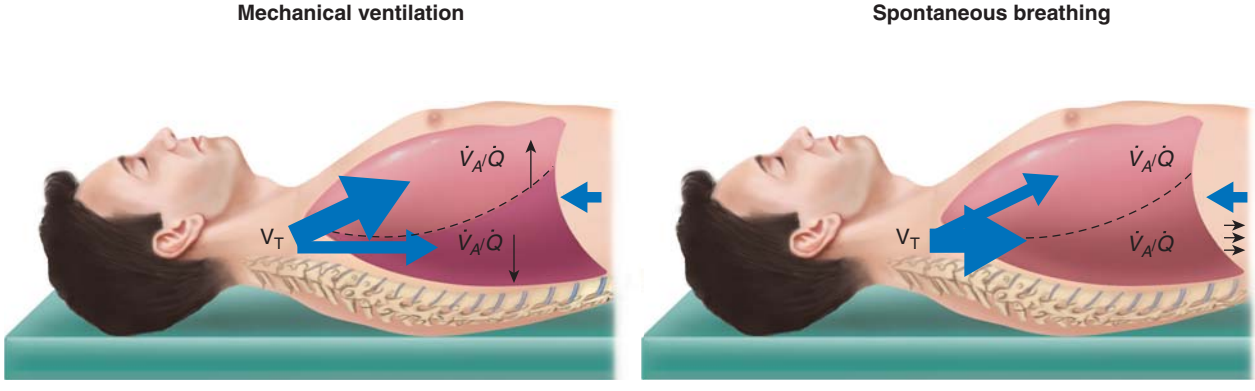

FIGURE 11-2 During spontaneous breathing, the posterior muscular sections of the diaphragm move more than the anterior tendon plate. Consequently, in the supine position, spontaneous ventilation is preferably directed to well-perfused, dependent lung regions. Conversely, a mechanically delivered tidal volume is directed primarily to nondependent lung areas, away from regions with maximal blood flow. Thus, spontaneous breathing contributes to better ventilation–perfusion ($\dot{V}_A/\dot{Q}$) matching.

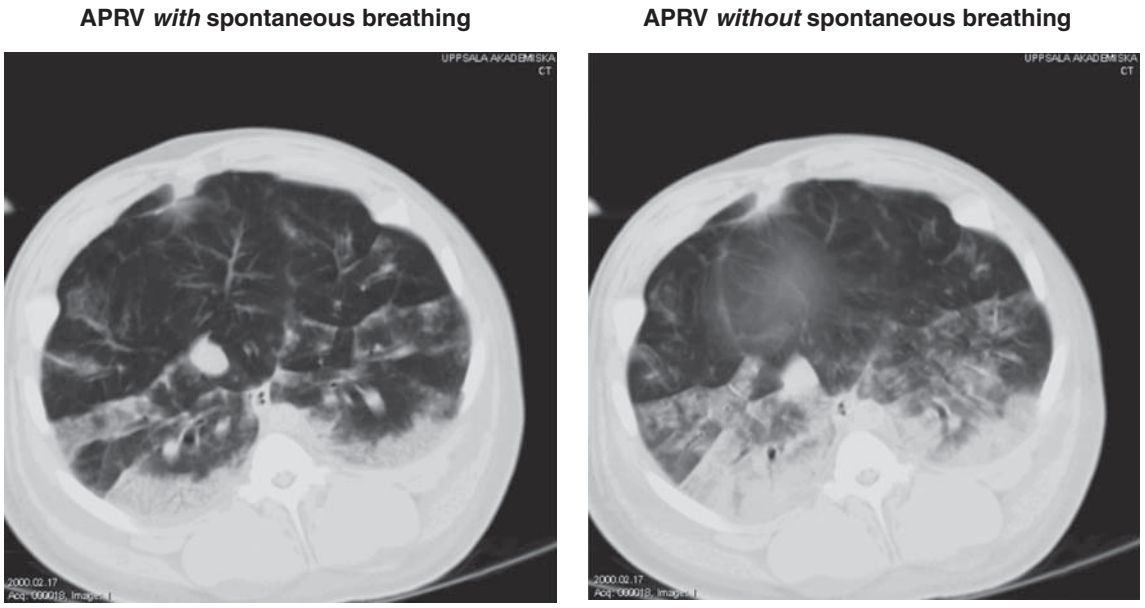

FIGURE 11-3 Computed tomography of a lung region above the diaphragm at end-expiration in oleic acid-induced lung injury with and without spontaneous breathing during APRV. Atelectasis formation is reduced with spontaneous breathing.

differences in aeration in regions close to the diaphragm between APRV with and without spontaneous breathing suggest that diaphragmatic contractions play a dominant role on the observed aeration differences and improvement of end-expiratory lung volume.[15–17] Experimental data suggest that recruitment of dependent lung areas may be caused essentially by an increase in transpulmonary pressure (Ptp) secondary to the decrease of pleural pressure (Ppl) with spontaneous breathing during APRV.[18]

Because the posterior muscular sections of the diaphragm contract more than the anterior tendon plate, a decrease in Ppl and the concomitant localized increase in Ptp should explain entirely the successful recruitment of atelectatic areas in the dependent lung regions adjacent to the diaphragm.[8,10,14–17] In the apical lung regions, differences in tidal volume distribution between the dependent and nondependent lung is not significantly different with spontaneous breathing.[15,16] Inhomogeneous distribution of tidal ventilation during CMV in patients with acute lung injury (ALI)[19,20] may be explained by regional differences in Ptp. A cephalocaudal decrease in Ptp may be partially explained by the transmission of abdominal pressure to the thoracic cavity,[12] decreasing from base to apex. In addition, compression of lung tissue by the weight of the lungs and the heart may differ regionally.[12,19,20] Although increase in Ptp caused by spontaneous breathing is maximal in the dependent lung areas adjacent to the diaphragm,[8,10,14–17] it is unlikely that the resulting absolute Ptp in the dependent lung regions is higher than in cephalad lungs areas in the absence of spontaneous breathing. This concept is supported by experimental findings that gas volume and aeration are not higher in dependent lung regions with spontaneous breathing than in cephalad lung regions in the absence of spontaneous breathing.[17] Furthermore, CT observations in experimentally induced lung injury demonstrate that, during spontaneous breathing with APRV a large portion of the V_T is distributed to the initially collapsed dependent lung regions, resulting in less cyclical alveolar collapse.[16]

Pulmonary Gas Exchange

In patients with ARDS, APRV with spontaneous breathing of 10% to 30% of the total minute ventilation (V_E) accounts for an improvement in $\dot{V}_A/\dot{Q}$ matching, intrapulmonary shunting, and arterial oxygenation.[13] These results confirm earlier investigations in animals with induced lung injury,[21–23] which demonstrated improvement in intrapulmonary shunt and arterial oxygenation during spontaneous breathing with APRV. An increase in arterial oxygenation in conjunction with greater pulmonary compliance indicates recruitment of previously nonventilated lung areas. Clinical studies in patients with ARDS show that spontaneous breathing during APRV does not necessarily lead to instant improvement in gas exchange. Instead, improvement in oxygenation continues over the 24 hours after the start of spontaneous breathing.[24]

In patients at risk of developing ARDS, maintaining spontaneous breathing with APRV resulted in lower venous admixture and better arterial oxygenation over a period of more than 10 days as compared to CMV with subsequent weaning.[25] These findings are supported by randomized controlled trials and case-matched analysis.[26–28]

Cardiovascular Effects

Application of a ventilator breath generates an increase in airway pressure and, therefore, in intrathoracic pressure, which, in turn, reduces venous return to the heart. In normovolemic and hypovolemic patients, this action produces a reduction in right-ventricular and left-ventricular filling and results in decreased stroke volume, cardiac output, and oxygen delivery.[29] To normalize systemic blood flow during mechanical ventilation, intravascular volume often needs to be increased and/or the cardiovascular system needs pharmacologic support. Reducing mechanical ventilation to a level that provides adequate support for existing spontaneous breathing should help reduce the cardiovascular side effects of ventilator support.[30]

Periodic reduction of intrathoracic pressure, achieved by maintaining spontaneous breathing during ventilator support, promotes venous return to the heart and right-ventricular and left-ventricular filling, thereby increasing cardiac output and oxygen delivery.[31] Experimental[21–23] and clinical[13,25] studies show that when spontaneous breathing during APRV achieves 10% to 40% of total V_E, with no change in V_E or airway pressure limits, the cardiac index increases. A simultaneous rise in right-ventricular end-diastolic volume during spontaneous breathing with APRV indicates improved venous return to the heart.[13] In addition, outflow from the right ventricle, which depends mainly on lung volume (the major determinant of pulmonary vascular resistance), may benefit from decrease in intrathoracic pressure during APRV.[13]

Patients with left-ventricular dysfunction may not benefit from either the augmentation of venous return to the heart or the increase in left-ventricular afterload that occurs with the lowering of intrathoracic pressure. Thus, switching abruptly from CMV to pressure-support ventilation (PSV) with a simultaneous reduction in airway pressure can cause further decompensation in patients with existing cardiac insufficiency.[32] Räsänen et al[33] showed a need for adequate ventilatory support and CPAP levels in patients with respiratory and cardiogenic failure. Provided that spontaneous breathing receives adequate support and that satisfactory CPAP levels are applied, maintaining spontaneous breathing during APRV should not be a disadvantage and is not per se contraindicated in patients with ventricular dysfunction.[33]

Oxygen Supply and Demand

An increase in cardiac index and arterial oxygenation (Pa_{O_2}) during APRV improves the relationship between tissue oxygen supply and demand because oxygen consumption remains unchanged despite the work of spontaneous breathing. In accordance with previous experimental[21,22] and clinical findings,[13] total oxygen consumption is not measurably altered by adequately supported spontaneous breathing in patients with low lung compliance. An increase in oxygen delivery with unchanged oxygen consumption indicates an improved tissue oxygen supply and demand balance, as reflected by a decrease in oxygen extraction ratio and higher mixed venous partial pressure of oxygen.

Organ Perfusion

By reducing cardiac index and venous return to the heart, CMV can have a negative effect on the perfusion and functioning of extrathoracic organ systems. An increase in venous return and cardiac index, secondary to the periodic fall in intrathoracic pressure during spontaneous inspiration, should significantly improve organ perfusion and function during partial ventilator support. In patients with ARDS during spontaneous breathing with APRV, renal perfusion and glomerular filtration rate improve.[34] Using the colored microsphere technique, Hering et al[35,36] observed (in an experimental model) that spontaneous breathing during APRV improves systemic and mucosal-submucosal blood flow in the gastrointestinal tract as compared to CMV (with and without permissive hypercapnia); hepatic arterial blood flow remained essentially unchanged. In the absence of an increased intracranial pressure, regional cerebral and spinal cord blood flows were higher with spontaneous breathing.[37]

RATIONALE, ADVANTAGES, AND LIMITATIONS

Based on physiologic observations, APRV is advantageous for recruiting atelectasis adjacent to the diaphragm, thereby improving pulmonary gas exchange in patients with ALI, ARDS, and atelectasis after major surgery. Because increase in Ptp is localized to the areas near the diaphragm and is caused by a decrease in pleural pressure, the concomitant decrease in intrathoracic pressure contributes to improved cardiovascular function. Areas of atelectasis not adjacent to the diaphragm may not be successfully recruited by spontaneous breathing during APRV.

To enable spontaneous breathing, lower levels of sedation (Ramsay Score of 2 to 3) are required. Less sedation helps to reduce the dosages of vasopressor and inotropic agents, while maintaining cardiovascular function stability. In addition, less sedation reduces the duration of ventilator support.[25] The use of APRV, however, has to be limited to patients who do not require deep sedation for management of their underlying disease (e.g., cerebral edema with increased intracranial pressure).

Two periods during the APRV cycle are particularly vulnerable to patient–ventilator asynchrony. When airway pressure release occurs during spontaneous inspiration and when restoration of CPAP occurs during spontaneous expiration, ventilation may be impaired because spontaneous and ventilator efforts oppose each other. Rarely, a

reduction in ventilatory efficiency, indicated by a decrease in alveolar ventilation and an increase in work of breathing, may result from temporary asynchrony. Synchronized APRV and optimizing ventilator settings and sedation may be required in this rare event.[38]

As a concept, APRV does not provide breath-to-breath assistance to spontaneous inspiration. Previous investigations demonstrated that separation from mechanical ventilation in difficult-to-wean patients may be prolonged with use of intermittent mandatory ventilation (IMV) and may be expedited with breath-to-breath assistance to inspiratory efforts during PSV.[4] Thus, APRV is not expected to be an advantage in difficult-to-wean patients.

INDICATIONS AND CONTRAINDICATIONS

Indications

Based on clinical[13,25,26–28,39] and experimental[15–17,21,22] data, APRV is indicated in patients with ALI, ARDS, and atelectasis after major surgery. APRV recruits atelectasis adjacent to the diaphragm, thereby restoring pulmonary gas exchange, and improves cardiovascular and extrathoracic organ function in patients with ALI or ARDS, and atelectasis after major surgery.

Contraindications

Because lower levels of sedation (Ramsay Score of 2 to 3) are used to enable spontaneous breathing, APRV should not be used in patients who require deep sedation for management of their underlying disease (e.g., cerebral edema with increased intracranial pressure).

To date, no data are available on use of APRV in patients with obstructive lung disease. Theoretically, use of a short release time should not be beneficial in patients with obstructive lung disease who have prolonged expiratory time constants. Currently, use of APRV is not supported in these patients by clinical research.

Likewise, use of APRV has not been investigated in patients with neuromuscular disease, and is not supported by any evidence.

COMPARISON WITH OTHER MODES

Airway Pressure Release Ventilation versus Pressure-Support Ventilation

APRV and PSV were compared in twenty-four patients with ALI and/or ARDS using equal V_E or airway pressure limits. Because insufflation during PSV is flow-cycled, alveolar end-inspiratory pressure may not reach the preset level. Thus, in patients with reduced lung compliance, equal airway pressure limits achieve a lower V_T during PSV as compared with APRV. Consequently, a compensatory increase in respiratory rate is required during PSV to maintain alveolar ventilation. To deliver APRV and PSV with comparable V_T at an acceptable respiratory rate, the pressure level has to be increased during PSV.[13]

In contrast to spontaneous breathing with APRV, assisted inspiration with PSV did not produce significant improvement in intrapulmonary shunt, gas exchange or cardiac output when compared with CMV.[13] Apparently, the spontaneous contribution to a mechanically assisted breath was not sufficient to counteract the $\dot{V}_A/\dot{Q}$ maldistribution and cardiovascular depression caused by positive-pressure ventilation. A possible explanation might be that inspiration is terminated by the decrease in inspiratory gas flow during PSV, which may reduce ventilation in areas of the lung that have a slow time constant.

Airway Pressure Release Ventilation versus Intermittent Mandatory Ventilation

In a randomized multicenter trial in fifty-two patients with ALI, APRV with lower peak airway pressures resulted in a better alveolar ventilation and equal arterial oxygenation as compared with IMV.[26] A similar trial in fifty-eight patients with ALI supports these findings, but did not show a difference in mortality.[40] In eight patients recovering from open-heart surgery, APRV provided adequate ventilation with lower airway pressures and less dead-space ventilation than did IMV or PSV.[41] Arterial oxygenation was not different between the modalities.

Airway Pressure Release Ventilation versus Assist-Control Ventilation

A comparison of 234 patients ventilated with APRV with 234 patients ventilated with assist-control ventilation in a case-matched analysis revealed no differences in days of mechanical ventilation or weaning, rate of reintubation, length of stay in the intensive care unit or the hospital, and mortality in the intensive care unit or the hospital.[28] In this study, APRV was used in almost all disease states that lead to acute respiratory failure. The doses and duration of sedatives and analgesics were not different between the groups and the amount of spontaneous ventilation during APRV was not reported. Likewise, a randomized controlled trial involving sixty-two trauma patients showed no differences between APRV and assist-control ventilation for ventilator days, length of stay in the intensive care unit, pneumothorax, ventilator-associated pneumonia, or mortality.[27]

VARIATION IN DELIVERY AMONG VENTILATOR BRANDS

Synchronized Airway Pressure Release Ventilation

Asynchronous interferences between spontaneous and mechanical ventilation may increase the work of breathing and reduce the effective support during APRV.[38] Synchronization of the switching between the two CPAP levels to spontaneous inspiration or expiration has been incorporated in all commercially available demand-valve APRV circuits to avoid asynchronous interferences between spontaneous and mechanical breaths. A trigger window of 0.25 seconds is usually used to enable synchronization of the switching between the two CPAP levels and spontaneous breathing efforts. Bench-model data indicate that the synchronization of spontaneous inspiration with the switch to the high CPAP level, but not the synchronization of spontaneous expiration synchronized with pressure release, may be beneficial. Patient data on the advantage of synchronized APRV are lacking currently. Because patient-triggered mechanical cycles during IMV are not advantageous for patients, there is no reason why this should be different for APRV. Synchronization during APRV may produce inconstant times for the high and low CPAP. Synchronization of APRV is switched off in the APRV mode of Dräger Evita IV, XL, and V500 ventilators. In the Servo I, the Bennett 840, Hamilton G5, and the Viasys Vela and Avea ventilators, APRV is synchronized with spontaneous ventilation.

Modifications of Airway Pressure Release Ventilation

Most commercially available ventilators offer hybrid modes of ventilation such as APRV + PSV and APRV + automatic tube compensation (Table 11-1). Very few of these combinations have been shown to benefit patients.[42] It is doubtful that simply combining different modalities will achieve an addition of their positive effects.[43,44] Indeed, it is possible that proven physiologic benefit of one modality might be minimized or even neutralized when it is by combined with another mode.

TABLE 11-1: MODIFICATIONS OF AIRWAY PRESSURE RELEASE VENTILATION

- Synchronized APRV
  - Change between CPAP levels is synchronized with spontaneous breathing
  - Advantage of synchronization is not proven
- Intermittent mandatory pressure release ventilation
  - Spontaneous breathing on the high CPAP level is assisted with PSV
  - Advantage is not supported by data
- APRV + PSV
  - Spontaneous breathing on the low CPAP level is assisted with PSV
  - Advantage is not supported by data
- APRV + ATC
  - Spontaneous breathing on both CPAP levels is assisted with ATC
  - May reduce work of breathing in selected patients without deteriorating gas exchange

Abbreviations: *APRV*, Airway pressure release ventilation; *ATC*, automatic tube compensation; *CPAP*, continuous positive airway pressure; *PSV*, pressure-support ventilation.

ADJUSTMENTS AT THE BEDSIDE

Setting Ventilation Pressures and Tidal Volumes during Airway Pressure Release Ventilation

Mechanical ventilation with positive end-expiratory pressure (PEEP) titrated above the lower inflection pressure of a static pressure–volume curve and a low V_T is thought to prevent tidal alveolar collapse at end-expiration and overdistension of lung units at end-inspiration in patients with ARDS.[45] This lung-protective strategy causes improvement in lung compliance, venous admixture, and Pa_{O_2} without causing cardiovascular impairment in ARDS.[45] Mechanical ventilation using V_T of not more than 6 mL/kg (ideal body weight) has been shown to result in a better outcome when compared with a V_T of 12 mL/kg (ideal body weight) in patients with ARDS.[45,46] Based on these results, CPAP levels during APRV should be titrated to prevent end-expiratory alveolar collapse and tidal alveolar overdistension.[45,46] When CPAP levels during APRV were adjusted in patients with ARDS according to a lung-protective strategy, occurrence of spontaneous breathing led to improved cardiorespiratory function without affecting total oxygen consumption secondary to the work of breathing.[13] Moreover, pulmonary compliance should be greatest in this range of airway pressures and, thus, a small change in transpulmonary pressure achieves normal tidal breathing with minimal elastic work of breathing (Fig. 11-4).[47] Because APRV does not provide assistance on every inspiratory effort, the CPAP levels need to be carefully adjusted to achieve efficient spontaneous ventilation with minimal work of breathing.

Setting Times during Airway Pressure Release Ventilation

The duration of the high-CPAP level needs to allow at least complete inflation of the lungs, as indicated by an end-inspiratory phase of no flow when spontaneous breathing is absent. Spontaneous breathing occurs normally on the

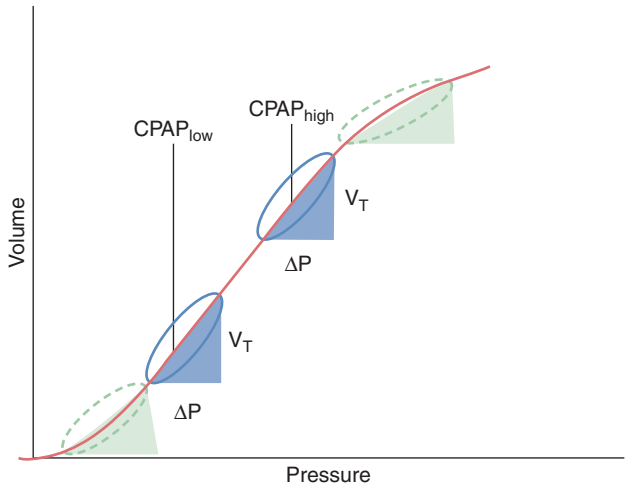

FIGURE 11-4 During airway pressure-release ventilation, both CPAP levels should be titrated to achieve the greatest compliance. Thus, a small change in transpulmonary pressure (*ΔP*) achieves normal tidal breathing (V_T), while elastic work of breathing (*shaded area*) is minimal. If the CPAP levels are too high or too low (*dashed lines*), elastic work of breathing will be increased unnecessarily (*shaded areas*).

high-CPAP level. Thus, duration of the high-CPAP level should be adjusted so that it is long enough to allow spontaneous breathing. If the release time is shorter than four times the time constant of the lungs (τ = compliance × resistance), alveolar pressure will not equilibrate at the low-CPAP level, and intrinsic PEEP (PEEPi) will result.[48,49] Incomplete expiration and the likelihood of PEEPi is indicated by gas flow at end-expiration (Fig. 11-5). In the presence of PEEPi, alveolar pressure amplitude will be reduced; consequently, alveolar ventilation decreases and partial pressure of carbon dioxide increases. To date, data do not indicate that PEEPi is superior to external PEEP in preventing derecruitment of the lungs. Thus, duration of the low CPAP level should be adjusted to allow complete expiration to resting lung volume.

Other Concepts of Setting Airway Pressure Release Ventilation

Other approaches use high-CPAP levels, which are briefly released to near-ambient pressure during APRV. Depending on the time constant of the lungs, brief release times may cause PEEPi. Clinical studies, however, demonstrate that external PEEP is superior to PEEPi in restoring gas exchange in patients with ALI. Not surprisingly,

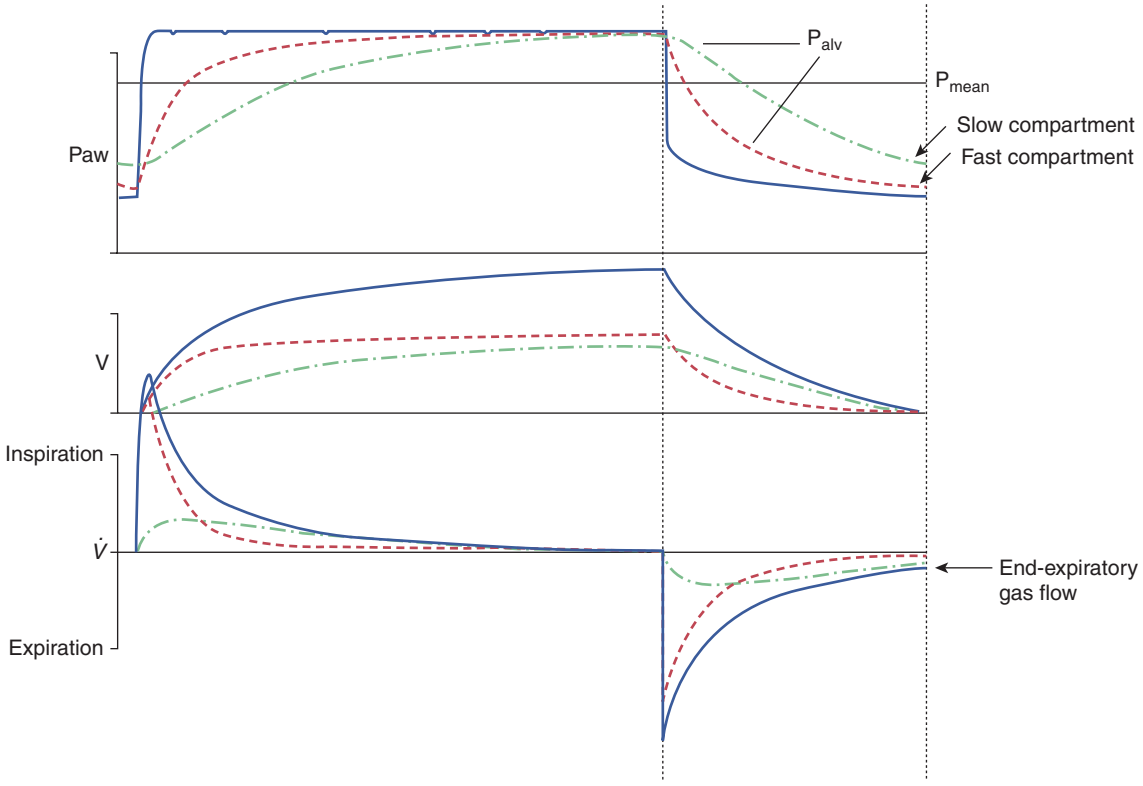

FIGURE 11-5 Computer simulation of airway pressure (*Paw*), volume (*V*), and gas flow ($\dot{V}$) for the respiratory system, and both a fast and slow lung compartment with a short release time. Expiration in the slow compartment is not completed at end-expiration; consequently, gas flow is still present at end-expiration and associated with intrinsic PEEP.

in patients with ARDS, Cane et al[26] observed an increase in atelectasis upon briefly releasing high-CPAP levels to near-ambient pressure during APRV. Recent trials and case series based on this method of adjusting APRV reported better oxygenation when APRV was used as a rescue strategy in severely hypoxemic patients with ARDS.[27,50,51]

TROUBLESHOOTING

Analgesia and Sedation during Airway Pressure Release Ventilation

Analgesia and sedation are used not only to ensure satisfactory pain relief and anxiolysis, but also to help the patient adapt to mechanical ventilation.[52] The additional use of neuromuscular paralysis is controversial.[53] The level of analgesia and sedation required during CMV is equivalent to a Ramsay score higher than 5; that is, a deeply sedated patient unable to respond when spoken to and who has no sensation of pain. During APRV, a Ramsay score of 2 to 3 can be targeted; that is, an awake, responsive, and cooperative patient. In nearly 600 postcardiac surgery patients,[39] and in patients with multiple injuries,[25] maintaining spontaneous breathing during APRV led to less consumption of analgesics and sedatives as compared with initial use of CMV followed by weaning with partial ventilator support. Higher doses of analgesics and sedatives used in patients managed with CMV are associated with the use of higher doses of vasopressors and inotropic agents to maintain stable cardiovascular function,[25] and have been suggested to produce a higher incidence of delirium, longer duration of mechanical ventilation and stay in the intensive care unit, and mortality.[54]

IMPORTANT UNKNOWNS

Although prospective randomized trials have found improved cardiopulmonary function in the absence of an increased mortality or longer duration of mechanical ventilation with the use of APRV, concerns have been raised as to whether an increased transpulmonary pressure consequent to spontaneous breathing efforts can contribute to ventilator-induced lung injury. In addition, the effect of lower levels of sedation during APRV on the incidence of delirium and mortality has yet to be investigated.

THE FUTURE

Randomized controlled studies and case-matched analysis have demonstrated that early spontaneous breathing with APRV in patients with ALI/ARDS and in patients with pulmonary dysfunction after trauma and major surgery leads to improved arterial oxygenation and cardiovascular function. Larger randomized multicenter trials are needed to test the validity of these results in critically ill patients.

SUMMARY AND CONCLUSION

Based on available data, it is suggested that spontaneous breathing during ventilator support does not need to be suppressed, even in patients with severe pulmonary dysfunction, if there is no contraindications (e.g., increased intracranial pressure). Improvement in pulmonary gas exchange, systemic blood flow, and oxygen supply to the tissue with less consumption of analgesics and sedatives has been observed even in severe ARDS. Maintaining spontaneous breathing with APRV has not yet been shown to significantly change outcome. CMV followed by weaning with partial ventilator support is the standard in ventilation therapy, but the place of spontaneous breathing with APRV should be reconsidered in view of available data. Today's standard practice should be to maintain spontaneous breathing as early as possible during ventilator support and to continuously adapt the level of support according to the individual needs of the patient.

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12

PROPORTIONAL-ASSIST VENTILATION

Magdy Younes

Proportional-assist ventilation (PAV) is a form of synchronized ventilator support in which the ventilator generates pressure in proportion to *instantaneous* patient effort (Fig. 12-1).[1] The ventilator simply amplifies inspiratory efforts. Unlike other modes of partial support, there is no target flow, tidal volume, or ventilation or airway pressure. Rather, PAV's objective is to allow the patient to comfortably attain whatever ventilation and breathing pattern his or her control system desires.[1] The main operational advantages of PAV are automatic synchrony with inspiratory efforts and adaptability of the assist to changes in ventilatory demand (Fig. 12-1).

BASIC PRINCIPLES AND ALGORITHMS: HOW CAN A VENTILATOR DELIVER PRESSURE IN PROPORTION TO PATIENT EFFORT WITHOUT DIRECTLY MEASURING EFFORT?

A simple PAV delivery system illustrates how this happens (Fig. 12-2).[2] Alveoli and chest wall are represented as an elastic compartment that opposes expansion. Elastic recoil pressure (Pel; hatched arrow in Fig. 12-2) is a function of how much lung volume deviates from passive functional residual capacity (FRC) and the stiffness of the system: Pel = V × E, where V is volume above FRC and E is respiratory system elastance. In a passive system, Pel increases alveolar pressure as the lung is artificially inflated. During assisted ventilation, inspiratory muscles are active. These muscles decrease alveolar pressure by an amount corresponding to their pressure output (Pmus) (Fig. 12-2). At any instant, alveolar pressure (Palv) is the difference between Pel (V × E), which tends to increase it, and Pmus, which tends to decrease it:

$$Palv = (V \times E) - Pmus \quad (1)$$

The elastic compartment is connected to the external tubing via airways and the endotracheal tube. The ventilator controls pressure at the external airway (Paw). Air flows into the lungs when Paw exceeds Palv. Flow is a function of the difference between Paw and Palv (resistive pressure) and the resistance of the intervening tubing (R). Thus

$$Flow = (Paw - Palv)/R \quad (2)$$

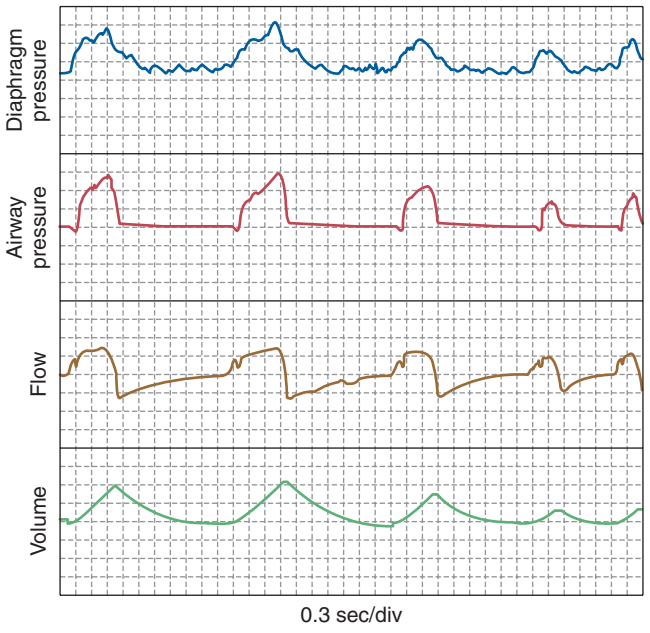

FIGURE 12-1 Relationship between assist provided (airway pressure) and independently measured diaphragmatic pressure in proportional-assist ventilation. Note that amplitude and duration of assist correspond to amplitude and duration of inspiratory efforts.

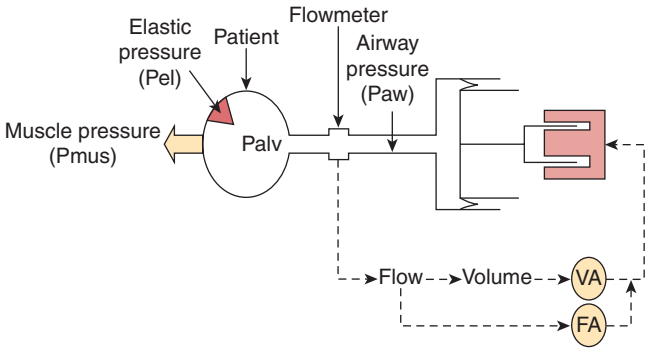

FIGURE 12-2 Diagram illustrating how a PAV delivery system generates pressure in proportion to effort. The gas-delivery system consists of a freely moving piston pressurized by a fast-acting motor. Force exerted by motor is a function of flow and volume leaving the ventilator. A stronger effort results in greater reduction in alveolar pressure (*Palv*), drawing more gas from the piston and resulting in more assist. If the volume-assist (*VA*) and flow-assist (*FA*) components are set to the same fraction of elastance and resistance, respectively, the pressure generated becomes proportional to effort (*Pmus*). See text.

Substituting equation (Eq.) 1 for Palv in Eq. 2 and rearranging, we get

$$\text{Flow} \times R = \text{Paw} - (V \times E) + \text{Pmus}$$

or

$$\text{Pmus} + \text{Paw} = \text{flow} \times R + V \times E \qquad (3)$$

This equation simply states that the distending force is the sum of patient-generated (Pmus) and ventilator-generated (Paw) pressures and that this distending force is opposed by the sum of resistive pressure drop (resistive pressure, or flow × R) and elastic recoil pressure (Pel, or V × E).

The gas-delivery system in Figure 12-2 is a freely moving piston pressurized by a fast-responding linear motor. This arrangement emphasizes that PAV gas-delivery systems must allow rapid and free flow of gas in response to changes in alveolar pressure. Flow and volume leaving the ventilator are measured. The gains of the flow and volume signals are adjustable by separate amplifiers: flow assist (FA) and volume assist (VA). The summed output of the two amplifiers is the input to the motor. Thus, the ventilator's pressure output is a function of instantaneous flow and volume that left the ventilator since triggering.

With this arrangement (see Fig. 12-2), a greater effort (more reduction in alveolar pressure) will draw more gas from the ventilator. This, in turn, results in more assist. This provides a positive relation between effort and assist but does not per se cause the assist to be proportional to instantaneous effort. Proportionality is achieved through customized adjustment of the FA and VA gains. The basis for these adjustments is as follows:

FA is the assist pressure per unit flow (in cm H_2O/L/s). These are resistance (R) units. If FA is 50% of R, the ventilator provides 50% of the resistive pressure (i.e., 50% of flow × R, Eq. 3). At 80% R, the ventilator assumes 80% of resistive work, and so on. Likewise, setting VA gain to 50% of E causes the ventilator to assume 50% of elastic pressure (i.e., 50% of V × E, Eq. 3), and so on. The total assist (Paw) is the sum of the flow and volume assists:

$$\text{Paw} = \%\text{flow} \times R + \%V \times E \qquad (4)$$

During the inspiratory phase, volume rises progressively, peaking at end inspiration. By contrast, flow peaks in early to middle inspiration and falls later. Thus, the relative contributions of resistive and elastic pressures vary considerably during the inspiratory phase. If the same percent is used for both components, total assist (Paw) represents the same percent of total pressure regardless of the relative contribution of each. Percent assist then is constant throughout. If different percent values are used for FA and VA, however, total assist (Paw) will represent a different percent of total applied pressure at different times. When percent assist (ventilator's contribution) is constant throughout inspiration, patient's percent contribution (i.e., 100 – percent assist) is also constant throughout and the relationship between Paw and Pmus (i.e., proportionality becomes constant) as given by

$$\text{Proportionality} = \text{percent assist}/(100 - \text{percent assist})$$

Thus, at 50% assist, proportionality is 1.0; Paw equals Pmus throughout. At 80% assist, proportionality is 4, and so on. Under these conditions, the shapes of the Pmus and Paw waveforms are identical, and the decline in Pmus at end inspiration is associated with a decline in Paw, ensuring synchrony (Fig. 12-3A). By contrast, if percent assist varies through inspiration (such as by using different percent

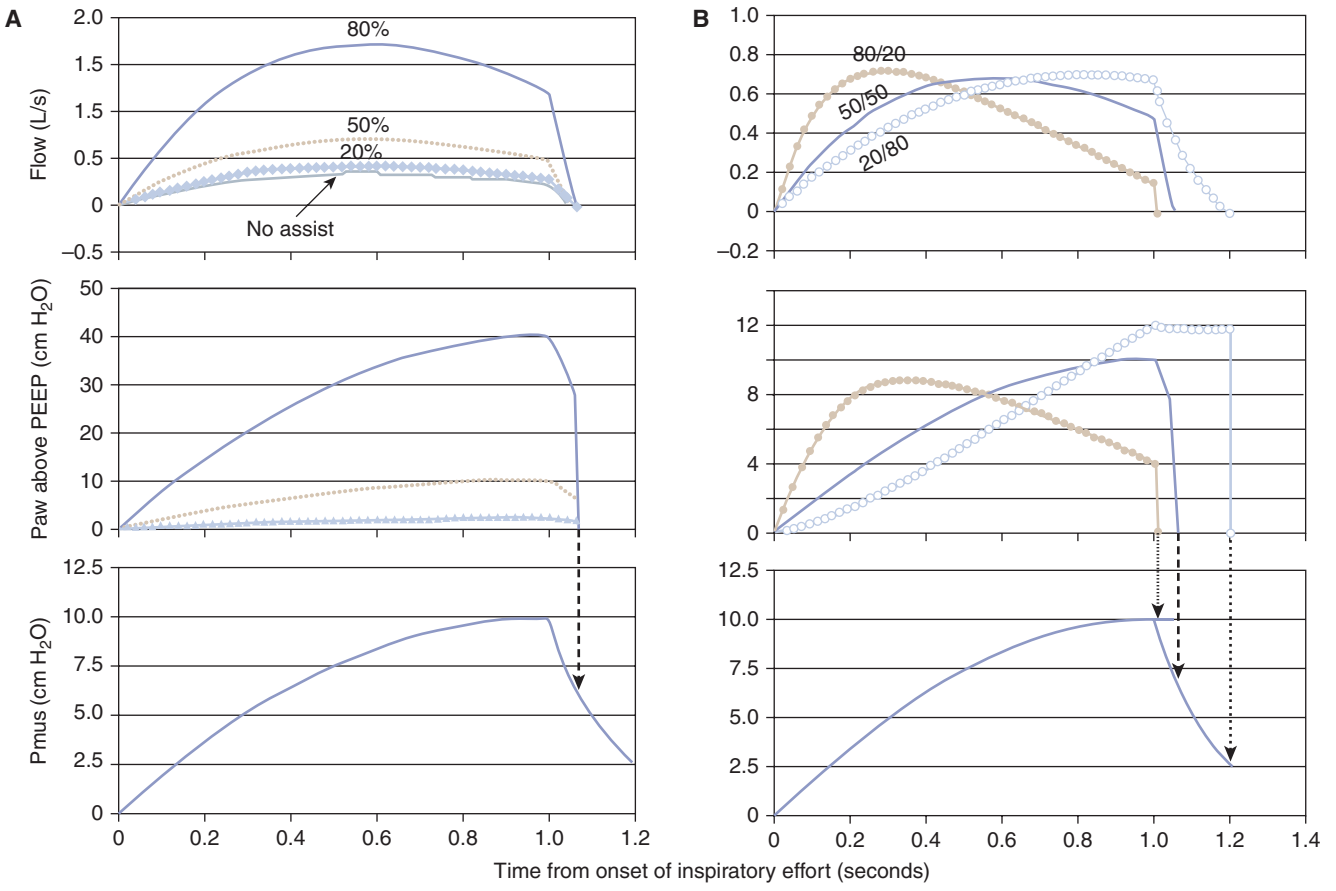

FIGURE 12-3 Model simulation showing the impact of using equal (A) versus unequal (B) percent assist for the flow and volume components. **A.** Three assist levels are shown: 20%, 50%, and 80%. When the same percent assist is applied to both components, the shape of the assist (airway pressure [*Paw*]) is identical to that of muscle pressure (*Pmus*), but the proportionality is different (Paw/Pmus = 0.25, 1.0, and 4.0, respectively). Note also that flow reaches zero (end of mechanical inspiration) at the same time during the declining phase of *Pmus* at all assist levels, including the no-assist situation (*top panel*). **B.** Flow assist is 80% of resistance, and volume assist is 20% of elastance (*solid dots*). Note that the assist (*Paw*) is more aggressive early in inspiration and terminates sooner relative to the balanced assist (*50/50 line*). A relatively greater volume assist (*open circles*) offers less assist early while cycling off is delayed.

values for FA and VA), proportionality between Paw and Pmus is no longer constant, and the shapes of the two waveforms differ (Fig. 12-3B).

PHYSIOLOGIC EFFECTS

Relevant Physiologic Principles

These principles are discussed first because they not only help to explain PAV's reported effects, but also make it possible to gain useful insights from a patient's responses to this mode; reference 3 provides more details. Responses to PAV may be mediated by changes in blood-gas tensions (chemical factors) or through modification of nonchemical sources of respiratory drive. Chemical responses are highly predictable, whereas the others are not. What happens, therefore, depends on what sources of respiratory drive are operative at the time of application.

SOURCES OF RESPIRATORY DRIVE

During sleep and anesthesia, chemical factors are the sole source of respiratory drive; artificially reducing the partial pressure of carbon dioxide (P_{CO_2}) under these conditions abolishes respiratory efforts.[4–6] Furthermore, in these states, respiratory muscle responses to changes in load are mediated exclusively via changes in blood-gas tensions.[7] Conversely, in alert individuals, other sources of respiratory drive exist; it is very difficult to produce apnea by assisted ventilation despite marked hypocapnia.[8–11] These drive inputs, collectively called the *consciousness factor,*[4] presumably arise from behavioral centers and from respiratory mechanisms that operate only during consciousness (e.g., nonchemical load-compensatory mechanisms[7]). Patients who require mechanical ventilation cover a wide spectrum of levels of consciousness. Therefore, it is difficult to make general conclusions about their drive inputs. The next few sections describe what should happen in response to PAV if respiratory output were driven solely by

chemical factors. Deviation from this expected behavior then might be attributed to nonchemical factors.

DETERMINANTS OF V_E AND Pa_{CO_2} IN THE ABSENCE OF NONCHEMICAL DRIVE SOURCES

Without Assist. A steady state in P_{CO_2} and minute ventilation ($\dot{V}_E$) can occur only if pulmonary carbon dioxide (CO_2) removal (the product of alveolar ventilation [$\dot{V}_E$] and alveolar CO_2 concentration [$F_{A_{CO_2}}$]) equals the CO_2 produced by the tissues ($\dot{V}_{CO_2}$). At a given $\dot{V}_{CO_2}$, if ventilation is increased artificially, $F_{A_{CO_2}}$, and hence Pa_{CO_2}, must decrease before a steady state is reached. Accordingly, at a given $\dot{V}_{CO_2}$, there is an inverse relationship between $\dot{V}_E$ and Pa_{CO_2} in the steady state—the metabolic hyperbola.[12] The actual equation is $Pa_{CO_2} = 0.86\ [\dot{V}_{CO_2}/\dot{V}_E(1 - V_D/V_T)]$,[12] where V_D/V_T is the dead-space-to-tidal-volume ratio. Figure 12-4A illustrates this relationship.

Ventilation increases progressively as a function of P_{CO_2}.[13] The slope of the response depends on the sensitivity of chemoreceptors (the sensory arm) and the effectiveness of the motor arm in generating ventilation. Thus, for a given chemoreceptor response, ventilatory response is less if respiratory muscles are weaker or mechanics are abnormal. Without nonchemical drive sources, there is a Pa_{CO_2} below which apnea develops,[4–6] the apneic threshold (AT; see Fig. 12-4).

Four subjects with different disorders are illustrated in Figure 12-4A. For each subject, there is only one possible steady state, namely, the point of intersection of the CO_2 response line and the hyperbola.[13] At this point, pulmonary CO_2 elimination equals tissue CO_2 production.

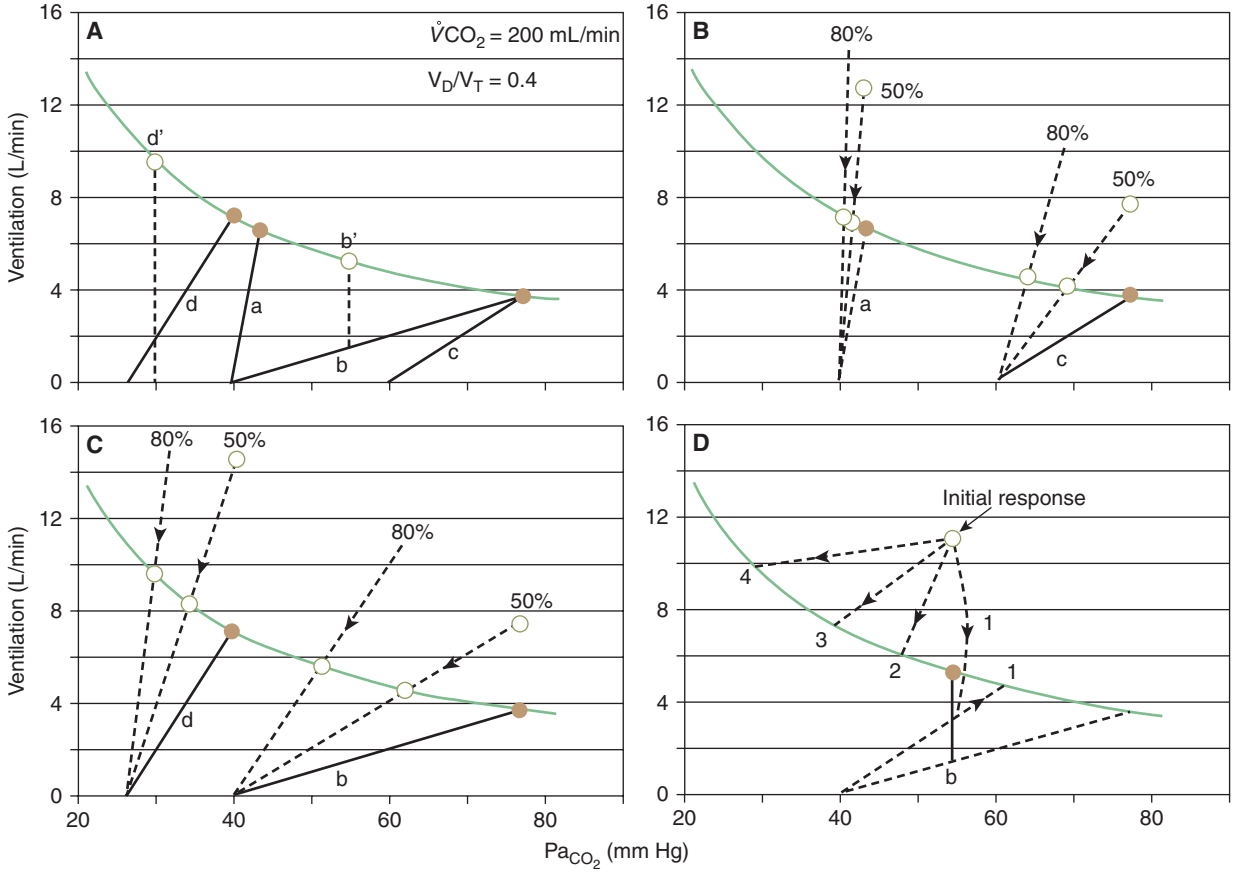

FIGURE 12-4 Effect of proportional assist on steady-state ventilation ($\dot{V}_E$) and Pa_{CO_2}. A metabolic hyperbola is shown for a subject with CO_2 production ($\dot{V}_{CO_2}$) of 200 mL/min and a dead-space-to-tidal-volume ratio (V_D/V_T) of 0.4. **A.** Unassisted breathing. The ventilatory responses to CO_2 in four subjects are shown: (*a*) normal, (*b*) acute hypercapnic failure, (*c*) chronic hypercapnic failure, and (*d*) acute nonhypercapnic failure with metabolic acidosis. In each case, the x intercept of the ventilatory response is the apneic threshold. The apneic threshold is shifted up in subject *c* and down in subject *d*. The intersection of ventilatory response line and the hyperbola gives steady-state values for $\dot{V}_E$ and Pa_{CO_2}. *Vertical dotted lines* represent additional nonchemical inputs that cause ventilation to be higher and Pa_{CO_2} to be lower than in their absence. **B** and **C.** Effect of 50% and 80% assist in the four subjects. In each case the ventilatory response slope doubles with 50% assist and increases fivefold at 80%. Open circles off the hyperbola are immediate responses not consistent with steady state. Open circles on the hyperbola are the steady-state values with assist. Note that the magnitude of change in $\dot{V}_E$ and Pa_{CO_2} is a function of the difference between unassisted Pa_{CO_2} (*solid circle*) and the apneic threshold. **D.** Response to proportional assist in the presence of nonchemical input (*vertical solid line*). Note that the response is highly unpredictable (see text).

Line *a* represents a normal subject. Ventilatory response is normal (2.2 L/min/mm Hg), and AT is 40 mm Hg. The intersection point is at a Pa_{CO_2} of 43 mm Hg and a $\dot{V}_E$ of 6.6 L/min. The difference between unassisted (no assist [NA]) steady-state P_{CO_2} and AT (i.e., $\Delta P_{CO_2, NA\text{-}AT}$) is very small (3 mm Hg). Line *b* represents a patient with severe acute hypercapnic respiratory failure. AT is the same, but the ventilatory response to CO_2 is greatly depressed because of abnormal mechanics. The intersection point is 76 mm Hg at a $\dot{V}_E$ of 3.8 L/min. $\Delta P_{CO_2, NA\text{-}AT}$ is very large (36 mm Hg). Line *c* describes a patient with chronic respiratory failure. Ventilatory response to CO_2 is depressed because of abnormal mechanics and/or weak respiratory muscles. In this case, however, AT is higher. $\Delta P_{CO_2, NA\text{-}AT}$ is larger than normal (16 mm Hg), but for the same steady-state Pa_{CO_2}, it is lower than in the patient represented by line *b*. Line *d* represents a patient with a reduced ventilatory response to CO_2 (0.6 L/min/mm Hg) because of abnormal mechanics or weak muscles but in whom the apneic threshold is low, for example, because of concomitant metabolic acidosis.[14] Steady-state P_{CO_2} and $\dot{V}_E$ are near normal, but $\Delta P_{CO_2, NA\text{-}AT}$ is large.

Expected Response to Proportional-Assist Ventilation Application. With PAV, respiratory motor output is amplified by an amount that is related to percent assist (see Fig. 12-3A). Within the linear range of the pressure-volume and pressure-flow relationships, the amplification of pressure results in a corresponding amplification of ventilation (see Fig. 12-3A). Thus, the net effect of PAV is to increase the slope of the ventilatory response to CO_2 (as well as to the partial pressure of oxygen [P_{O_2}] and pH). For simplicity, we will assume that P_{CO_2} is the only stimulus and that resistance and elastance are constant in the tidal volume range. Under these conditions, at 50% assist, delivered assist equals Pmus, and the combined pressure (patient + ventilator) is twice Pmus. Accordingly, the slope of the CO_2 response is doubled. At 80% assist, Paw is four times Pmus (see Fig. 12-3A), and pressure output is amplified by a factor of five. The ventilatory response should increase nearly fivefold, and so on.

In the normal subject (line *a*), 50% assist doubles the CO_2 response (see Fig. 12-4B). $\dot{V}_E$ immediately doubles (*upper open circle*). Pulmonary CO_2 output now exceeds $\dot{V}_{CO_2} \cdot Pa_{CO_2}$ falls. Respiratory efforts decrease, and $\dot{V}_E$ follows along the new CO_2 response line until the metabolic hyperbola. A steady state is now possible. The same would happen at higher percent assist. Because steady-state values must be above the AT, and $\Delta P_{CO_2, NA\text{-}AT}$ is very small, $\dot{V}_E$ and Pa_{CO_2} cannot change much. Furthermore, because $\dot{V}_E$ hardly changes, virtually all the assist (Paw) is used to reduce respiratory motor output, and percent reduction in Pmus is similar to percent assist.

A similar analysis for the patient with chronic respiratory failure (line *c* in Fig. 12-4B) shows that at 50% assist, Pa_{CO_2} decreases by 7 mm Hg and $\dot{V}_E$ increases by 10%, whereas at 80% assist, Pa_{CO_2} decreases by 13 mm Hg and $\dot{V}_E$ increases by 20%. Because $\dot{V}_E$ increased significantly, the decrease in respiratory muscle output (Pmus) is less than percent assist. For example, at 50% assist, Pmus is contributing 50% to a higher $\dot{V}_E$ (110%). The decrease in Pmus is 45% instead of 50%. Because the difference between Pa_{CO_2} at 80% assist and AT is now very small, increasing assist beyond 80% would have little further effect even though Pa_{CO_2} is still high. Thus, when AT is high, it is not possible to acutely normalize Pa_{CO_2} using PAV (or any other strictly assist mode).

In the patient with severe acute hypercapnic failure (line *b* in Fig. 12-4C), the changes are even greater. At 50% and 80% assist, Pa_{CO_2} decreases by 14 and 25 mm Hg, respectively, and $\dot{V}_E$ increases by 23% and 50%. Even at 80% assist, the difference between Pa_{CO_2} and AT is still large, and further reduction in Pa_{CO_2} is possible. Because $\dot{V}_E$ increases substantially, the decrease in Pmus is much less than percent assist (39% and 70%, for the 50% and 80% assist, respectively).

Finally, in the patient represented by line *d* in Figure 12-4C, increasing PAV assist results in progressive hypocapnia. By normalizing mechanics, the effect of the concomitant metabolic acidosis is now exposed.

In summary, *in the absence of nonchemical drive sources*, whether and by how much ventilation and Pa_{CO_2} change following institution of a given percent assist are determined by the unassisted ventilatory response to CO_2, the apneic threshold, and the position of the metabolic hyperbola. These determine the difference between unassisted Pa_{CO_2} and AT. Because the more $\dot{V}_E$ increases, the less Pmus decreases, the same three factors determine the extent to which the assist is used to increase ventilation versus decrease muscle output.

EFFECT OF NONCHEMICAL DRIVES ON RESPONSE TO PROPORTIONAL-ASSIST VENTILATION

The action of nonchemical drive inputs can be viewed as additive with chemical drive. They cause ventilation to be higher at a given Pa_{CO_2} than if chemical drive were the sole source (points *b′* and *d′* in Fig. 12-4A). Total drive is made up of a CO_2-sensitive component and a component that reflects consciousness-related reflexes and unpredictable behavioral influences.

Figure 12-4D illustrates how these inputs may modify the response to PAV. Without nonchemical influences, Pa_{CO_2} would be 76 mm Hg. Because of the nonchemical input (*solid vertical line*), however, steady-state $\dot{V}_E$ is 5.5 L/min at a Pa_{CO_2} of 55 mm Hg. A 50% assist results in an immediate increase in $\dot{V}_E$ to 11 L/min (both components are amplified). Pa_{CO_2} must fall. What happens then depends on the response of the nonchemical component. At one extreme, it may disappear (e.g., the patient may fall asleep when assisted). $\dot{V}_E$ would fall to the new CO_2 response line (*diagonal dashed line*). Should $\dot{V}_E$ at this point be below the hyperbola, Pa_{CO_2} and $\dot{V}_E$ will rise along the CO_2 response line, reaching the hyperbola at point 1. Here the assist is followed by an increase in Pa_{CO_2}, but the patient is working

much less. If the nonchemical stimulus remains the same, Pa_{CO_2} and $\dot{V}_E$ will decrease along a path parallel to the CO_2 response line, meeting the hyperbola at point 3. Here, there is no longer a CO_2 stimulus, and ventilation is sustained by the twice-amplified nonchemical influence. An intermediate value (point 2) may result if the nonchemical influence partially decreases. Finally, at the other extreme, the patient may become agitated with the assist, increasing the nonchemical stimulus, and this, when amplified, may reduce Pa_{CO_2} to very low levels (point 4). It is clear that with nonchemical stimuli (alert individuals), the ventilatory response to PAV is theoretically unpredictable.

Reported Physiologic Responses

RESPIRATORY MUSCLE OUTPUT

PAV resulted in significant reduction in muscle output in all studies where this was tested.[15–30] Typically, Pmus decreased by 30% to 45% at 50% assist and by 55% to 70% at 80% assist. The less-than-expected reduction is caused by (a) differences between assumed and actual E and R (see "Accuracy and Stability of Respiratory Mechanics Values" below), (b) imperfect delivery by the ventilator (see "Ventilator Response Time" below), (c) dynamic hyperinflation (see "Dynamic Hyperinflation" below) or nonlinearity in the pressure–volume relationship (see "Nonlinearity in the Pressure–Volume Relationship within the Tidal Volume Range" below), and (d) an associated increase in $\dot{V}_E$ (see "Ventilation and Partial Pressure of Carbon Dioxide" below). As indicated earlier, when some of the assist is used to increase $\dot{V}_E$, less is used to reduce muscle output.

VENTILATION AND PARTIAL PRESSURE OF CARBON DIOXIDE

Application of PAV to normal sleeping subjects results in an immediate increase in tidal volume (V_T) and $\dot{V}_E$, which decrease over several breaths to near-baseline levels.[17] Steady-state responses are minimal,[6,17] and the decrease in end-tidal CO_2 tension ($P_{ET}CO_2$) is very modest (approximately 3 mm Hg[6,17]). These results are consistent with a small difference between unassisted Pa_{CO_2} and AT secondary to a normal ventilatory response to CO_2 (subject represented by line *a* in Fig. 12-4B).

By contrast, in experienced, awake resting normal subjects, PAV results in an important increase in $\dot{V}_E$ and a more pronounced reduction in Pa_{CO_2}, and the decrease in respiratory muscle output is only modest.[18] Pa_{CO_2} generally decreases below the apneic threshold (e.g., 30 ± 5 mm Hg[18]), reflecting the presence of nonchemical drive inputs that fail to be eliminated. PAV applied to inexperienced, awake subjects is followed by unpredictable responses extending to severe hyperventilation (personal observations), reflecting erratic behavioral responses.

When PAV is applied to normal subjects during steady exercise[31] or during inhalation of CO_2-enriched air,[28] there is little change in ventilation. Thus, during ventilatory stimulation the assist is primarily utilized to reduce respiratory muscle output rather than to increase ventilation. Georgopoulos et al[32] measured Pmus during CO_2 rebreathing with and without PAV unloading. They found that Pmus was the same when measurements were compared at the same end-tidal P_{CO_2}. Thus, it appears that during exercise-induced or CO_2-induced ventilatory stimulation the downregulation of Pmus, at the same exercise level or the same fraction of inspired carbon dioxide (FI_{CO_2}), is mediated by small reductions in systemic P_{CO_2}.

There are numerous reports on the changes in $\dot{V}_E$ and Pa_{CO_2} with PAV in patients with respiratory failure.[15,16,19–26,33–39] Responses ranged from virtually no change or even a decrease in $\dot{V}_E$ as assist increased[33–36] to large increases in $\dot{V}_E$ and decreases in Pa_{CO_2}.[16,19,25,37] These differences can be explained readily if one considers the experimental circumstances of the various studies or patients.

1. *Intubated ventilator-dependent patients with normocapnia.* It is clearly not possible to establish steady-state values of $\dot{V}_E$ and Pa_{CO_2} during unassisted breathing in these patients as they rapidly develop distress. The effect of PAV is, accordingly, determined over a range of assist above a minimum value (e.g., 80% vs. 40%). Furthermore, in such patients, Pa_{CO_2} at the minimum tolerable assist is normal. All such studies demonstrated very little change or even a small decrease in $\dot{V}_E$ as assist increased.[33–36] Pa_{CO_2} decreased, but the change was small (2 to 4 mm Hg). These patients, therefore, behave like the subject represented by line *a* in Figure 12-4B, who has no nonchemical inputs and a small $\Delta P_{CO_2, NA\text{-}AT}$. This state, however, is reached only at some finite assist. It therefore would appear that these patients become comfortable only when their Pa_{CO_2} is a few millimeters of mercury above AT. Under these conditions, $\dot{V}_E$ cannot increase further by PAV application (Figure 12-4B, line *a*); the extra assist is used simply to decrease muscle output. The decrease in $\dot{V}_E$ observed in some cases[34,36] is caused by a reduction in V_D/V_T and/or $\dot{V}_{CO_2}$ (secondary to decreased respiratory muscle work) because in all such cases, Pa_{CO_2} was lower even though $\dot{V}_E$ was lower.[34,36]

   The preceding observations lead to an interesting conclusion: Ventilator-dependent patients who show little change in $\dot{V}_E$ and Pa_{CO_2} over a relatively wide PAV assist do not tolerate a Pa_{CO_2} that is much above AT. This indicates a high degree of chemosensitivity that likely contributes to their ventilator dependence. *Chemosensitivity,* as used here, does not refer to ventilatory responses (which are affected by mechanics and muscle strength) but to central effects of Pa_{CO_2} on respiratory sensation and muscle activation.
2. *Chronic hypercapnia with and without acute exacerbation.* In virtually all reported studies, $\dot{V}_E$ and Pa_{CO_2} on PAV were compared with values obtained during a period of

unassisted breathing.[16,19–21,23,25,26,40] Unlike the preceding group, there always was a significant increase in $\dot{V}_E$ and a decrease in Pa_{CO_2}. The changes were modest, however (approximately 25% increase in $\dot{V}_E$ and a 3- to 6-mm Hg decrease in Pa_{CO_2}). Such a response is consistent with a somewhat larger difference between AT and unassisted P_{CO_2} (subject represented by line *c* in Fig. 12-4B). Pa_{CO_2} remained abnormally high in all cases, consistent with a high AT. The changes in $\dot{V}_E$ and Pa_{CO_2} likely would have been greater if the hypoxic stimulus did not change. In all but one study,[19] Pa_{O_2} was quite low during unassisted breathing and improved with PAV. Because a higher Pa_{O_2} decreases the ventilatory response to CO_2,[13] an increase in Pa_{O_2} mitigates the increase in CO_2 response produced by PAV, resulting in a smaller increase in ventilatory response. The assist provided in this case is used preferentially to decrease muscle output as opposed to increasing $\dot{V}_E$. In one study,[19] the hypoxic drive was negligible at baseline (Pa_{O_2} = 99.5 mm Hg). Here, the increase in $\dot{V}_E$ was much greater (38%[19]). Although the changes in Pa_{CO_2} and Pa_{O_2} undoubtedly contributed to the reduction in respiratory muscle output, most of these patients were alert, so a reduction in nonchemical inputs may have been partly responsible.

3. *Acute hypercapnic failure.* Gay et al[38] reported an average 8 mm Hg decrease in Pa_{CO_2} (60 to 52 mm Hg) within a half hour of instituting noninvasive PAV. Likewise, in a study by Busterholtz et al on patients with acute cardiogenic pulmonary edema, Pa_{CO_2} decreased from 51 ± 25 to 41 ± 25 mm Hg and Pa_{O_2} increased from 66 ± 18 to 130 ± 30 mm Hg within 30 minutes of applying PAV.[41] Considering that not all patients in these two studies were hypercapnic and that the nonhypercapnic patients likely did not contribute to the average decrease (see 4 below), the decrease in Pa_{CO_2} in the hypercapnic group must have been greater. In another study,[37] there were four patients with acute hypercapnic failure not associated with central depression. In them, Pa_{CO_2} declined 17 mm Hg on average (66 to 49 mm Hg) within a half hour of instituting PAV. These observations suggest that patients with acute hypercapnia secondary to severe acute mechanical abnormalities do sustain large increases in $\dot{V}_E$ and reductions in Pa_{CO_2} on institution of PAV (see line *b*, Fig. 12-4C). Interestingly, Pa_{CO_2} remained above normal (approximately 50 mm Hg) in some patients for a few hours.[37] It is possible that the apneic threshold increased somewhat during the preceding period of severe hypercapnia.
4. *Acute hypoxemic failure.* Information about this group is scant. Although patients were included in three previous reports,[37–39] only in one study were the results of the normocapnic group (four patients) separated from those of hypercapnic patients.[37] In these four patients, Pa_{CO_2} did not change despite distress decreasing dramatically. The likely explanation for failure of Pa_{CO_2} to decrease is that respiratory muscle output to a large extent was related to nonchemical inputs, which decreased substantially on unloading (pathway 1 in Fig. 12-4D).

RESPIRATORY RATE AND BREATHING PATTERN

With one exception,[16] when there was no clinical distress at the lowest level of assist, application of PAV or further increases in percent assist did not result in appreciable changes in ventilator rate (i.e., >2 to 3 breaths/min). This applied to normal sleeping subjects,[6,17] intensive care unit (ICU) patients in whom percent assist was changed over a wide range above a comfortable level,[33–36] and ambulatory patients with chronic respiratory failure in whom the lowest level was spontaneous breathing.[19,20,24–26,40] In the only exception,[16] respiratory rate (RR) deceased substantially when PAV was applied, but in this case there were clear signs of runaway (i.e., patient was no longer in the PAV mode).

In patients with acute exacerbation of chronic obstructive pulmonary disease (COPD), RR on PAV was lower than during spontaneous breathing (3 to 5 breaths/min[21,23]). The pH, however, was low at baseline, and some degree of distress may have been present then. When PAV is applied to patients with clear respiratory distress, RR decreases dramatically along with relief of distress.[37–39]

From these observations it is clear that PAV does not per se change RR. RR changes only when PAV relieves respiratory distress. In physiologic studies in which respiratory drive is deliberately increased, RR does not increase until moderate levels of stimulation.[18,42] This applies whether stimulation is produced by hypercapnia, hypoxemia, acidosis, or an increase in metabolic rate.[43] Thus, a change in RR with assist level indicates that respiratory drive is in a range where RR is sensitive to drive and hence probably excessive, whereas failure of RR to change over a range of PAV assist indicates that respiratory drive is only modest over this range. There are two important clinical implications to these observations on PAV:

1. Failure of RR to change over a range of PAV assist indicates that respiratory drive is only modest over this range and that the RR observed in this range is the undistressed value preferred by the patient's control system. Importantly, undistressed RR, so defined, ranges from 12 to 46 breaths/min.[33,34] That undistressed RR varies widely among patients is consistent with the wide range in normal subjects (8 to 25 breaths/min).[44] The main difference between ICU patients and normal subjects is that the average undistressed rate is 10 breaths/min higher.[33] A number of factors may contribute to this, including body temperature, irritation of tracheal receptors by the endotracheal tube, disease-related effects on pulmonary and other receptors, neuropathology, and drug effects.[33]
2. Because the undistressed RR can be quite low, a change in RR as assist level is changed is more important than absolute RR at the low assist. For example, an increase from 20 to 25 breaths/min may indicate distress, although

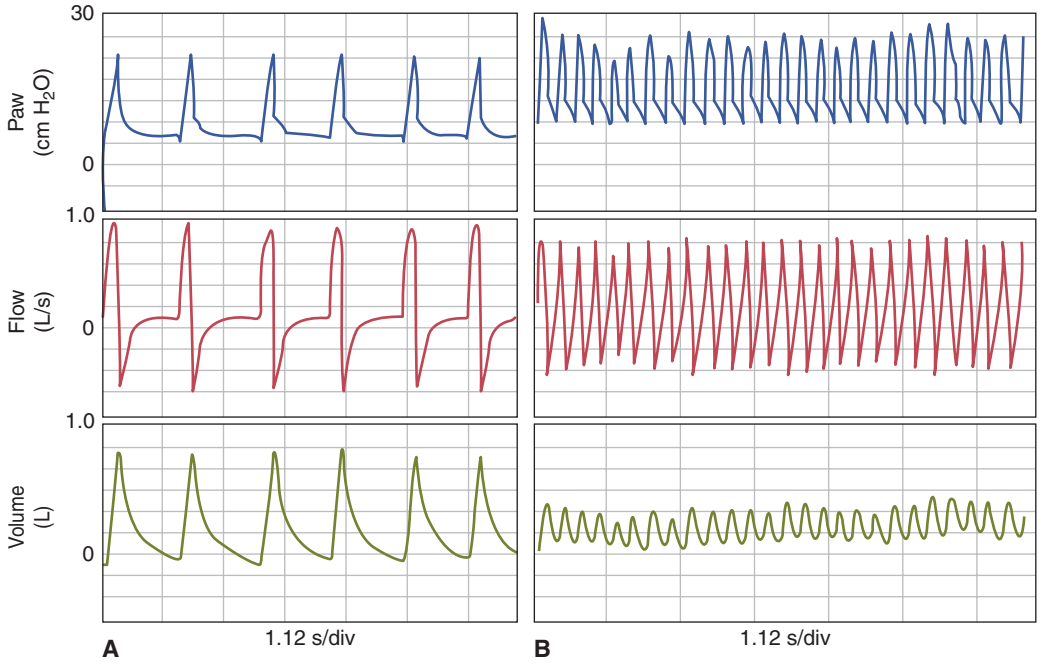

FIGURE 12-5 Tracings from two patients on high PAV assist showing extremes of undistressed breathing pattern. *Paw*, airway pressure.

25 breaths/min is not usually considered a sign of distress. By contrast, RR in excess of the usual cutoff of 35 breaths/min need not reflect distress.

Tidal volume responses mirror the $\dot{V}_E$ responses and obviously share the same mechanisms (see "Ventilation and Partial Pressure of Carbon Dioxide" above). It is important to note that in normocapnic patients, once a distress-free assist level is reached, further increases have little effect on V_T.[33,34] Accordingly, every patient has a preferred or target V_T that cannot be exceeded with more PAV assist. As with normal subjects,[44] the preferred V_T varies widely among patients (4 to 15 mL/kg[33,34]).

PAV has made it possible to determine the undistressed breathing pattern in ICU patients. This proved quite variable. Figure 12-5 shows two extremes. With this wide range, a one-size-fits-all strategy of mechanical ventilation (e.g., setting a target V_T) is clearly not ideal (see "Physiologic Consequences of Operational Differences" below).

Large breath-by-breath variability in V_T is characteristic of normal breathing, particularly in wakefulness.[45,46] Variability decreases in patients with abnormal mechanics.[47,48] Probably because PAV improves neuroventilatory coupling, breath-by-breath variability tends to be large in this mode (see, e.g., Fig. 12-1). Coefficients of variation of 25% or more are not unusual,[23,25,35–37] and spontaneous sighs may be frequent. As with normal subjects,[49] breathing variability on PAV is less in sleeping and obtunded patients (personal observations).

VENTILATORY INSTABILITY

The tendency for the respiratory system to become unstable is described by the so-called loop gain.[50–52] A value of 1 indicates that recurrent cycling will occur spontaneously (e.g., Cheyne-Stokes breathing). The lower the value, the more stable is the system. Ventilatory response to chemical stimuli is an important determinant of loop gain.[50–52] Because PAV increases ventilatory responses, we were concerned initially that it might precipitate periodic breathing.[1] This, however, did not materialize. Although PAV may aggravate preexisting Cheyne-Stokes breathing,[53] there are no reports of PAV-induced Cheyne-Stokes breathing in the usual ICU patient, and we have observed only a few in whom breathing became periodic on high PAV support.

The resistance to Cheyne-Stokes breathing was explained recently. Normal subjects require threefold to fourfold amplification of ventilatory responses to develop periodic breathing.[6,17,54] Thus, when respiratory muscles and mechanics are normal, native loop gain is less than 0.3. In the average ICU patient, respiratory muscle strength is 50% of normal,[55] resistance is four times normal (14 vs. 3 to 4 cm H_2O/L/s[56]), and elastance is two to three times normal (28 vs. 10 to 14 cm H_2O/L[57]). Collectively, these abnormalities should decrease ventilatory responses to 20% of the normal value. For PAV to induce periodic breathing in the average patient, it first must normalize ventilatory responses (i.e., a fivefold increase in the average patient) and then three to four times more, a greater than 10-fold amplification. This is very difficult to achieve because of technical and physiologic limitations (see "Limitations" below). Accordingly, if periodic breathing develops on PAV, it suggests that (a) respiratory muscles and mechanics are near normal, and the patient likely does not need ventilator support, and/or (b) the chemical control system is inherently unstable, and one should suspect disorders that result in Cheyne-Stokes breathing, chiefly heart failure.

A third condition that may precipitate periodic breathing is the runaway phenomenon (see below). Here, large tidal volumes may result, precipitating hypocapnia and recurrent central apneas. The pattern is unlike the crescendo–decrescendo Cheyne-Stokes breathing variety, however, and more like that produced by pressure support (several large breaths alternating with apnea[6,58]).

The ability of PAV to increase loop gain by measurable quantities is currently being used to study mechanisms of instability during sleep.[52,59]

RESPONSES DURING EXERCISE

Application of PAV during submaximal exercise in patients with severe COPD increased endurance time and reduced the rate of progression of dyspnea.[29,60–62] Patients with very severe COPD who received PAV during exercise in a rehabilitation program demonstrated greater improvement in unassisted exercise tolerance relative to a control group.[63] A beneficial effect of assist was not evident in mild COPD.[64] Application of PAV during submaximal exercise also increased endurance time and reduced dyspnea in patients with idiopathic pulmonary fibrosis[65] and in obese patients.[66]

Apart from its potential therapeutic role, PAV also has been used to examine the role of respiratory muscles in limiting exercise in normal subjects and in patients with COPD, with highly interesting results.[31,67–74]

COMPARISON WITH OTHER MODES

Operational Differences between Proportional-Assist Ventilation and Other Modes

With PAV, the assist (i.e., Paw) varies directly with the intensity of patient effort (see Fig. 12-1). By contrast, with pressure-support ventilation (PSV), the assist is the same breath after breath regardless of intensity of effort. With volume-controlled ventilation (VCV), assist varies inversely with effort (Fig. 12-6). This is so because flow and volume are preset. If the patient's contribution increases, the ventilator must deliver less assist (Paw), and vice versa. Otherwise, delivered flow and volume will deviate from set values. These different relations have been well documented.[18,22,75]

With PAV, the end of the ventilator cycle is synchronized automatically with the end of patient effort (see Fig. 12-1), whereas with other modes it is not. Although ventilator response delays tend to delay cycling off somewhat,[76] the effect is fairly trivial compared with the situation in other modes (see "Ventilator Response Time" below). In VCV, there is no relationship whatsoever; the patient determines the end of his effort, whereas the caregiver determines the end of the ventilator's cycle. Any synchrony is happenstance. The ventilator may continue inflation well after the end of effort, when patient wants to exhale (e.g., breath 1 in Fig. 12-6), or may cycle off, withdrawing support before the end of effort while patient is still trying to inhale (e.g., breath 4 in Fig. 12-6).

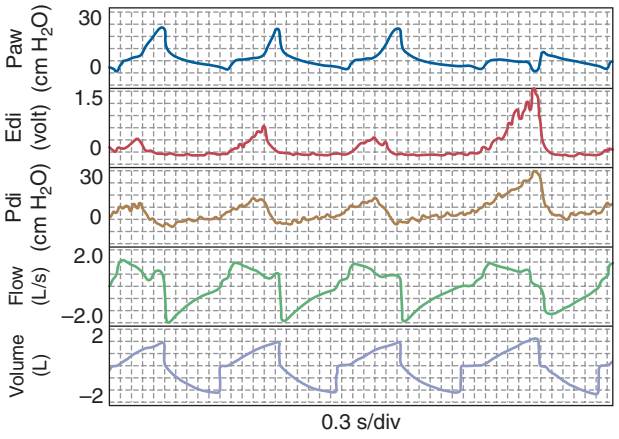

FIGURE 12-6 Tracings from a patient on volume-controlled ventilation. Note that ventilator cycles extend beyond inspiratory effort in the first three breaths while terminating during the effort in the last breath. Note also that patient received little or no assist when his effort was greatest (last breath). *Edi*, diaphragmatic activity; *Paw*, airway pressure; *Pdi*, diaphragmatic pressure.

With PSV, synchrony between the ends of the ventilator's and the patient's inspiratory phases may or may not occur depending on the patient's respiratory mechanics and the relation between PSV level and Pmus.[77,78] Ventilator cycles often extend well beyond inspiratory effort[34,79] or may be almost completely out of phase with them[79] (Fig. 12-7A). At times, inflation extends over two or more efforts (Fig. 12-8A).[34]

The operational characteristics of NAVA[80–82] are very similar to those of PAV in that the assist is proportional to instantaneous effort in both cases. Thus, in both cases the assist will increase when effort increases and vice versa, and in both cases the ventilator cycle will terminate soon after the end of inspiratory effort. The main difference is in the signal used to drive the ventilator: PAV uses an indirect noninvasive estimate of effort (calculated Pmus) whereas NAVA uses a direct estimate of diaphragmatic activity obtained from internally inserted esophageal electrodes. This gives NAVA an advantage with respect triggering in that with NAVA the assist can, theoretically, begin very soon after the onset of diaphragmatic activity in the presence of important dynamic hyperinflation or circuit leaks, whereas with PAV the assist will not start until flow becomes inspiratory, and triggering and assist may be adversely affected in the presence of significant leaks (see "Limitations" below). On the other hand, because the diaphragm participates in many nonrespiratory activities (such as postural changes and vomiting), control of airway pressure by diaphragmatic activity could result in undesirable large increases in airway pressure during such activities. For example, the diaphragm contracts vigorously during vomiting to increase abdominal pressure. This may be expected to cause a large increase in airway pressure in

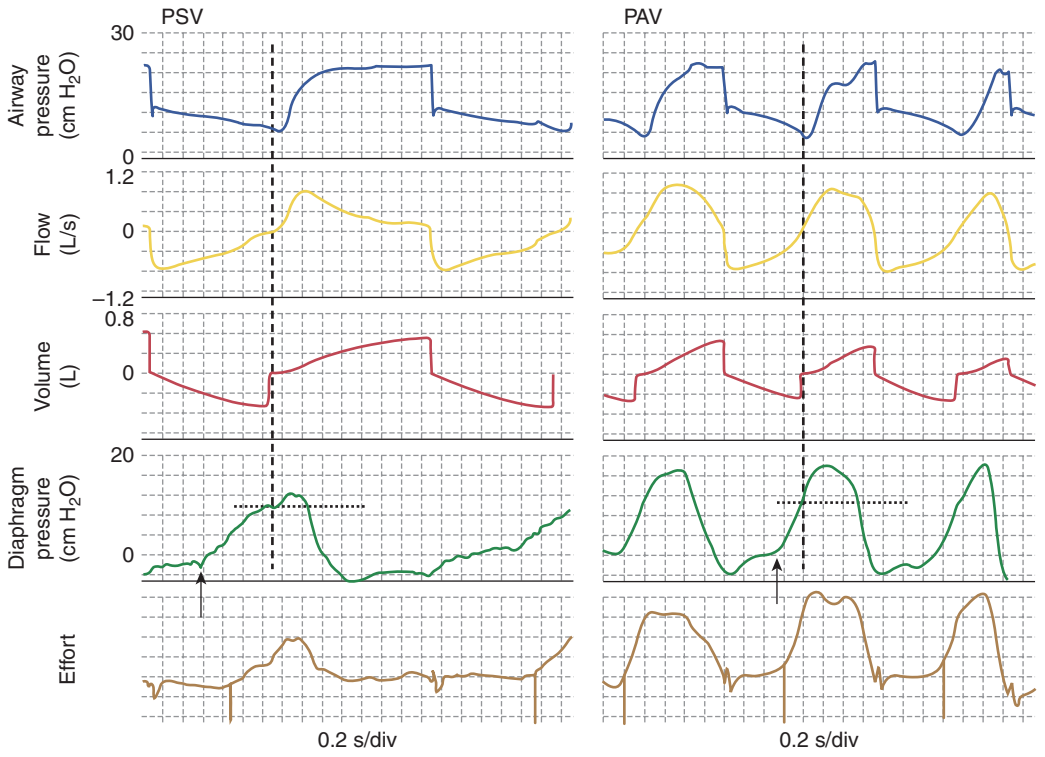

FIGURE 12-7 Comparison of pressure-support ventilation (PSV) and proportional-assist ventilation (PAV) in a patient with severe dynamic hyperinflation. With both modes, inspiratory muscles had to generate 10 cm H_2O before inspiratory flow could be generated and the ventilator triggered (*vertical dashed lines*). Note that in PSV, ventilator cycle extends well into neural expiration. There also were many ineffective efforts (not shown). This is not the case in PAV. Note also that diaphragmatic output is considerably higher in PAV. As a result, delay between onset of effort (*arrows*) and triggering is much less. In addition, respiratory rate is higher with PAV. With severe dynamic hyperinflation, it is difficult to maintain respiratory muscle output at a low level in PAV. See Figure 12-13 for transition from PSV to PAV in this patient. *Bottom tracing.* A semiquantitative effort signal generated without knowledge of respiratory mechanics[117] that can be used to identify onset and end of efforts noninvasively in real-time (*event marks*). Note that the onset of effort (*downgoing marks*) can be identified well before inspiratory flow crossing. If used for triggering, this essentially can eliminate the extra work associated with dynamic hyperinflation.

the case of NAVA. PAV, in contrast, is not susceptible to this problem because diaphragmatic descent and reduction in intrathoracic pressure are prevented by concurrent contraction of the expiratory muscles.

Physiologic Consequences of Operational Differences

The following sections deal with consequences as they relate to conventional assist modes (PSV and VCV). Because NAVA has similar operational characteristics, its consequences vis-a-vis conventional assist modes are expected to be similar (see Chapter 13 and reference 82 of this chapter). There are no studies in which NAVA and PAV have been compared directly so as to ascertain the clinical impact of NAVA's triggering advantage in the presence of dynamic hyperinflation and leaks.

RESPONSE TO DIFFERENT LEVELS OF ASSIST

Figure 12-9 illustrates what, theoretically, should happen when assist level is varied in different modes (see refs. 3 and 83 for more details). The response of RR to changes in Pa_{CO_2} near the AT is key to understanding these plots. As indicated earlier, RR is fairly constant over a range of Pa_{CO_2} above the AT. For example, average difference between spontaneous RR and RR just before apnea is less than 1 breath per minute.[6] At AT, breathing simply stops. There is no gradual reduction in RR.

The effect of different levels of PAV (see Fig. 12-9A) was discussed earlier (see Fig. 12-4). A steady state is possible at all assist levels, except in rare cases where chemical control is highly unstable (see "Ventilatory Instability" above). Once the AT is approached, it is not possible to increase $\dot{V}_E$ further.

The relationship between P_{CO_2} and ventilation during PSV is extremely complex.[3,34,77,83] For simplicity, it is shown as a parallel shift in the ventilatory response, reflecting the fact that the assist is independent of P_{CO_2}. Exactly what happens, however, to the slope of the ventilatory response is not terribly important here. What is important is that with PSV a minimum V_T is delivered once the ventilator is triggered. This minimum V_T is a function of PSV level and respiratory mechanics.[6,77] For example, in a patient with an elastance of 25 cm H_2O/L and a resistance of 12 cm H_2O/L/s, the minimum V_T at PSV of 7, 14, and 20 cm H_2O will be approximately 0.22, 0.43, and 0.64 L, respectively.[6,77] If the patient's RR near the AT is a conservative 16 breaths/min, and every

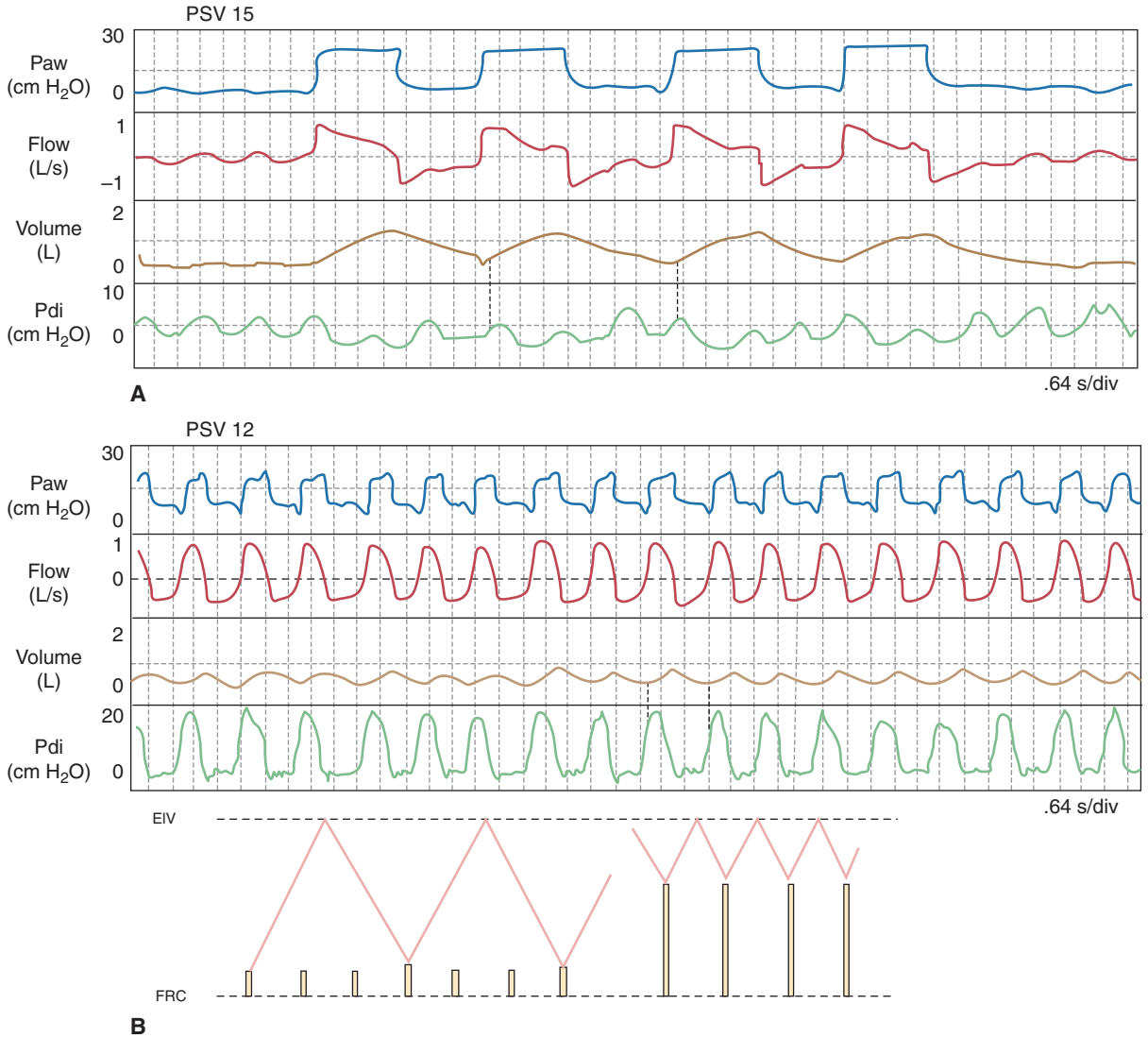

FIGURE 12-8 A dramatic example of a marked shift from slow, deep breathing (panel A) to very rapid, shallow breathing (panel B) following a small reduction in pressure support (PSV). The increase in respiratory rate was artifactual and related to improved synchrony (note that the rate of diaphragmatic efforts was unchanged). The small tidal volumes are related to dynamic hyperinflation (note that Pdi increases substantially before flow becomes inspiratory) (*vertical dotted lines*). Inset shows schematically the mechanism of shallow breathing. Height of *solid lines* represents effort amplitude. See text for additional details. *EIV*, end-inspiratory volume; *FRC*, functional residual capacity; *Paw*, airway pressure; *Pdi*, diaphragmatic pressure.

effort triggers the ventilator, minimum $\dot{V}_E$ near the AT will be 3.5, 6.9, and 10.2 L/min for the three levels, respectively (see Fig. 12-9). A higher minimum RR (range: 12 to 46 breaths/min; see "Respiratory Rate and Breathing Pattern" above) would increase minimum $\dot{V}_E$ correspondingly.

For the patient in Figure 12-9, applying PSV at level 1 will boost ventilation initially above the metabolic hyperbola. Pa_{CO_2} falls along the response line of that level. Because minimum $\dot{V}_E$ is below the hyperbola (*left end of line 1*), a steady state can be reached (*solid dot on line 1*). For level 2, a steady state still can be reached, but Pa_{CO_2} will be just above the AT, and efforts will be very feeble. At level 3, a steady state is not possible because minimum $\dot{V}_E$ is above the metabolic hyperbola. When Pa_{CO_2} is above the AT, $\dot{V}_E$ is above the hyperbola, and P_{CO_2} must fall. When it falls below the AT, $\dot{V}_E$ becomes zero. The only steady-state $\dot{V}_E$ is the open circle. This is not possible, however, if all efforts trigger the ventilator. For average $\dot{V}_E$ to equal $\dot{V}_E$ at the open circle, ventilator rate must decrease below the patient's minimum RR. This occurs in one of two ways depending on the time constant of the respiratory system (resistance/elastance [R/E]). If R/E is very short (e.g., severe, restrictive disease), ventilator cycles will not encroach on neural expiration,[77,78] allowing lung volume to return to FRC before the next effort. Here it is possible to continue triggering until the AT, and recurrent central apneas develop. When R/E is long, the ventilator cycle is also long[77,78] and extends into neural expiration. As efforts weaken, more and more efforts fail to trigger the ventilator. Here, ineffective efforts are scattered between triggered breaths. Depending on R/E, ineffective efforts may appear

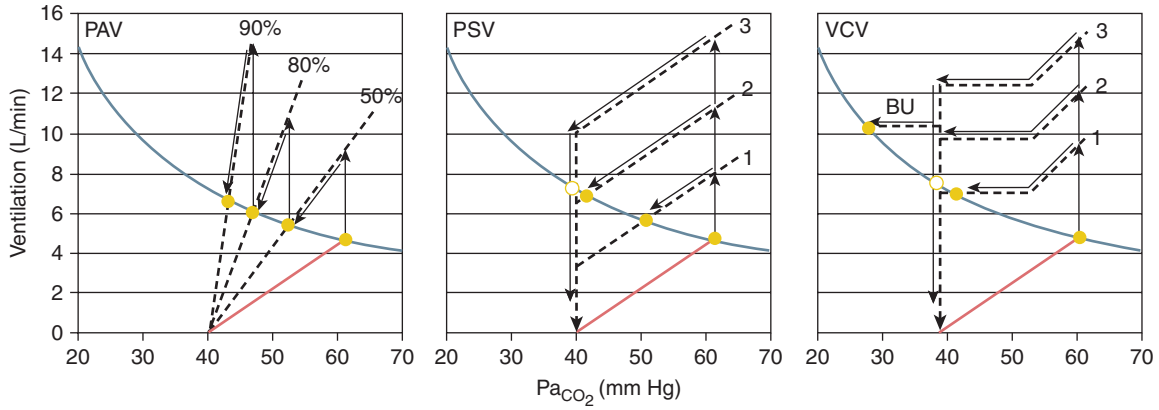

FIGURE 12-9 Responses to different levels of assist with proportional-assist (PAV), pressure-support (PSV), and volume-controlled ventilation (VCV). The ventilatory response to CO_2 is shown for three assist levels in each case. The format is as in Figure 12-4. Note that in PAV the ventilatory response line intersects the metabolic hyperbola at all levels of assist. A steady state thus is possible at all levels. In PSV and VCV, the response lines intersect the hyperbola over a limited range of assist. At higher levels, a steady state is not possible, and nonsynchrony must result (see text). In this simulation, respiratory rate is shown to increase when Pa_{CO_2} exceeds 53 mm Hg. This accounts for the increase in ventilation above this Pa_{CO_2} in VCV. *BU*, backup rate.

well before the AT. Because R/E is more commonly long than short, intermittent ineffective efforts are more common than recurrent central apneas.[34,84]

In summary, with neither PAV nor PSV is it possible to decrease average Pa_{CO_2} below the AT. What is different is that with PAV, V_T is independent of assist level near the AT, and ventilator cycles cannot extend substantially into neural expiration. Thus, a steady state can be reached at all levels without nonsynchrony.[34] With PSV, by contrast, V_T increases monotonically with assist. At some level the product $V_T \times$ minimum RR exceeds the $\dot{V}_E$ required for steady state, and nonsynchrony must occur. These differences have been demonstrated experimentally.[34]

With VCV, $\dot{V}_E$ is constant over the range where RR is independent of drive and is given by patient RR × set V_T. As set V_T increases, $\dot{V}_E$ increases and remains at that level as efforts decline (*horizontal lines, right panel,* Fig. 12-9). If steady-state Pa_{CO_2} associated with this fixed $\dot{V}_E$ is above the AT, a steady state with maintained synchrony can result (e.g., *line 1*). If not (*lines 2 and 3*), and there is no or minimal backup rate, ineffective efforts or recurrent central apneas must result (as with PSV), and nonsynchrony will increase as set V_T increases.[84] With a backup rate, once the AT is reached, $\dot{V}_E$ will decrease to set $V_T \times$ backup rate. If this $\dot{V}_E$ is below the hyperbola at the AT, periods in which the ventilator is triggered by the patient will alternate with periods in which it is self-triggered as Pa_{CO_2} oscillates about the AT. If backup $\dot{V}_E$ is above the hyperbola (line *BU* in Fig. 12-9), Pa_{CO_2} must fall further. Depending on ventilator settings, marked hypocapnia may develop.

In summary, with PSV and VCV there is a limited range of assist that is consistent with synchrony. Above this range, ineffective efforts or recurrent central apneas must develop. It is evident that the "appropriate" assist range depends on the metabolic hyperbola (a function of metabolic rate and V_D/V_T) and minimum patient RR near the AT (see Fig. 12-9). Because these may change with time, a suitable level may become unsuitable at another time. Several studies confirm that nonsynchrony is quite common with PSV and VCV[24,34,79,84] while being virtually nonexistent at all levels of PAV.[19,24,34] Ineffective efforts do occur at times during PAV, but they are very infrequent[34] and usually occur when a large breath (spontaneous sigh or runaway breath) is followed by a weak effort.

RESPONSE TO CHANGES IN VENTILATORY DEMAND

Figure 12-10 is a representative example of spontaneous changes in $\dot{V}_E$ over a 2-hour period. The changes are not trivial; the highest level was almost twice the lowest. This is not surprising because many influences that affect ventilatory demand can change in these patients, for example, pain, anxiety, sleep–wake cycles, metabolic rate, pH, and drugs. It is therefore useful to examine what happens with the three modes in response to such changes.

Figure 12-11 illustrates two metabolic hyperbolas, representing two metabolic rates. The unassisted ventilatory response (*solid line*) is identical and would be associated with a Pa_{CO_2} of 62 mm Hg. Initial ventilator settings with the three modes were adjusted to produce identical $\dot{V}_E$ (6 L/min) and Pa_{CO_2} (48 mm Hg) at the lower metabolic rate. Ventilatory demand increases by 50% (upper hyperbola). Efforts increase, but RR initially does not. With PAV, assist increases, and $\dot{V}_E$ increases along a relatively steep response line, reaching the higher hyperbola at a Pa_{CO_2} of 51 mm Hg. With PSV, assist is constant. As a result, the ventilatory response is no better than the unassisted slope. The higher hyperbola is reached at 57 mm Hg. With VCV, ventilation cannot increase until RR increases. Without

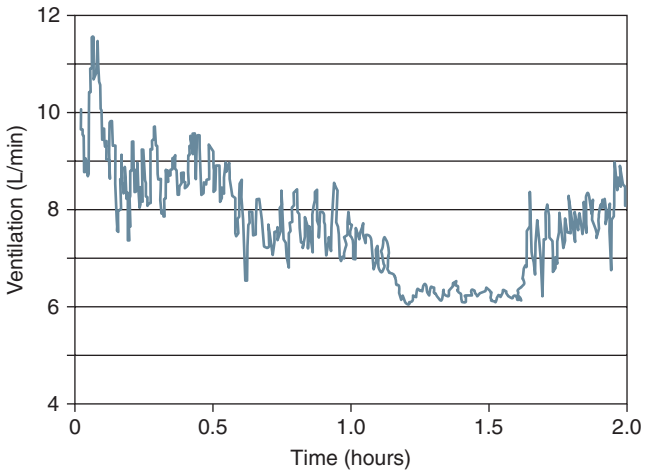

FIGURE 12-10 One-minute moving average of ventilation over a 2-hour period on PAV. Note large spontaneous changes in ventilatory demand.

tachypnea, the metabolic hyperbola is reached at a Pa_{CO_2} of 70 mm Hg.

It is clear that the likelihood of respiratory distress and tachypnea developing is higher with VCV and PSV. With VCV, there is the added problem that ventilator inspiratory time (T_I) does not change as patient respiratory cycle time (T_{TOT}) decreases. Less time remains for exhalation, promoting nonsynchrony.[84] Nonsynchrony occurring at a time of high respiratory drive may trigger anxiety. Of course, both PSV and VCV can be readjusted to provide adequate support at the higher demand. This level, however, will be excessive when ventilatory demand returns to the lower level.

The different responses to CO_2 challenge under the three modes were well illustrated in normal subjects.[18] In ventilator-dependent patients, Ranieri et al[75] showed that following addition of dead space during PAV, V_T increased with no change in RR (20.1 to 19.8 breaths/min). When added during PSV in the same patients, there was little change in V_T, and RR increased dramatically (from 16.4 to 33.2 breaths/min). By contrast, a recent repetition of this study[85] failed to demonstrate differences between PSV and PAV in the ventilatory, pressure-time product or transdiaphragmatic pressure responses to added dead space even though the magnitude of assist increased with PAV and not with PSV. There are several reasons to explain this negative result. Although both studies added the same amount of dead space (150 mL), the challenge was much greater in the Ranieri[75] study, as evidenced by a much greater increase in V_E (approximately equal to 13.5 vs. 2.1 L/min), Pa_{CO_2} (approximately equal to 19.0 vs. 2.0 mm Hg), and pressure-time product per minute (185 vs. 32.4 cm H_2O.s/min) on PSV of 10 cm H_2O. The reason for the large difference in challenge presented by the same addition of dead space is not clear. Nonetheless, with a minimal challenge, as was delivered in the study of Varelmann et al,[85] it is difficult to obtain significant responses given the noise in such studies (spontaneous changes in respiratory drive). It is worth noting that in the latter study,[85] Pa_{CO_2} increased more when dead space was added with PAV (5 mm Hg on PAV vs. 2 mm Hg on PSV) even though V_T and V_E increased more during PAV, albeit not significantly so. Thus, ventilatory demand was greater during added dead space on PAV than when it was added during PSV. Also, as pointed out by Mols et al[86] the two studies used different ventilators (Winnipeg Ventilator vs. Dräger Evita 4) with very different response characteristics.

Muscular exercise represents the most extreme form of ventilatory stimulation. The impact of PAV and PSV on exercise endurance and dyspnea in COPD patients was compared in one study.[61] PAV was found superior.

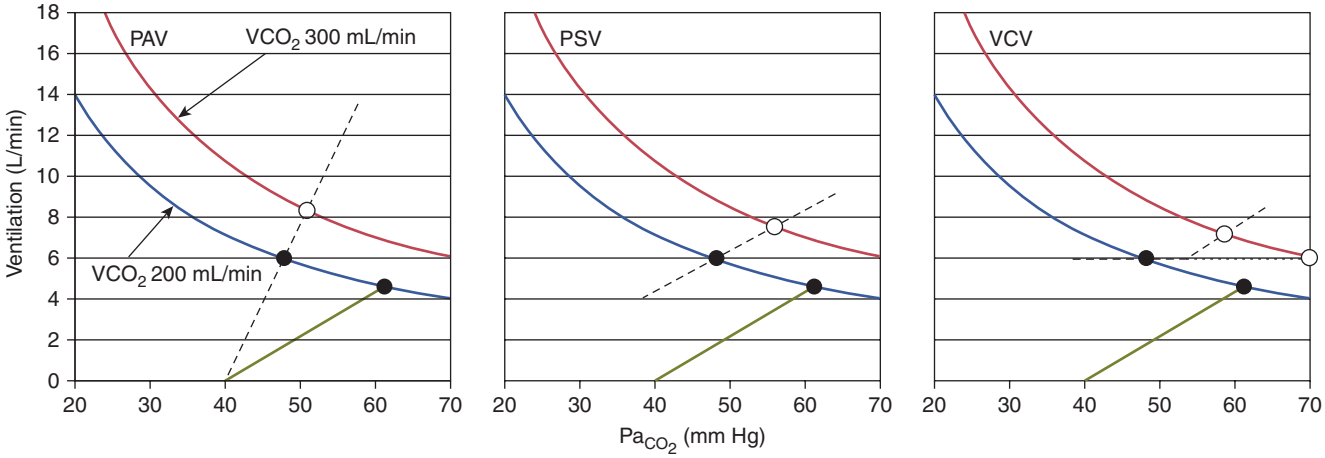

FIGURE 12-11 Responses to a 50% increase in ventilatory demand with proportional-assist (PAV), pressure-support (PSV), and volume-controlled ventilation (VCV). The unassisted ventilatory response to CO_2 is given by the *solid diagonal line* in each panel. The three modes were set during the low-demand period to produce the same ventilation and Pa_{CO_2} (*solid circles/dashed lines*). Because of the higher ventilatory-response slope on PAV, the new ventilation could be reached with a much smaller increase in Pa_{CO_2} (*open circles*). See text for more details.

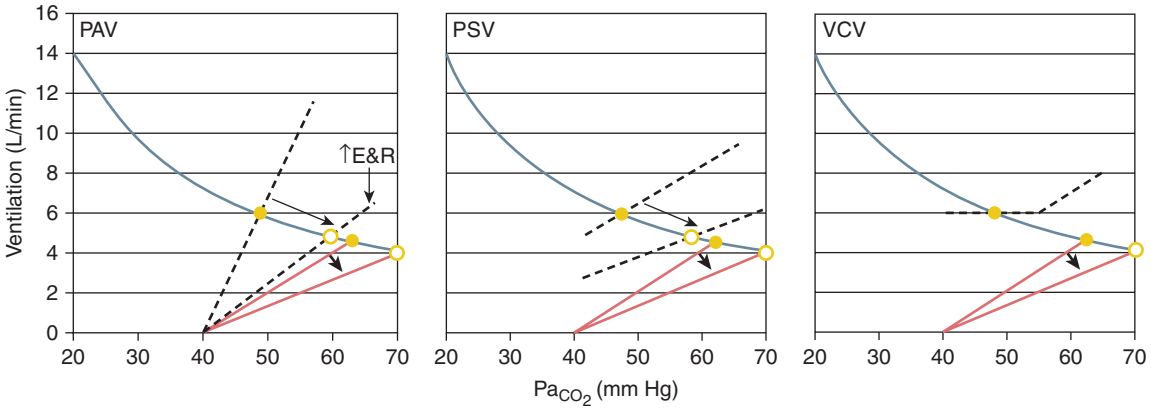

FIGURE 12-12 Responses to a 50% increase in elastance and resistance with proportional-assist (PAV), pressure-support (PSV), and volume-controlled ventilation (VCV). *Solid diagonal lines*: Unassisted ventilatory responses before and after the change in mechanics. *Dashed lines*: Ventilatory responses on assisted ventilation. All modes were set before the change to produce the same ventilation and Pa_{CO_2} (*solid circles/dashed lines*). As mechanics worsen, Pa_{CO_2} increases and ventilation decreases with PAV and PSV (*open circles*) but not with VCV.

RESPONSE TO CHANGES IN RESPIRATORY MECHANICS

Substantial changes in resistance (R) may occur from time to time.[56] Although similar information about elastance (E) is not available, there is every expectation that it also changes from time to time (e.g., secondary to changes in lung water, abdominal pressure, or atelectasis). Accordingly, it is important to consider the response to changes in mechanics.

Figure 12-12 illustrates the effect of a combined 50% increase in R and E. At a given Pmus, ventilation is inversely related to mechanical properties. Thus, a 50% increase in E and R reduces the unassisted ventilatory response to CO_2 to 67% of baseline.

An increase in R and E will reduce the slope of the ventilatory response under PAV for two reasons. First, percent assist is now lower. For example, if $\dot{V}_A$ were 70% E, and E increased by 50%, $\dot{V}_A$ would become 47% (70/150). This reduces the amplification factor (from 3.3 to 1.88 in this case; amplification factor = 100/[100 − percent assist]). Second, the slope of the ventilatory response that is being amplified also has decreased to 67% of the initial value. As a result, ventilatory response on PAV is now 38% of its initial value. $\dot{V}_E$ must fall, Pa_{CO_2} must rise, and distress may develop.

The situation is comparable with PSV. The already low ventilatory slope becomes even lower because the unassisted slope is now lower. Furthermore, the same pressure assist will be less effective in boosting V_T because of worse mechanics. As a result, the ventilatory response is displaced downward as well (e.g., Fig. 4 in ref. 22). A new steady state is reached at a lower $\dot{V}_E$ and higher Pa_{CO_2}. The changes in $\dot{V}_E$ and Pa_{CO_2} are comparable in the two modes.

By contrast, with VCV, a change in E and R will have no effect on ventilation. The ventilator will deliver the same V_T. Because there is no change in Pa_{CO_2}, there is no increase in effort. In this respect, therefore, VCV is superior to both PAV and PSV.

Grasso et al[22] compared responses to an increase in elastance with PAV and PSV. Surprisingly, they found that with PAV, V_T decreased less, RR increased less, and the increase in dyspnea was less. It is not clear why this was so. Regardless, the better results in this study were not expected and should not be viewed as intrinsic to PAV.

An improvement in mechanics also can create problems with PAV and PSV but not with VCV. If percent assist is high before the change, a reduction in R or E may cause the percent assist to exceed 100% of the new R or E, resulting in runaway. With PSV, improvement in mechanics at the same assist level will increase $\dot{V}_E$ and decrease Pa_{CO_2}. Asynchrony may appear.

In summary, on standard PAV, changes in mechanics may be followed by distress or excessive ventilator alarming (runaways). This emphasizes the need for using PAV systems equipped with algorithms that continuously monitor respiratory mechanics. This problem is mitigated by the fact that monitoring passive R and E continuously is possible in the PAV mode (see "Noninvasive Monitoring of Respiratory Mechanics, Pmus, and Work of Breathing" and "Commercially Available Proportional-Assist Ventilation Delivery Systems" below). Kondili et al[87] studied the response to changes in respiratory mechanics in ventilator-dependent patients using such a PAV delivery system (PAV+, Covidien). They found that the increase in all indices of respiratory effort was significantly less when the load was added during PAV+ than when added during PSV.

RESPIRATORY RATE IN DIFFERENT MODES

With all modes, patient RR will increase if assist is inadequate. Patient RR, however, is also sensitive to reflexes, independent of chemical drive. Continued inflation during neural expiration prolongs neural expiration and, by extension, reduces RR.[88–90] This reflex is less pronounced in ICU patients[90] than in alert patients[88,89] but is still quite evident. Its

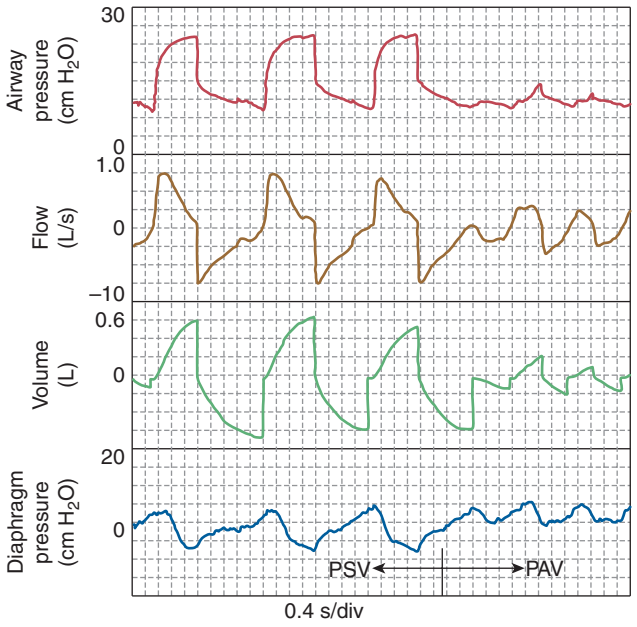

FIGURE 12-13 Transition from pressure-support ventilation (PSV) to PAV in the same patient as in Figure 12-7 with marked dynamic hyperinflation. Efforts were quite weak on PSV and barely succeeded in triggering the ventilator. On switching to PAV, the patient receives very little assist because, unlike PSV, assist cannot outlast inspiratory effort. Effort must increase in order to advance triggering and obtain adequate ventilation (see Fig. 12-7*B*). Note that respiratory rate increased suddenly on the switch. Because efforts were still quite weak and the response was immediate, the increase in rate was not caused by a high respiratory drive (i.e., distress) and almost certainly was reflexive in origin secondary to removal of inflation during neural expiration (see text).

gain varies widely among patients.[90] Figure 12-8 shows a very weak response. Note that patient RR was the same whether efforts occurred during inflation or deflation. In contrast, Figure 12-13 illustrates a strong response. Here, on PSV, ventilator cycle extended well into neural expiratory time. When PSV was discontinued, there was a marked increase in patient RR (from 20 to 33 breaths/min). This cannot represent distress because it occurred immediately, and diaphragmatic swings were still very low (approximately 5 cm H_2O). Thus, with PSV, nonsynchrony may reduce patient RR for reasons that have little to do with relieving distress. As a corollary, reduction in asynchrony, as would occur if PSV levels were reduced,[34,77] may result in acceleration of patient RR that is unrelated to distress. This is not a problem with PAV because the ends of patient and ventilator inspiratory phases are synchronized. Therefore, changes in RR on PAV reflect level of distress more reliably.

TIDAL VOLUME IN DIFFERENT MODES

As indicated earlier (under "Respiratory Rate and Breathing Pattern"), with PAV, V_T is determined by the patient, and the preferred V_T ranges from 4 to 15 mL/kg, with an average of 7 mL/kg.[33,34] With VCV, V_T is set without knowledge of the patient's preferred V_T. PSV is also usually adjusted to yield a given V_T. In either case, the set V_T almost always will be larger than necessary. For example, if V_T is set to 10 mL/kg, it will be greater than preferred V_T in most patients. In the others, it will be inadequate. If one individualizes the assist to comfort level, V_T still will be higher than with PAV for two reasons: first, when V_T is titrated to the lowest level consistent with comfort, the chosen V_T is greater than the average V_T during spontaneous breathing.[8,91] Second, if V_T or PSV level is set to comfort level at a given point, a change in ventilatory demand (see, e.g., Figs. 12-10 and 12-11) will cause it to become either excessive or too little later. If it becomes excessive, it will not be adjusted down. If it becomes inadequate (increase in demand), however, it will be increased and remain at the high level after, when demand decreases again. On average, V_T will be larger than if it were allowed to vary with demand (i.e., PAV).

Another peculiarity unique to PSV is that dynamic hyperinflation may cause tidal volume to be inversely related to inspiratory effort (see, e.g., Fig. 12-8). This is so because at a given PSV, the end-inspiratory volume, relative to passive FRC, at which the ventilator cycles off, in the absence of effort (Vth), is fixed.[77] A stronger effort will trigger the ventilator at a higher volume relative to FRC, leaving less difference between the onset of the breath and Vth (see inset of Fig. 12-8). With high PSV, it is possible to reduce chemical drive to very near the AT, resulting in very weak efforts (see, e.g., Fig. 12-8A). Triggering then can occur only when volume is very close to FRC. When a breath is triggered, volume must increase by a large amount before the ventilator cycles off. Large protracted V_Ts result (see Fig. 12-8A). If efforts increase, either spontaneously or after reducing PSV level, breaths can be triggered at a higher volume and hence closer to Vth. A small V_T will cause Vth to be reached. Once effort ceases, flow decreases to the cycling-off threshold, and the ventilator cycle ends. Synchrony is reestablished, but breathing becomes faster and shallower (see Fig. 12-8). Thus, paradoxically, under these conditions V_T is largest when effort is weakest, and changes in V_T no longer reflect effort.

This scenario can never happen with PAV in part because in the presence of dynamic hyperinflation it is not possible to reduce efforts to the very low levels that can be reached with high-level PSV (see "Dynamic Hyperinflation" below) and in part because the inflation cycle ends when patient effort ceases regardless of the end-inspiratory volume reached.

COMFORT

Comfort, of course, cannot be compared in obtunded patients. Whenever PSV and PAV were compared in alert patients with respiratory distress, however, PAV was preferred.[23,38,39]

HEMODYNAMIC EFFECTS

Mechanical ventilation has complex effects on the circulation (see Chapter 36). Data comparing hemodynamics on PAV with other modes are very limited. Patrick et al[92] found

that cardiac output was 22% higher during PAV than during VCV in eight patients with septic shock (see Fig. 14-9 in ref. 93). Blood pressure also was higher. These results likely were secondary to lower airway pressure, and hence mean intrathoracic pressure, during PAV promoting higher venous return. Kondili et al[94] compared hemodynamics on PAV and PSV when mean airway pressure was matched in the two modes. Cardiac index was slightly but significantly higher during PAV. There is no information on the effect of PAV versus other modes in patients with left-ventricular dysfunction. Such information is needed because, in theory, a lower intrathoracic pressure may not be helpful in these patients (higher afterload).

Clinical Consequences of the Physiologic Differences

PATIENT MANAGEMENT ISSUES

Noninvasive Monitoring of Respiratory Mechanics, Pmus, and Work of Breathing. PAV has unique features that allow estimation of passive mechanics noninvasively.[56,57] In PAV, end of ventilator cycle occurs during the declining phase of inspiratory Pmus (see Figs. 12-1 and 12-14A). A brief end-inspiratory occlusion coincides with the terminal part of the declining phase and the decline of Pmus after the occlusion presents as a rise in airway pressure during the first part of occlusion (Fig. 12-14A). This phase ends shortly after the onset of occlusion, and its end is readily recognizable as the rise in airway pressure stops (Fig. 12-14A).[57] Paw at the end of this phase provides the passive recoil pressure associated with occluded volume. This is not the case with VCV or PSV because the end of the ventilator cycle may occur during an active inspiratory or expiratory phase. This approach has been validated,[57] and an automated version was included in new 840 PAV+ software (Covidien). A multicenter study confirmed its reliability ($r^2 = 0.92$ compared with elastance measured concurrently by esophageal catheter[95]). A more recent study found a significant correlation between elastance measured on controlled mechanical ventilation and that measured during PAV.[96] There was, however, much scatter. This can be explained by the fact that, unlike the previous study,[95] the two measurements were separated by hours and were obtained with different modes and breathing patterns.

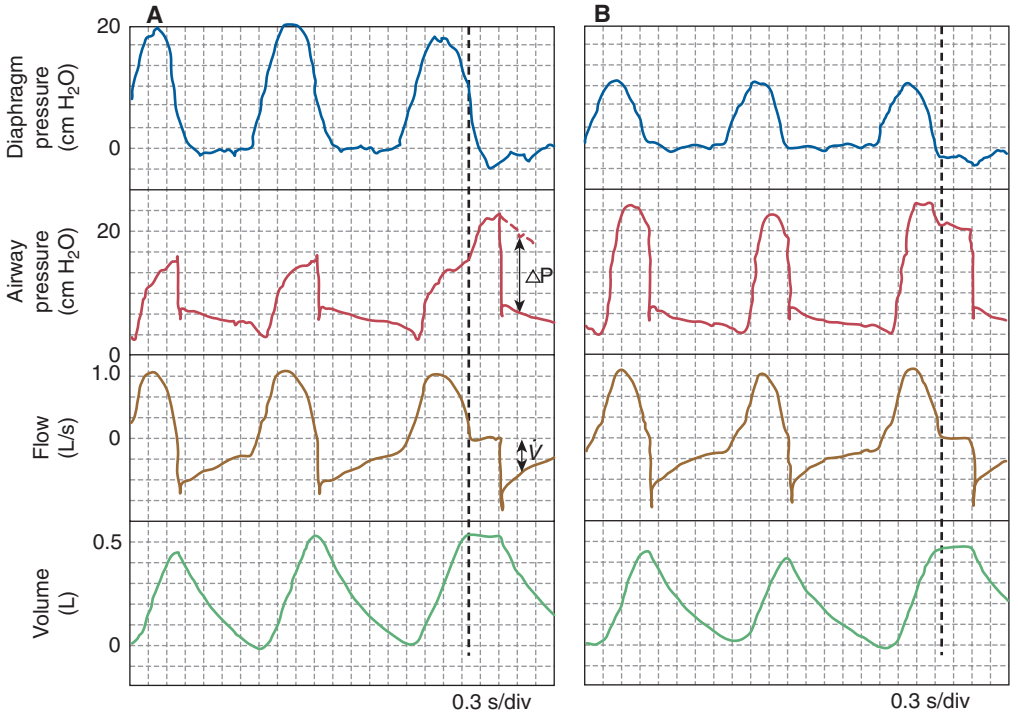

FIGURE 12-14 Tracings from a patient on the 840 PAV+ option (Covidien) illustrating the random brief end-inspiratory occlusions. **A.** Forty percent assist. **B.** Eighty percent assist. Note the minimal change in breathing pattern and lower amplitude of diaphragmatic pressure swings. Airway pressure rises early during the occlusion in panel A, reflecting the fact the inspiratory phase ended during the declining phase of inspiratory pressure (*vertical dashed line*). During occlusion, airway pressure is inversely related to muscle pressure. By the end of occlusion, airway pressure had plateaued, corresponding to inspiratory pressure reaching its baseline level. In panel B, there is no rising phase during the occlusion because inspiratory pressure had returned to baseline already; at high assist, the inspiratory phase tends to end at a later point on the declining phase.[76] Note that airway pressure is approximately the same at end occlusion in both cases. Elastance is determined from ([end-occlusion pressure – positive end-expiratory pressure]/V_T). Expiratory resistance is determined from flow early in expiration and ΔP (the difference between airway pressure and elastic recoil at the same point). Elastic recoil is obtained from end-occlusion pressure minus an amount corresponding to the volume expired and elastance (*dotted line*).

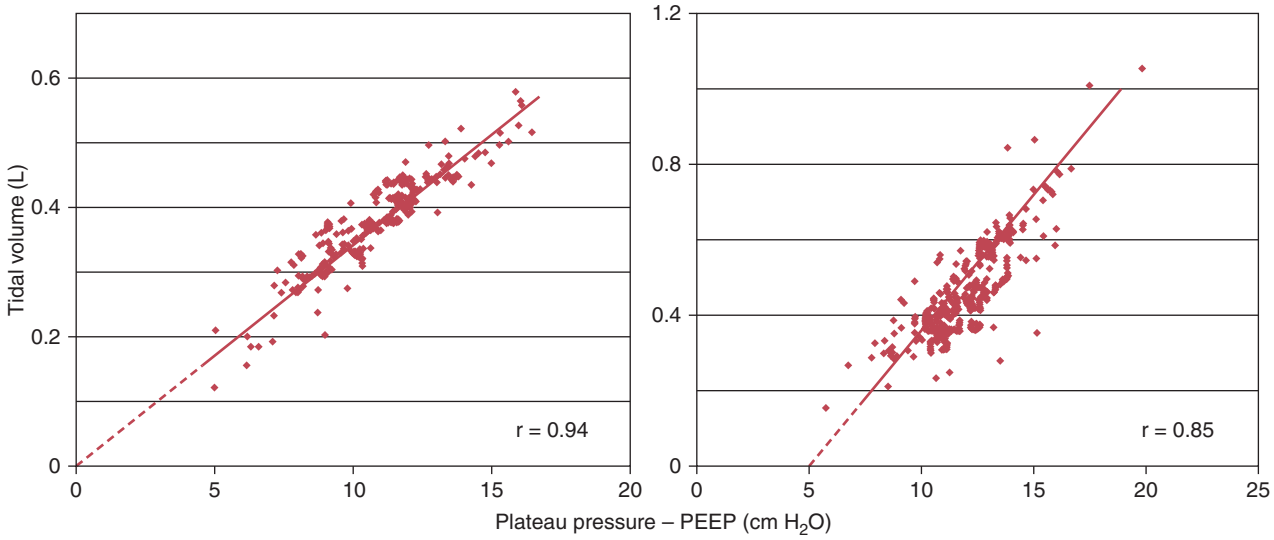

FIGURE 12-15 Relationship between occlusion pressure and tidal volume. Data collected over approximately an hour of recording with randomly applied occlusions. The range of volumes was the result of spontaneous tidal volume variability. In both cases, a highly significant correlation was obtained. **A.** Pressure intercept not different from positive end-expiratory pressure (PEEP), indicating no dynamic hyperinflation. **B.** Patient with dynamic hyperinflation. Note the positive intercept.

Because V_T is usually variable on PAV, random end-inspiratory occlusions frequently produce a wide range of V_Ts and plateau pressures from which confident estimates of the slope and pressure intercept can be obtained (Fig. 12-15). A positive intercept indicates either dynamic hyperinflation or a respiratory system that is stiffer in the lower part of tidal ventilation (see "Nonlinearity in the Pressure-Volume Relationship within the Tidal Volume Range" below). Because both abnormalities respond to increasing positive end-expiratory pressure (PEEP), changes in intercept can be used to set the PEEP level associated with best elastance. This process (display of plateau pressure vs. V_T) can obviously be incorporated in PAV delivery systems to help with the management of dynamic hyperinflation.

Because Paw at the end of brief occlusions reflects passive recoil at end inspiration, it is possible to estimate passive *expiratory* resistance[97] (see Fig. 12-14A). This approach was incorporated in the 840 PAV+ option (Covidien). Its main limitation is that expiratory resistance in the PAV+ option is measured around the time of peak expiratory flow. Although this is acceptable in patients without severe COPD, it results in *underestimation* of resistance in COPD patients who display a sharp expiratory flow spike in early expiration (see, e.g., Fig. 12-5A). This early flow spike incorporates a large component derived from central airway collapse at the beginning of expiration and does not reflect the flow of air from the alveoli.[98,99] Because alveolar flow is overestimated at this point, and flow is the denominator of the resistance equation, resistance can be markedly underestimated in the presence of this artifact. On the other hand, if the early expiratory flow spike is avoided, and resistance is measured later in expiration, resistance may be overestimated because of flow limitation. Thus, in the presence of severe expiratory flow limitation with an early flow spike, adjustment of PAV assist using an expiratory resistance value is not recommended. An alternate method that estimates inspiratory resistance from brief pressure pulses during inspiration has been described and validated.[56]

Apart from overcoming the major practical limitation to implementing PAV, namely, knowing passive mechanics, continuous monitoring of passive R and E should help in monitoring disease progression and in the timely identification of complications (e.g., changes in lung water, accumulation of secretions, and bronchospasm). If a patient's condition deteriorates, it should be possible to sort out what happened to mechanics by observing recent trends in R and E. Furthermore, when R and E are known, it is possible to calculate patient-generated pressure (Pmus) and work of breathing in real time. Real-time estimates of Pmus can be used to trigger the ventilator, thereby eliminating the major remaining technical problem with PAV, namely delayed triggering in the presence of severe hyperinflation.

Improved Reliability of Ventilator Rate as a Measure of Distress and Weaning Failure. As indicated earlier (under "Physiologic Consequences of Operational Differences"), an increase in ventilator rate is not specific to distress in PSV and VCV. In either mode, a simple increase in effort, occurring spontaneously or as result of reduction in assist, may decrease ineffective efforts and result in an artifactual, sometimes dramatic increase in ventilator rate (see Fig. 12-8). Although this artifact can be identified from flow and Paw tracings,[34] considerable expertise is required. Furthermore, even if true RR is counted and found to have increased, the

increase may be reflexive and not secondary to true distress (see "Respiratory Rate in Different Modes" above). With PAV, ineffective efforts are very rare, and inflation extends minimally into neural expiration. Accordingly, ventilator rate faithfully reflects patient rate.[20,34,96] When it increases, distress can be inferred more reliably. Because a substantial increase in ventilator rate following a reduction in assist is used commonly to infer continued ventilator dependence, this feature of PAV should reduce false weaning failure verdicts.

The occurrence of an absolute RR of more than 35 breaths/min during a weaning trial is used commonly as a sign of weaning failure.[102,103] Yet some patients breathe at rates greater than 35 breaths/min, even when assist is very high and efforts are very weak (see Fig. 12-8A).[34,100] Thus, in some patients, a high absolute RR need not indicate distress. PAV can be used to determine whether absolute tachypnea observed during a weaning trial is distress-related. Failure of RR to decrease as PAV assist is increased to high levels would indicate that tachypnea is not distress-related (see "Respiratory Rate and Breathing Pattern" above). Such a test would not be feasible with other modes because in such patients (high intrinsic RR), ventilator or even patient rate invariably will decrease as assist increases because of nonsynchrony. It remains to be determined, however, whether tachypnea that is not relieved by ventilator support is a reason to continue mechanical ventilation.

Choice of Ventilator Settings. With VCV and PSV, one does not know what is appropriate for each patient. Given what we know now about variability in undistressed (preferred) breathing pattern and time-to-time changes in demand, no general guidelines will be suitable for all patients; in most cases, the assist delivered will exceed what is necessary (see "Tidal Volume in Different Modes" above). With PAV, there is no uncertainty about what the patient wants or needs or how to set the level of assist. There is only one variable to consider (percent assist), and when percent assist is increased to a point where V_T and RR no longer respond to further increases, the values observed are what the patient needs.

This apparent simplicity of setting PAV was mitigated early on by a number of practical limitations, which proved problematic when simple PAV delivery systems were used (see "Limitations" below). These included the need to measure respiratory mechanics frequently and frequent alarming when the patient takes a large tidal volume or during runaways. To compound matters, troubleshooting these problems requires considerable expertise. These problems have now been largely overcome through introduction of methods for continuous monitoring of respiratory mechanics during PAV application, modification of alarm systems to allow for the spontaneous variability of tidal volume during PAV, and measures to avoid and limit runaways. A recent study[101] on critically ill patients compared the number of interventions (ventilator settings and sedatives, analgesics and vasoactive medication dose manipulations) when patients were on PSV with the number while using a PAV system equipped with the above features (PAV+, Covidien). The number of interventions was significantly less on PAV+.

CLINICAL OUTCOME

It is reasonable to inquire as to whether the physiologic advantages of PAV translate into better clinical outcome. Unfortunately, information about outcomes is very scanty. This is so chiefly because, until very recently, available ICU ventilators (Winnipeg ventilator and Dräeger Evita) were not equipped with means to provide smooth, nuisance-free PAV delivery over the extended periods required for outcome studies. It is hoped that with newly available systems such studies will be carried out. In the meantime, one is limited to speculation about how physiologic advantages may improve outcome.

Noninvasive Ventilation. Two studies compared outcomes with PSV and PAV in acute respiratory failure.[38,39] Both found greater comfort and acceptance rate and a lower incidence of facial ulcers and conjunctivitis with PAV. One study found faster improvement in respiratory rate and Pa_{CO_2} with PAV.[38] Neither study found a difference in intubation rate. Both studies, however, were seriously underpowered in this respect. When faced with a choice between severe distress and a somewhat uncomfortable way to relieve it, most people will opt for relief of dyspnea. Thus, nonacceptance rate with PSV is low (15% vs. 3% in PAV[39]). Furthermore, intubation rate in such patients is also low (approximately 20% to 30%[38,39]). It is estimated that more than 1000 patients are required to determine whether a new intervention reduces rate of intubation.[39] Rusterholtz et al randomized thirty-eight patients with acute cardiogenic pulmonary edema to receive noninvasive PAV or continuous positive airway pressure.[41] They found no difference in failure rate (seven in each group) as defined by the onset of predefined intubation criteria, severe arrhythmias, or patient refusal. Again, the study size is insufficient to establish differences in clinical outcome.

Clinical Outcome in the Intensive Care Unit Setting. PAV may improve clinical outcome in a number of ways:

1. *Sedative use.* Most ICU patients are heavily sedated if they are not spontaneously unconscious. Sedatives may affect clinical outcome adversely.[104,105] It is not clear to what extent patient–ventilator interactions contribute to need for sedation. To the extent that they may, PAV may result in less sedative use and reduction in sedation-related complications.
2. *Impact on sleep.* Poor patient–ventilator interaction may affect sleep adversely in the ICU.[58,106] Sleep deprivation may increase blood pressure, depress immune function, and promote a negative nitrogen balance, actions that can affect morbidity adversely (for review, see ref. 106). By improving patient–ventilator interaction, PAV may help to reduce these complications. Bosma et al[107] monitored sleep for two consecutive nights in thirteen patients in the

weaning phase. PAV and PSV were each used on one night and the order was randomized. The number of arousals and awakenings per hour of sleep was significantly lower on PAV and there was significantly more slow wave (deep) and rapid eye movement sleep. Interestingly, the number of arousals correlated with number of asynchrony events, which was greater with PSV.

3. *Barotrauma and ventilator-induced lung injury.* Excessive lung distension may result in further lung injury (see Chapter 44) and possibly multisystem organ failure[108] (see Chapter 42). There are a number of reasons why V_T will, on average, be smaller in PAV (see "Tidal Volume in Different Modes" above). Furthermore, neural reflexes terminate inspiratory muscle activity if lung distension exceeds a certain threshold that is well below physiologic total lung capacity (TLC) (e.g., Hering-Breuer reflex). For example, when tidal expansion approaches TLC during exercise, further increases in ventilation are achieved automatically via increases in RR.[109] Because the assist terminates automatically with PAV when respiratory muscles are inhibited, overdistension beyond physiologic TLC (transpulmonary pressure approximately equal to 40 cm H_2O) is virtually impossible (except in patients with denervated lungs, such as after bilateral transplantation). Figure 12-16 shows average plateau pressure on PAV in forty-eight patients with a wide range of elastance. Plateau pressure was less than 30 cm H_2O above PEEP in all, and less than 20 cm H_2O above PEEP in all but four. These findings were confirmed in another recent study.[96] Considering that plateau pressure also includes chest wall recoil, lung distension was even less. It is reasonable to expect that this behavior will reduce barotrauma. It also may make it possible to achieve the objectives of permissive hypercapnia (small V_T) without the need for sedation or even hypercapnia (because RR increases automatically as end-inspiratory volume approaches TLC).

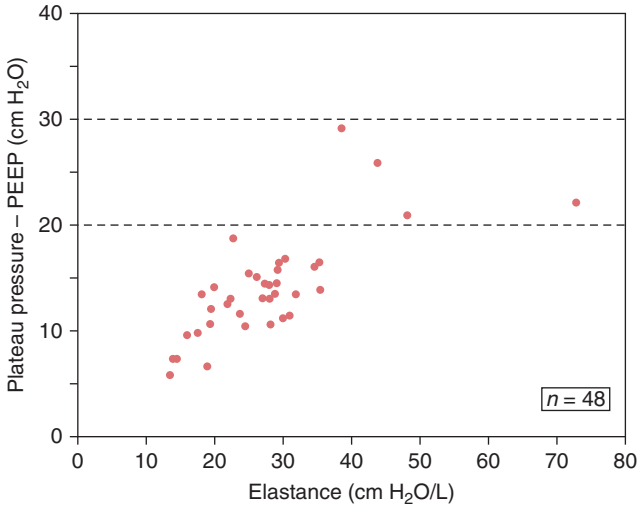

FIGURE 12-16 Average plateau pressure (minus PEEP) in forty-eight patients with a wide range of elastance.

4. *Weaning.* The greater reliability of ventilator rate as a measure of distress (see "Improved Reliability of Ventilator Rate as a Measure of Distress and Weaning Failure" above) should decrease instances of false ventilator dependence. Tachypnea as the sole reason for a declaration of weaning failure accounted for 37% of all weaning failures in two large trials[102,103] (A. Esteban, personal communication). It is tempting to speculate that some of these patients were not ventilator-dependent, so their identification under PAV will reduce ventilator time.

   With PSV and VCV, Pa_{CO_2} may decrease to very near the AT, resulting in extremely weak efforts, particularly during periods of reduced demand (see "Physiologic Consequences of Operational Differences" above). With VCV in the assist-control mode, it is also possible to produce protracted apnea. With PAV, a modest to moderate level of activation is present at all times, including during sleep. The likelihood of disuse atrophy of respiratory muscles (see Chapter 43) may be less, and this may facilitate weaning.

   Most ineffective efforts occur during mechanical expiration. Accordingly, the inspiratory muscles are being lengthened during their activation. This type of contraction has been associated with muscle injury.[110,111] Because ineffective efforts are very common with PSV and VCV[84] but not with PAV, this type of injury may be mitigated.

5. Continuous noninvasive monitoring of passive mechanics, made possible by PAV, may lead to better PEEP management and early detection and management of complications.

   To date there has been only one study that compared clinical outcome with PSV and PAV in critically ill ventilated patients.[96] Xirouchaki et al[96] randomized 208 critically ill patients, mechanically ventilated on controlled modes for at least 36 hours, to receive either PSV (n = 100) or PAV + (n = 108). Specific written algorithms were used to adjust the ventilator settings in each mode. The patients were observed for 48 hours following transition from controlled ventilation unless they met predefined criteria either for switching back to controlled modes (failure criteria) or for breathing without ventilator assistance. Failure rate was significantly lower with PAV+ (11.1% vs. 22.0%, P = 0.040, odds ratio [OR] 0.443, 95% confidence interval [CI] 0.206 to 0.952) and the proportion of patients exhibiting major dyssynchronies was also significantly lower (5.6% vs. 29.0%, P < 0.001).

COMMERCIALLY AVAILABLE PROPORTIONAL-ASSIST VENTILATION DELIVERY SYSTEMS

The BiPAP Vision (Respironics) is the only ventilator currently suitable for noninvasive use. The Vision is equipped with leak-compensation algorithms. It also has excellent response characteristics and trigger sensitivity and has

performed very well in several clinical trials.[21,23,38,39] The Vision offers pathology-specific default startup settings as well as custom settings.

Until recently, the Evita ventilator (Dräeger) was the only commercial ICU ventilator capable of delivering PAV. It is a basic PAV system with no capability to monitor passive mechanics in real time and with standard alarms. As indicated earlier, such basic systems (including the Winnipeg ventilator) have proven difficult to use except by experts and for short periods.

Covidien's 840 ventilator currently has a PAV+ option. The ventilator monitors mechanics continuously by applying random brief end-inspiratory occlusions (see Fig. 12-14). The results have been validated.[95] In addition, algorithms were added to limit the maximum elastic assist to a set level and the alarms were modified to allow for pressure and volume limits to be reached occasionally without the alarms sounding off. With this option, the maximum possible airway pressure, including PEEP, is 35 cm H_2O. This may be a limitation in a few patients receiving high levels of PEEP whose resistance is also high. Another limitation is that the resistance used to adjust the flow assist during inspiration is measured around peak expiratory flow. In the presence of an early expiratory flow spike (as in very severe COPD), this measurement can greatly underestimate the patient's true resistance and result in underassist (see "Noninvasive Monitoring of Respiratory Mechanics, Pmus, and Work of Breathing" above).

LIMITATIONS

The following mechanisms may result in excessive sounding of alarms and occasional instances in which patients are in distress despite a high percent assist. Fortunately, the underlying reasons for these difficulties are well understood, and auxiliary algorithms have become available that should mitigate most, if not all, of these problems.

Runaway Phenomenon

Despite its ominous-sounding name, the runaway presents no danger in modern ventilators with properly set pressure and/or volume limits. It is simply a nuisance in that, when it happens, it can trigger alarms, which can be annoying to staff and may promote anxiety in alert patients. Nonetheless, it is important to understand its mechanism and recognize its features, as this will be useful in managing PAV in patients who require a very high level of assist. The nuisance factor is much reduced in delivery systems with smart alarms, which allow for pressure and volume limits to be reached occasionally without the alarms sounding off.

Runaway occurs when the volume assist component (%assist [estimated V × estimated E]) exceeds the actual elastic recoil pressure of the respiratory system (actual V × actual E) and/or the flow assist component of the assist (percent assist [flow × estimated R]) exceeds the actual pressure dissipated against respiratory resistance (actual flow × actual R). In modern PAV delivery systems in which the percent assist is used to adjust PAV, the percent assist cannot exceed 100. Thus, runaway occurs when flow and its integral, volume, are overestimated (e.g., uncompensated leaks) and/or estimated E and/or estimated R are greater than the actual values.

The runaway pattern depends on whether the resistive or elastic component is overassisted. With elastic overassist, the elastic pressure provided exceeds actual elastic pressure by an amount that increases as a function of volume. If flow is not overassisted, the resistive pressure provided is less than actual resistive pressure by an amount that is related to flow. So long as excess elastic pressure is less than the deficit in resistive pressure, a runaway does not occur because total applied pressure (Paw) is less than the sum of actual resistive and elastic pressures. Runaway occurs when excess elastic pressure cannot be absorbed by the deficit (or reserve) in resistive pressure.

With elastic overassist, excess elastic pressure increases progressively during inspiration because volume rises throughout. By contrast, reflecting flow pattern, deficit/reserve in resistive pressure is highest in early and middle inspiration and decreases later. The point at which elastic overassist will exceed the reserve in resistive pressure (i.e., runaway) necessarily will occur late in inspiration. When VA is just greater than E, the runaway will occur at the very end of the inspiratory phase when flow is near zero (Fig. 12-17A). This fact has been put to use to measure actual patient E in sleeping or obtunded patients.[6,17,93] VA is dialed up in small steps until the characteristic runaway pattern appears (Fig. 12-17B). At this point, VA is just greater than E. The more the elastic overassist, the sooner, in the inspiratory phase, runaway will develop (Fig. 12-17). Likewise, runaway occurs earlier if the difference between actual R and percent assist × estimated R is small because the deficit in resistive pressure will be less and more readily overcome by excess elastic pressure.

Once a runaway develops as a result of elastic overassist pressure and volume will continue to rise beyond the end of inspiratory effort (see Fig. 12-17B) until the cycle is stopped by (a) a set pressure or volume limit, or (b) volume approaching the stiffer upper part of the pressure–volume curve of the respiratory system (Fig. 12-18A). The latter results in a progressive increase in actual elastance that cancels the overassist. Thus, the nonlinearity of the pressure–volume relationship of the respiratory system acts as natural protection against excessive overdistension.

By analogy, with resistive overassist, runaway will occur when the excess resistive pressure provided by the ventilator exceeds the deficit/reserve in applied elastic pressure. This point invariably will occur at the very beginning of inspiration, where volume, and hence elastic assist, is near zero, and there is no possibility for the elastic deficit/reserve to absorb the excess resistive pressure.

The pattern of flow runaway depends on whether the pressure-flow relation is linear (Fig. 12-19). A linear

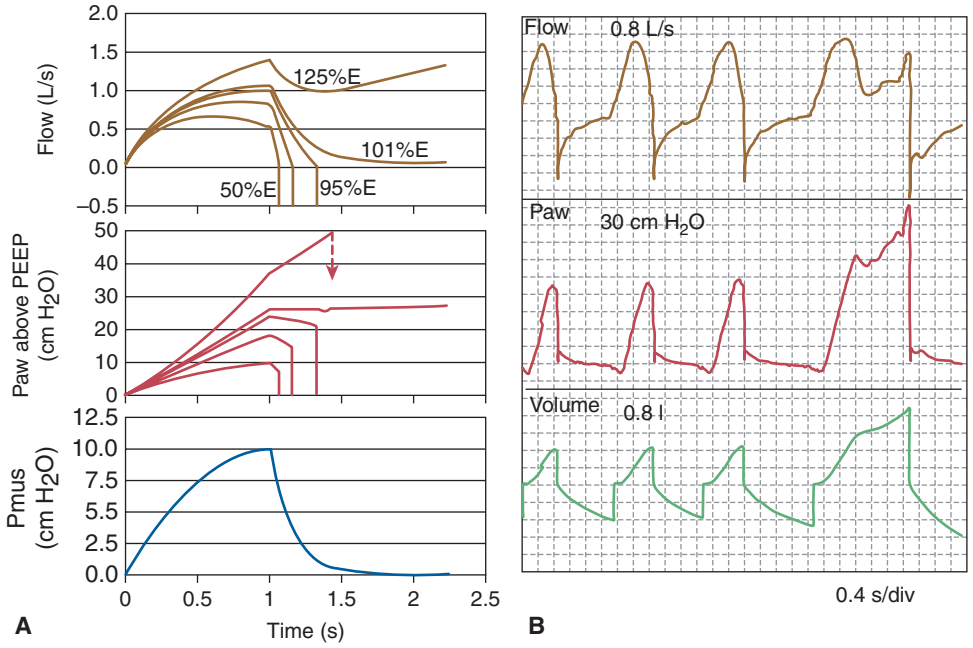

FIGURE 12-17 Runaway. **A.** Model simulation of effect of increasing percent of elastance used for volume assist (VA). Note that as soon as VA exceeds elastance (101% E), flow fails to return to zero at the end of inspiratory phase. At higher levels, the runaway begins earlier, and flow and pressure increase progressively until the cycle is terminated by a physiologic or ventilator limit. **B.** Patient with COPD and moderate dynamic hyperinflation, 90% assist. Note the spontaneous occurrence of a runaway breath (last breath). The pattern is intermediate between the 101% and 125% in the *left panel*. Note that in the breath preceding the runaway, exhaled volume exceeded inhaled volume, suggesting less dynamic hyperinflation at the beginning of the runaway breath. See text for more details. The runaway breath was terminated by the ventilator's high-pressure limit.

pressure-flow relation occurs when breathing via the mouth, thereby excluding the nonlinear nasal pressure-flow relation, or when the nonlinear relation of the endotracheal tube is offset independently by automatic tube compensation (ATC). Here, as flow assist just exceeds actual resistive pressure, there is a very rapid increase in flow and pressure that can be aborted only by a ventilator limit (see Fig. 12-19A). The inflation phase is very brief. By contrast, when the pressure-flow relation is nonlinear, there is no discrete change as FA exceeds R. Rather, change is gradual and consists of a progressive shift in peak flow to earlier points in inspiration (see Fig. 12-19B). Flow pattern at high levels of overassist resembles that of PSV. The rapid increase in flow early in inspiration may truncate the breath, however, and sound an alarm if peak pressure limit is reached.

The development of algorithms to continuously monitor mechanics and their incorporation in commercial PAV delivery systems has greatly reduced this problem when such systems are used.

Runaways need not occur on every breath (see, e.g., Fig. 12-17). Because true elastance (E) may vary breath by breath (see "Dynamic Hyperinflation" and "Nonlinearity in the Pressure–Volume Relationship within the Tidal Volume Range" above), estimated E may exceed actual E in some breaths, even though it is less than average E. Assume that average E, determined from a number of end-inspiratory occlusions, is 30 cm H_2O/L, with a range of 24 to 36 cm H_2O/L. At 90% assist (i.e., 27 cm H_2O/L), some breaths may develop runaway. The higher the percent assist, the more frequent are the runaways.

Accuracy and Stability of Respiratory Mechanics Values

Knowledge of R and E is not necessary in noninvasive applications. Feedback from the alert patient ensures that VA and FA are appropriate. In the usually obtunded ICU patient, subjective feedback is not possible, and setting PAV properly requires knowledge of passive mechanics. This has created problems for two reasons: first, measuring passive mechanics in the usual way (under sedation, hyperventilation, and/or paralysis) is cumbersome, requires expertise, cannot be done frequently, and the results may not reflect the E and R values on PAV (because of differences in V_T, flow rate, dynamic hyperinflation, and so on). Second, passive mechanics frequently change (see "Response to Changes in Respiratory Mechanics" above). Values that are accurate at one point may become inaccurate later.

When differences between actual and assumed R and E values are small (e.g., <25%) and percent assist is not high, the impact is operationally insignificant. For example, with a 20% error at 50% assist, actual assist will be 40% or 60% depending on the direction of the error. Either value is

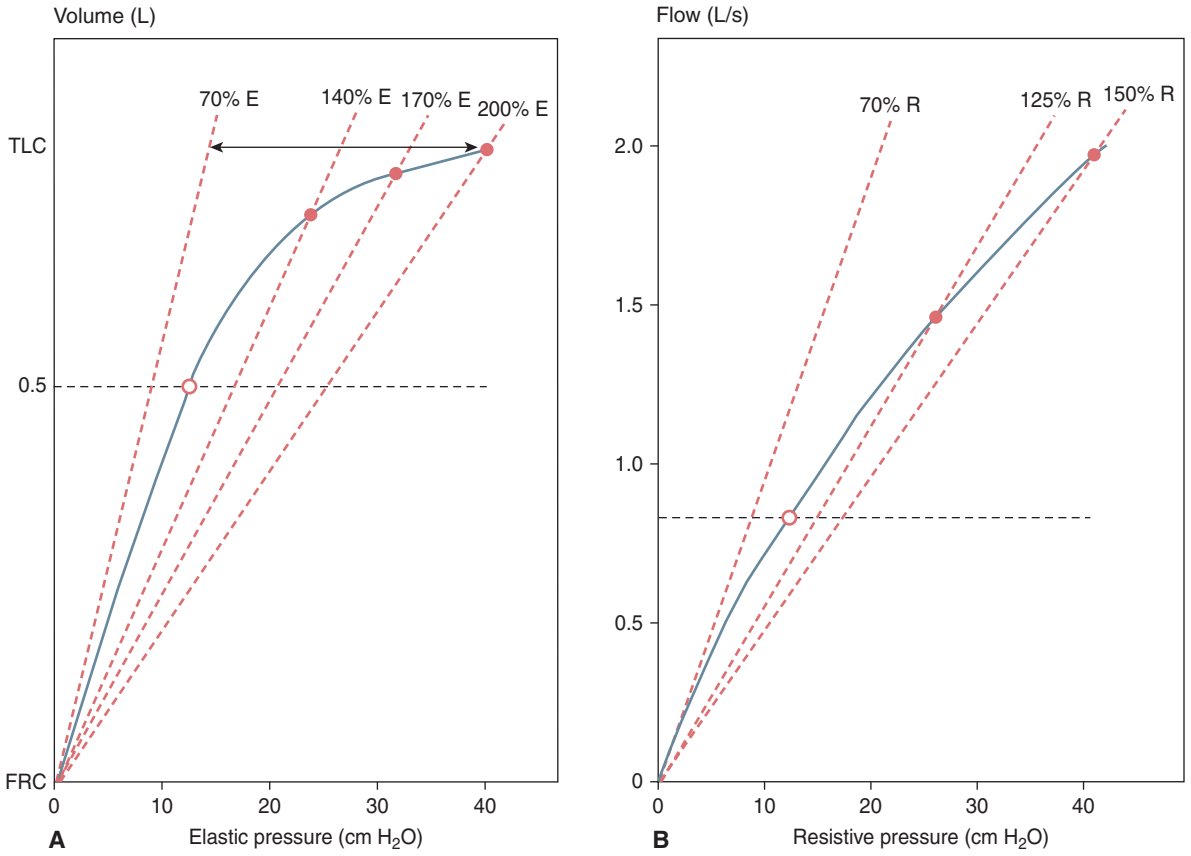

FIGURE 12-18 Physiologic limits to runaway. **A.** Typical pressure–volume curve in an average ventilated patient. Elastance (E) at a tidal volume (V_T) of 0.5 L (the average V_T on PAV in this case) is 25 cm H_2O/L (*open circle*). *Left diagonal line*: Volume assist = 70% E. The elastic pressure delivered by the ventilator is less than elastic recoil at all volumes (no runaway). The next three diagonal lines represent progressively increasing overassist. An excess elastic pressure is delivered in the spontaneous tidal volume range (horizontal distance between diagonal lines and pressure–volume line), forcing a volume runaway. Because of the stiffening of the system near TLC, however, excess pressure decreases as volume increases. Runaway ends when the diagonal line meets the pressure–volume line because there is no longer an excess pressure. Note that even with a marked overassist (200% E), runaway stops at an elastic pressure of 40 cm H_2O, corresponding to a physiologic TLC value. **B.** Typical pressure-flow relationship in an average patient (airway resistance is 10 cm H_2O/L/s with a no. 8 endotracheal tube). Total resistance at a flow of 0.8 L/s is 15 cm H_2O/L/s. A flow assist in excess of this value will cause a flow runaway (*right two diagonal lines*). Because the pressure-flow relationship is not linear, excess resistive pressure decreases as flow increases. Flow runaway stops when the diagonal line meets the pressure-flow line. Excessive overdistension of the lung is also mitigated in this case by nonlinearity of the pressure–volume curve. Note that if VA is less than E (*left diagonal line, panel A*), the deficit in elastic pressure increases dramatically near TLC (*horizontal arrow, panel A*). This helps offset the excess resistive pressure and aborts the flow runaway below physiologic TLC. *FRC*, functional residual capacity; *TLC*, total lung capacity.

consistent with proper functioning, and if the assist is insufficient, there is room to increase it. By contrast, with a 50% error at 80% assist, actual assist will be 40% or 120%. In the former case, assist may be insufficient, resulting in distress when the patient is "supposedly" receiving high assist, and there is little room for further increases. In the latter case, runaway will develop, with frequent sounding of the alarms, even though it should not happen (percent assist <100). In my opinion, the discrepancy between assumed and actual R and E is the most important source of implementation difficulties. Fortunately, this has now been largely resolved (see "Noninvasive Monitoring of Respiratory Mechanics, Pmus, and Work of Breathing," and "Commercially Available Proportional-Assist Ventilation Delivery Systems" above).

Leaks

Leaks affect PAV delivery in much the same way as overestimation of E and R does. For example, if half the gas leaving the ventilator leaks out, assist will be twice that intended, or analogous to 100% overestimation of E and R. Thus, the magnitude of overestimation is related directly to the magnitude of the leak. As in the case of overestimation of E and R (see preceding section), a small leak will not have much impact if percent assist is low or moderate and will cause runaway if assist is high. Large leaks would result in runaway at all but the lowest assist levels.

In noninvasive applications, leaks can be huge. For this reason, noninvasive PAV delivery systems must be equipped

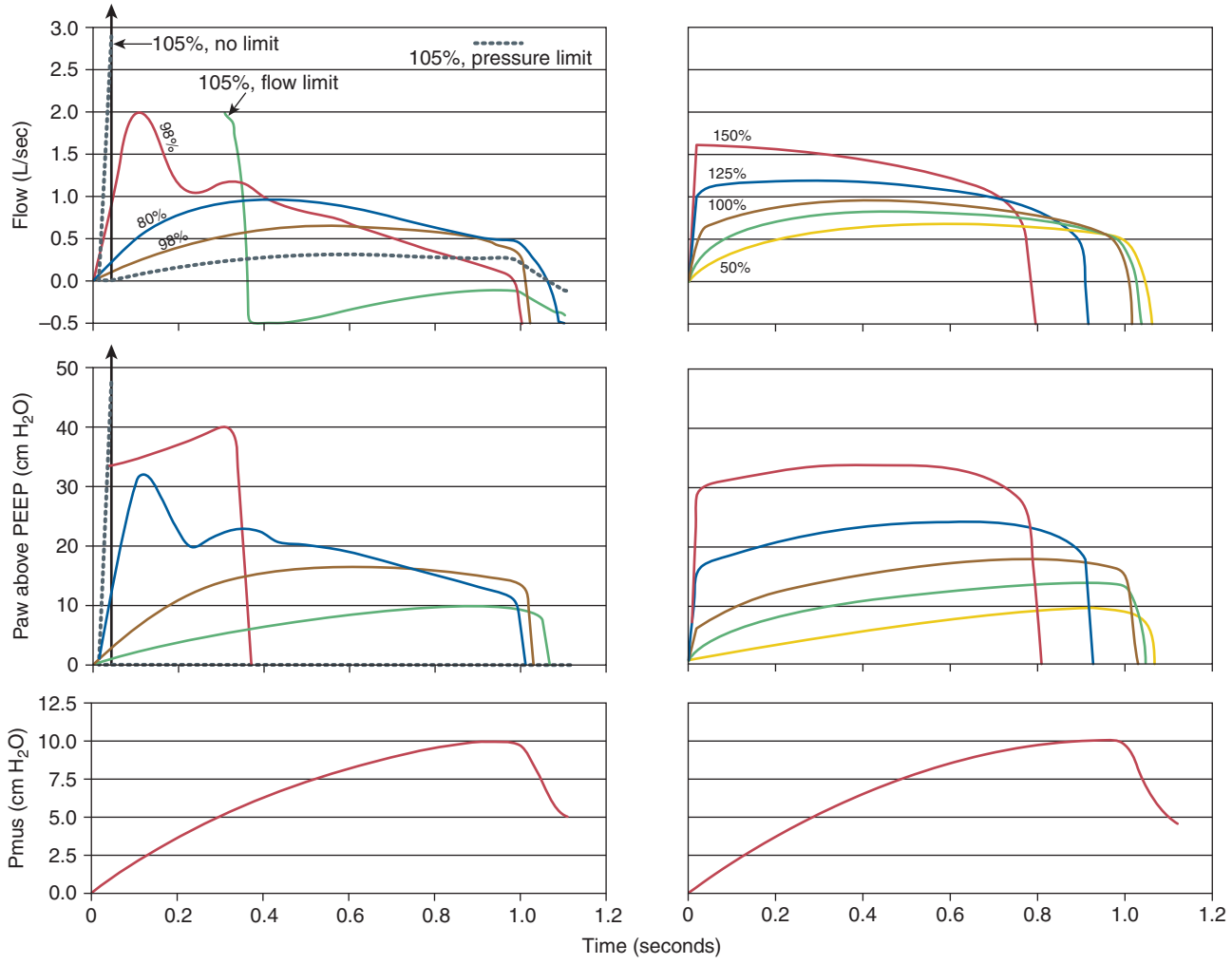

FIGURE 12-19 Patterns of flow runaway. Percent denotes ratio of flow assist to resistance at a reference flow (0.5 L/s in panel B). **A.** Linear pressure-flow relationship. FA is increased in steps beginning with 50% R. As the assist approaches 100% R, some oscillations become apparent. At just above 100% R, there is a sudden change in response. Without any ventilator limits, flow and pressure increase very rapidly to extremely high levels at the beginning of inspiration. Termination of runaway depends on ventilator limits. With activation of peak-pressure limit, the cycle is aborted rapidly. If the maximum flow capability of the ventilator (e.g., 2 L/s) is reached before the peak-pressure limit, the cycle continues a while more at the maximum flow and then self-terminates rapidly. With a constant resistance, therefore, transition of assist to above 100% is abrupt. **B.** Nonlinear pressure-flow relationship (e.g., in the presence of an endotracheal tube). Runaway is blunted by the increasing resistance at higher flow (see Fig. 12-18B). There is no clear change in response at 100% assist. Rather, change is gradual and consists of a progressive shift in peak flow to earlier points in inspiration. *Paw*, airway pressure; *Pmus*; respiratory muscle pressure.

with leak-compensation algorithms. In the ICU setting, leaks are usually very small, except in bronchocutaneous fistulas. Nonetheless, checking for leaks should be undertaken if alarms begin sounding excessively when they did not before.

Inclusion of automatic mechanics in PAV delivery systems essentially should eliminate leak-related problems. Thus, when a leak exists, the end-inspiratory occlusion technique (see Fig. 12-14) will underestimate E by an amount corresponding to the leak (provided inspired volume is used to compute E). This should offset the error at the ventilator level. Likewise, the pulse technique (resistance)[56] will underestimate inspiratory resistance in the presence of leaks, thereby offsetting the pressure-delivery error at the ventilator level.

Dynamic Hyperinflation

Dynamic hyperinflation (DH) presents occasional implementation difficulties, particularly when severe and associated with marked respiratory muscle weakness. Thus:

1. By definition, DH means that elastic recoil pressure is greater than zero at inspiratory onset. Inspiratory muscles must generate enough pressure to offset this elastic recoil before the ventilator is triggered (see, e.g., Figs. 12-7 and 12-8). Therefore, by the time the ventilator is triggered, a finite fraction of the patient's inspiratory phase will have elapsed. This delay is a function of magnitude of DH and the rate of rise of Pmus (see Fig. 12-7).

When DH is large (e.g., 10 cm H_2O in Fig. 12-7A) and the rate of rise of Pmus is low, triggering may not occur until near the end of inspiratory effort (see, e.g., Fig. 12-7A). In PSV and VCV, once triggering occurs, a substantial breath will be delivered. Although volume delivery will be almost entirely during the patient's expiratory phase, adequate ventilation nonetheless will be delivered, making it possible for chemical drive to remain low. In PAV, the ventilator will provide support only for the remaining duration of inspiratory effort. When triggering is much delayed, the duration of support may be very brief, resulting in inadequate ventilation (see, e.g., Fig. 12-13). The only way the patient can receive reasonable ventilation is to increase the rate of rise of inspiratory effort in order to advance triggering (see, e.g., Fig. 12-7B). This will occur naturally at the expense of a higher chemical drive. When respiratory muscle reserve is high, the required increase in respiratory muscle output may be tolerated. When DH is very high and muscle reserve is quite low, distress may develop.

2. As illustrated in Figure 12-20, the effective assist received is less than the percent assist dialed in. This is so because the ventilator is unaware of the Pmus generated before triggering; the assist is applied only to that part of Pmus in excess of that required for triggering. Thus, not only does the patient have to generate more pressure to advance triggering, but the maximum percent assist that can be delivered effectively also is less. Distress may occur even at the highest possible assist.
3. Even if an assist level is found with which the patient is comfortable, runaway still may develop in occasional breaths, causing confusion (as percent assist is technically less that 100% E). The duration of expiration of spontaneous efforts can be quite variable. A breath preceded by a long expiratory time begins at a lower absolute volume (less DH). The same percent assist that was not associated with runaway when end-expiratory volume was higher may now cause runaway (see Fig. 12-17B). This can be appreciated by moving the VA line downward in Figure 12-20B. It will be noted that at some point

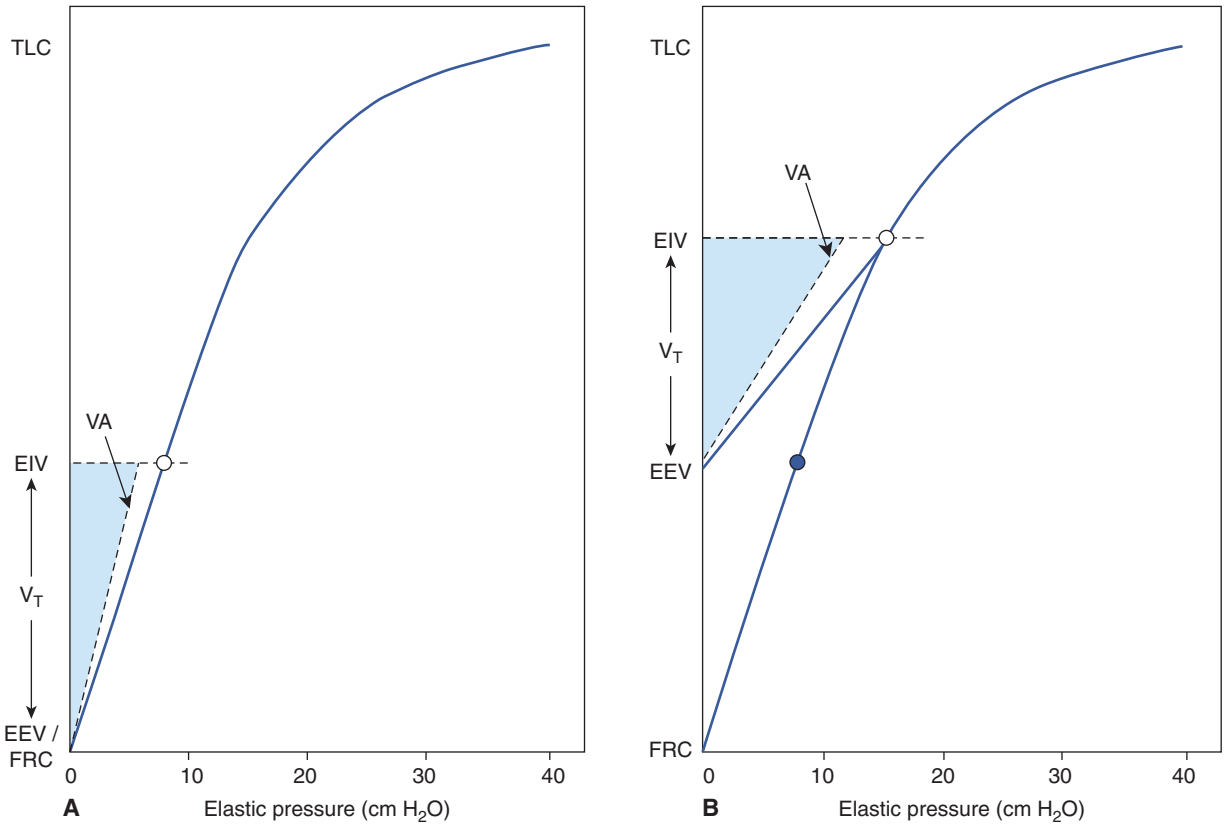

FIGURE 12-20 Impact of dynamic hyperinflation (DH) on PAV delivery. **A.** No DH (FRC and end-expiratory volume are the same). If 80% assist is dialed, the elastic work done by the ventilator (*shaded triangle*) is 80% of the total elastic work (*sum of shaded and open triangles*). **B.** DH: elastic recoil pressure at end-expiratory volume is 8 cm H_2O (*solid circle*). Measured elastance (E = plateau pressure/V_T) overestimates actual elastance because V_T, the denominator, underestimates the difference between end-inspiratory volume and FRC (compare the solid diagonal line with the slope of the main pressure-volume curve in the V_T range). At 80% of this inflated elastance (*VA line*), the ventilator is providing only 50% of elastic work (compare the shaded triangle with the pressure-volume area in the V_T range). There is little room to increase the assist. Forcing VA to exceed measured elastance will result in runaway. In such cases, therefore, the maximum assist that can be delivered is limited. *EEV*, end-expiratory volume; *FRC*, functional residual capacity; *TLC*, total lung capacity; *VA*, volume assist; V_T, tidal volume.

the VA line will cross to the right of the pressure-volume line (i.e., overassist).

The preceding account should not suggest that patients with severe COPD or other causes of DH are difficult to support. As judged by numerous reports[19–21,24–26,36,39,40] and my own experience, the vast majority can be supported very comfortably. Even in patients with severe COPD, elastic recoil at end expiration is usually approximately 3 to 5 cm H_2O,[114–116] a level that is accommodated easily by most patients. Nonetheless, a very high expiratory resistance combined with a high ventilatory demand and weak muscles may make it difficult to achieve adequate support.

The adverse impact of severe DH on PAV's performance can be mitigated in some patients by increasing PEEP. This is effective, however, only when the high expiratory resistance is related to expiratory flow limitation in the lung. Where the high resistance is in the tubing, raising PEEP simply increases lung volume without relieving DH. The impact of DH can be eliminated completely if the ventilator is made to trigger at the onset of inspiratory effort instead of being triggered by inspiratory flow or airway pressure. Because it is possible to measure passive E and R during PAV, it is also possible to generate a continuous estimate of Pmus in real time. Such a signal can be used to begin the assist at the time of onset of inspiratory effort, instead of the onset of inspiratory flow. Another method for noninvasive identification of the onset of effort in real time has also been developed recently (see "effort channel" in Fig. 12-7).[100] With either system, PAV assist continues to be a function of flow and volume, but the reference flow is the expiratory flow at onset of effort (as opposed to zero flow, as is currently practiced). In this fashion, assist would apply throughout inspiratory effort.

Nonlinearity in the Pressure–Volume Relationship within the Tidal Volume Range

The relation between volume and elastic recoil is sigmoid.[112] Most patients breathe in the linear midrange, and E is nearly constant within the V_T range. In others, the pressure–volume relationship is not linear within V_T. This creates some difficulties because there is no fixed E to use for the sake of setting the volume assist. The difficulties depend on whether V_T falls within the stiff upper range (high-end nonlinearity) or the stiff lower range (low-end nonlinearity).

1. *High-end nonlinearity* (Fig. 12-21A). This occurs when end-inspiratory volume approaches TLC, such as when external PEEP is excessive or in very severe restrictive disease (e.g., severe acute respiratory distress syndrome). Here, the maximum elastic assist that can be provided without runaway is limited, and the highest V_T, with or without runaway, is constrained by physiologic TLC (Fig. 12-21A). Should this V_T be inadequate for the patient's ventilatory demand, distress will develop and cannot be relieved by increasing percent assist. Unless heavily sedated, such patients (high demand plus very stiff respiratory system) require supraphysiologic distending pressures for adequate ventilation, and PAV is not suitable.
2. *Low-end nonlinearity* (see Fig. 12-21B). Here, the system is stiffest in the low range of tidal volume, for example, when end-expiratory volume is close to residual volume (abdominal distension and obesity[118–120]) or when derecruitment of airways or alveoli occurs within the tidal volume range. The impact of this abnormality on PAV delivery is similar to that of dynamic hyperinflation (see "Dynamic Hyperinflation" above); the assist received by patient is less than intended (see Fig. 12-21B). When assist requirement is low, this behavior presents no difficulty. When assist level must be high (e.g., 80%), however, the patient may be comfortable, but because of the usually large breath-by-breath variability in V_T, runaways may occur during large breaths, triggering alarms (see Fig. 12-21B). Therefore, in some patients it may be difficult to reach an assist level that is both adequate and free of frequent alarming. This problem can be eliminated by increasing PEEP, thereby placing V_T in the linear pressure–volume range.

Ventilator Response Time

Response delays are unavoidable in electromechanical systems. Excessive response delay would result in less assist than intended as well as delays in cycling off. In the original Winnipeg ventilator, the delay was approximately 40 milliseconds. I had assumed that the delay simply would result in a parallel shift relative to the target Paw waveform[93] and thought this would be acceptable. However, Du et al[76] demonstrated that ventilator response delay becomes compounded during the inspiratory phase, resulting in cycling-off delays that are longer than the nominal ventilator delay. In a recent study, cycling off delay while using the PAV+ option in ventilator-dependent patients averaged 0.25 second (range: 0.17 to 0.51 second).[117] This is acceptable, particularly when considering that transition from inspiration to expiration does not normally occur at peak Pmus but during the declining phase of inspiratory activity,[49,121–123] so that some delay is inevitable even without a ventilator. Nonetheless, that response delays become compounded during PAV delivery[76] emphasizes the need for fast-responding gas-delivery systems in this mode.

Excessive Alarming

Standard ventilator alarms that sound off every time a limit is reached proved to be a considerable nuisance in the PAV mode. Because of the spontaneous variability in breathing pattern, one or more limits may be reached frequently. Furthermore, without automatic mechanics, runaway breaths were frequent. With incorporation of automatic mechanics (see "Noninvasive Monitoring of Respiratory Mechanics, Pmus, and Work of Breathing" above), occurrence of

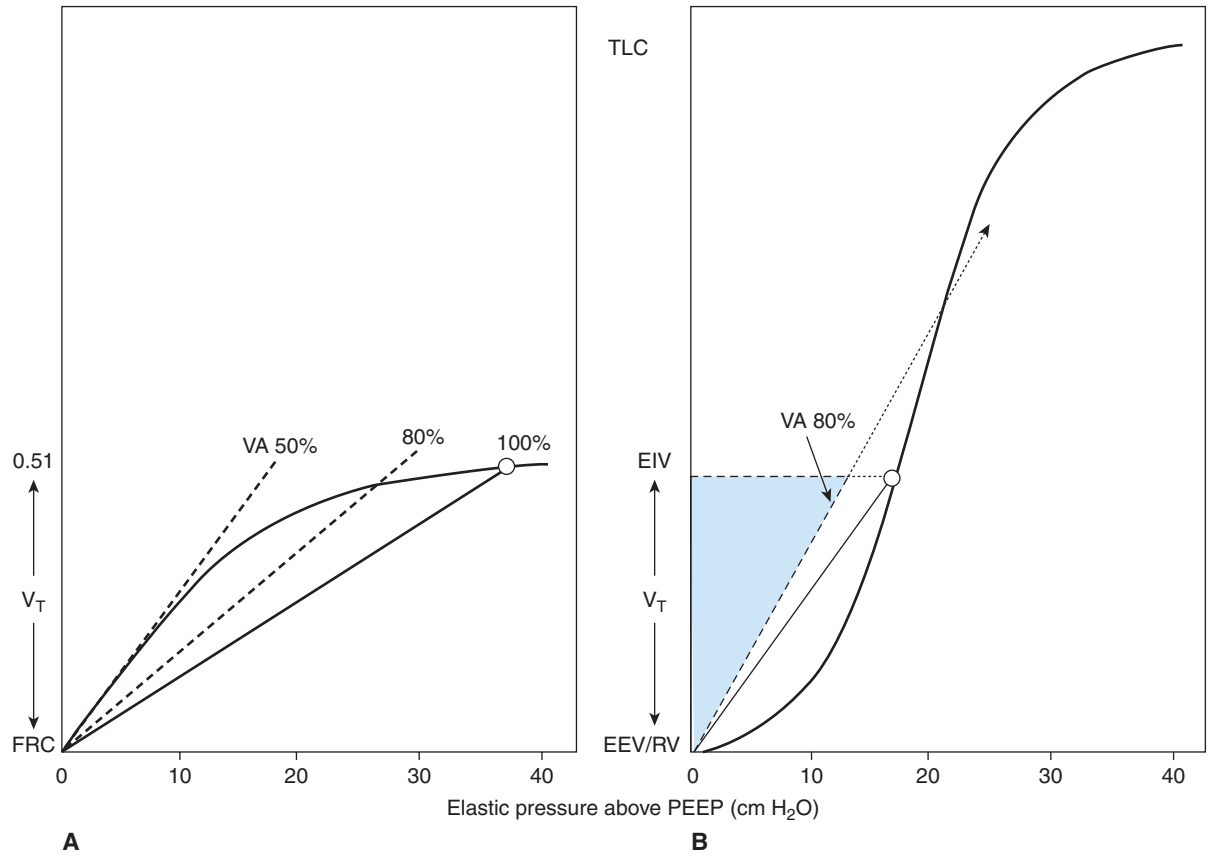

FIGURE 12-21 Impact of nonlinearity in the pressure–volume relationship within tidal volume. **A.** High-end nonlinearity. The pressure–volume relationship becomes quite flat within 0.5 L of FRC. Elastance at a volume of 0.5 L is 75 cm H_2O/L (pressure and volume values at the *open circle*). The maximum VA that can be given without runaway is 50%. At higher assist, runaway develops until the flat region is reached. In either case, the maximum V_T that can be obtained with PAV is limited by physiologic TLC. **B.** Low-end nonlinearity. Elastance is determined at an average V_T given by the open circle. At a VA of 80% E, the elastic assist received is only 55% (compare the *hatched area* with the total area inside the pressure–volume line). Furthermore, if the patient makes a larger effort and obtains a larger V_T, elastic assist may exceed elastic recoil, and runaway may occur (*arrow*). At 50% assist, runaways would not occur, but the patient receives only 35% assist (not shown). *EEV*, end-expiratory volume; *FRC*; functional residual capacity; *TLC*, total lung capacity; *VA*, volume assist; V_T; tidal volume.

runaway will be greatly reduced, but some may still occur (see "Dynamic Hyperinflation" and "Nonlinearity in the Pressure–Volume Relationship within the Tidal Volume Range" above), and spontaneous variability will remain as a possible source for activating alarms. Accordingly, alarms in the PAV mode should take into account the breath-by-breath variability in breathing pattern and mechanics. A reasonable approach (e.g., 840 PAV+ option) is to use special filters whereby ventilator limits still function as such for safety reasons, but alarms sound off only when the frequency of reaching a ventilator limit exceeds a threshold value.

INDICATIONS AND CONTRAINDICATIONS

PAV is appropriate to use in all but a few situations:

1. *Respiratory depression.* Safe use of PAV requires that the patient's respiratory muscle output be responsive to changes in Pa_{CO_2}, Pa_{O_2}, and pH. Absolute contraindications are patients with central apnea or very weak efforts and *no respiratory distress despite an abnormally low pH*. Patients who are intubated for respiratory depression (e.g., overdose or neuropathology) or who had to be heavily sedated for intubation should not be placed on PAV initially. The situation is different in patients already being ventilated with another mode. Here, weak efforts and even no efforts (e.g., on assist-control ventilation or having recurrent central apneas on PSV[58]) are almost invariably secondary to overventilation. The assist with the other mode should be reduced first to establish that efforts resume at a reasonably normal pH before switching to PAV.

Care should be exercised when initiating PAV in a patient with known or suspected chronic CO_2 retention whose Pa_{CO_2} and pH were normalized by another ventilation mode. Such patients often respond poorly to CO_2 until Pa_{CO_2} reaches a level commensurate with their preintubation value. This may result in acute hypercapnia and acidemia following a switch to PAV. Chronic CO_2 retention per se is clearly not a contraindication, and many

such patients were treated adequately with PAV. Patients who develop shallow, relatively slow breathing *with no distress* on PAV should have their blood gases checked, and if they are acidemic, they should be switched to another mode. These patients likely had undocumented prior chronic CO_2 retention.

2. *Need for heavy sedation*: The respiratory response to heavy sedation is unpredictable. When heavy sedation is required acutely for control of severe agitation or seizures, it is better to switch the patient to another mode until it is clear that the patient is making efforts at an acceptable pH.
3. *Severe neuromuscular weakness*: These patients may have difficulty triggering the ventilator and when triggering occurs it may be close to the end of inspiratory effort. Because with PAV, unlike other modes, the ventilator cycle terminates at the end of inspiratory effort, the inflation cycle may be very brief and ventilation may be inadequate.
4. *Bronchocutaneous fistulas.* Patients with bronchocutaneous fistulas should have their leak measured before switching to PAV. If the leak is high on another mode (e.g., exhaled volume less than 75% of inhaled volume), it is better not to use PAV unless the ventilator is equipped with automatic mechanics or leak-compensation algorithms.

Use of Sedatives in Patients on Proportional-Assist Ventilation

Sedatives are not contraindicated when PAV is used. When the response of a patient to sedatives is not known, the dose should be titrated initially until the amount required to attain the desired effect without severe depression is learned. Because backup systems always must be available on PAV delivery systems, the inadvertent use of an excessive amount of sedatives should not be hazardous.

ADJUSTMENT AT THE BEDSIDE

Noninvasive Application

General instructions regarding noninvasive ventilation are similar to those for other modes and are not discussed here (see Chapter 18). The following procedure pertains to BiPAP Vision (Respironics).

STARTUP

It is neither necessary nor recommended to attempt to measure respiratory mechanics. Patients are alert, and settings are best accomplished using patient feedback. Before attaching the ventilator to the mask, the limits should be set initially to a maximum pressure of 20 cm H_2O, a maximum volume of 1.5 L, and a maximum inspiratory duration of 3 seconds. Expiratory positive airway pressure should be set to the minimum value (4 cm H_2O). Many patients prefer a lower expiratory positive airway pressure, but 4 cm H_2O is the lowest setting on the BiPAP Vision. Set the ventilator in the "custom" mode to permit manual adjustment. Percent assist should be set to 99%. In this fashion, the E and R inserted in the ventilator are the actual VA and FA delivered to the patient. Set E and R initially to 2 and 1, respectively.

After attaching the ventilator to the patient and waiting a few breaths for the patient to adapt, inform the patient that the assist will be increased in steps and that he or she should signal approval/disapproval by some agreed-on system. Increase E in steps of one, waiting a few breaths between steps, until the patient signals that the assist is too high. Go back one or two steps. Repeat using the R input. Increase expiratory positive airway pressure by 1 cm H_2O. If the patient signals approval, keep increasing expiratory positive airway pressure. Most will not want more. Finally, perform final adjustment of E. Some patients will prefer a somewhat lower E setting once the other variables are optimized.

Observe the screen display for the range of airway pressure and V_T. Set the high limits a reasonable amount above the observed ranges. For example, if peak Paw ranges up to 15 cm H_2O and V_T ranges up to 0.7 L, set the pressure limit to 20 cm H_2O and the volume limit to 1 L.

SUBSEQUENT MANAGEMENT

This is guided by clinical course. If distress progresses or reappears, the values of E and R should be retitrated. Nasal congestion should be avoided. Ask the patient if his or her nose is congested. If so, use decongestant, or switch to full face mask. If distress persists, then other methods of therapy should be considered. With clinical improvement, percent assist is reduced in steps guided by patient feedback. Because improvement may occur rapidly, it is a good idea to ask the patient at intervals whether the assist is too much and to see whether a lower percent assist is tolerated.

TROUBLESHOOTING

Although the ventilator corrects for leaks, it takes it three to five breaths to adjust to a leak change. A sudden change (e.g., mouth opening or loosening of mask) may result in a transient increase in applied pressure (up to the set limit). Patients should be instructed to keep their mouth closed. For talking or feeding, percent assist can be reduced to zero (or the ventilator disconnected) temporarily. When the problem occurs without mouth opening, the straps need to be tightened.

Frequent activation of alarms may be secondary to the alarm levels being set too low relative to the prevailing ventilatory demand ($\dot{V}_E$ and V_T demands may have increased) or to improvement of mechanics since the last titration, with the assist now becoming excessive. Note the range of V_T on the display, in particular the highest volumes. Reduce percent assist by 20% or so. If the large V_Ts are eliminated and alarming stops, the problem was an improvement in mechanics, and the large breaths were runaways. Retitrate

E and R. Conversely, if the large volumes continue to occur, then the problem is large ventilatory demand or marked breath-by-breath variability. In such cases, the limits should be adjusted upward.

Intubated Patients

The following pertains to the PAV + option on the 840 ventilator because it is currently the only ventilator available with automatic mechanics and "smart" alarms. The procedure for setting basic PAV systems has been described elsewhere.[124] As indicated earlier, such systems are difficult to manage for extended periods. If other systems are used, *full* (i.e., 100%) automatic tube compensation should be avoided. With complete compensation for the nonlinear component of resistance, very small errors in estimated R may cause aggressive flow runaway with rapid loss of the assist secondary to ventilator limits (see "Runaway Phenomenon" above).

The following algorithm for start up and subsequent management (Fig. 12-22) was developed jointly by the author and Dr. D. Georgopoulos, based on experience with hundreds of patients with various pathologies. It was originally published in the *International Journal of Intensive Care*[125] and partly reproduced in *Essential Practices in Respiratory Care*.[126] The reader is alerted to errors in the flowcharts printed in these two publications which, accordingly, should not be followed.

A. INITIAL VENTILATOR SETTINGS:

1. Enter ideal body weight (IBW). *This is an important step.* IBW does not have to be precise but should be a reasonable approximation of reality. It takes the ventilator four breaths to determine actual E and R. In the interim, it uses default values based on normal E and R values for a patient of the specified size. Should the specified IBW value be for a much smaller patient, the first few breaths may be overassisted.
2. Enter endotracheal or tracheostomy tube size. This input is also quite important because part of the delivered assist is based on stated tube size.
3. Set expiratory sensitivity (Esense) to 3 (default value).
4. Set triggering to flow modality at 3 L/min.
5. Enter humidifier volume if applicable.
6. Set high tidal volume limit (V_{TI} limit) to a value corresponding to 15 mL/kg IBW.
7. Set high peak pressure (HIP) limit to 40 cm H_2O (default). The ventilator caps the assist at the HIP limit less 5 cm H_2O or 35 cm H_2O, whichever is less (i.e., breath is not terminated, but pressure cannot increase beyond this level). Setting HIP to a higher value has

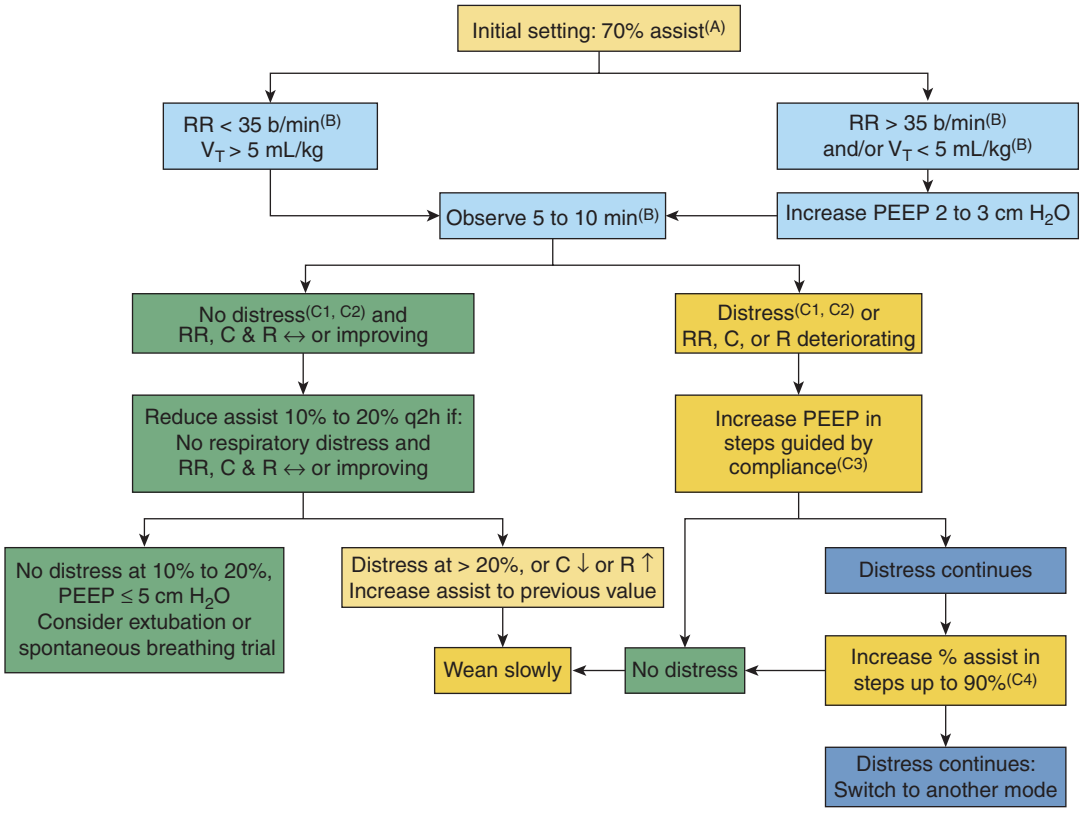

FIGURE 12-22 Proposed algorithm for PAV management. *C*, compliance; *R*, resistance; *RR*, respiratory rate; V_T, tidal volume. Superscripts refer to paragraphs in the text (under "adjustments at the bedside": Intubated Patients) with important clarifications.

no effect in this option. Setting it to a lower value may restrict the assist given unnecessarily.

8. Set percent assist to 70%. It is better to start on the low side and increase if necessary. Most patients do very well at 70%. The use of higher values at the outset, before enough mechanics values have accumulated, may result in overassist.
9. Set PEEP to 5 cm H_2O unless a higher value is deemed necessary for oxygenation.
10. Activate the PAV mode.

B. IMMEDIATE RESPONSES FOLLOWING TRANSITION TO PROPORTIONAL-ASSIST VENTILATION

The immediate response following a switch to PAV varies considerably depending on what the ventilator settings were before the switch and, in particular, on whether the patient was overassisted or there was significant nonsynchrony.

In patients who are not overassisted (i.e., have good triggering efforts) and have no ineffective efforts before the switch, ventilator rate will remain the same (Fig. 12-23) or increase slightly immediately (i.e., first one to two breaths) following the switch. An immediate increase in respiratory rate in this case (i.e., no ineffective efforts before) is the result improved expiratory asynchrony, with the ventilator cycle terminating soon after the end of effort, as opposed to continuing well into the expiratory phase before the switch (see, e.g., Fig. 12-13). Tidal volume typically decreases immediately, because the ventilator uses normal resistance and compliance values in the first breath. Tidal volume gradually increases as the actual respiratory mechanics are obtained from data during the brief inspiratory plateaus (see Figs. 12-14 and 12-23). Tidal volume often continues to increase for a minute or so before stabilizing. The final tidal volume and respiratory rate are generally not different from PSV unless the patient was overassisted on PSV. In the latter case, V_T and V_E may be slightly lower.

In patients with ineffective efforts before the switch there is an immediate increase in ventilator rate as a result of immediate disappearance of the ineffective efforts. This can be dramatic (Fig. 12-24). Concurrently, V_T decreases, often markedly so, in part because resistance and elastance are underestimated initially, but mostly because the inspiratory phase of the ventilator is much shorter than before as a result of disappearance of the preexisting expiratory asynchrony (see Fig. 12-13). V_T then gradually increases, in part because the estimated resistance and compliance become closer to actual values. Because, however, excessive ineffective efforts before the switch generally reflect weak efforts[77] and overassist, P_{CO_2} and efforts gradually increase. The final breathing pattern is invariably rapid and shallow relative to what it was before. This is so because V_E in assist modes cannot exceed the level dictated by the metabolic hyperbola and the apneic threshold. For example, in a patient whose metabolic hyperbola is similar to that in Figure 12-9 (VCO_2 = 0.2 L/min^{-1} and V_D/V_T = 0.4) and an apneic threshold of 40 mm Hg, V_E cannot exceed 7 L/min^{-1} or the patient becomes apneic. Assume that before the switch V_T was 0.6 L and ventilator rate was 10 min^{-1}, for a V_E of 6 L/min^{-1}.

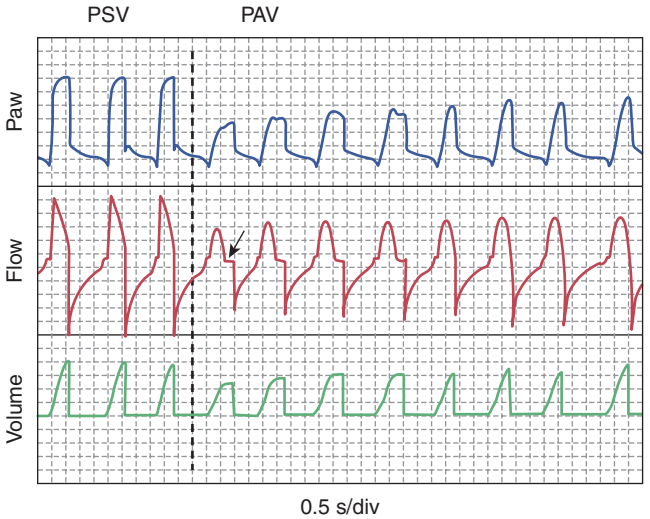

FIGURE 12-23 Example of transition to PAV from PSV in a patient with good efforts (note triggering artifact during PSV) and no important nonsynchrony (no ineffective efforts). Note the brief plateau (*arrow*) in the first four breaths, used to determine respiratory mechanics. Assist increases gradually as the values of resistance and compliance are updated. Breathing pattern is ultimately similar to the pattern on PSV but the patient is now in a mode that will automatically adjust the assist if there are changes in ventilatory demand or in respiratory mechanics.

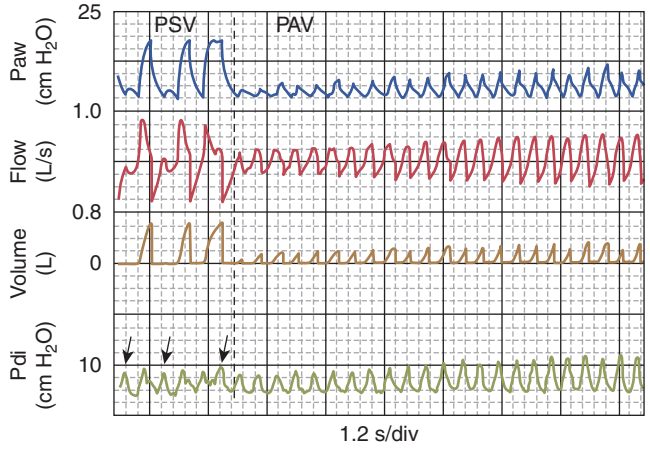

FIGURE 12-24 Example of transition to PAV from PSV in a patient with numerous ineffective efforts on PSV (*arrows*). Note the immediate increase in ventilator rate despite no change in patient's respiratory rate, reflecting the disappearance of ineffective efforts. Tidal volume decreases immediately and rises slowly as the values of resistance and compliance are updated and Pdi increases. Within 45 minutes, tidal volume had increased to approximately half of what it had been on PSV and now ventilator rate is 32 min^{-1}, twice the rate on PSV. Note, however, that despite a modest increase in Pdi, the patient's respiratory rate is actually lower that it was on PSV (36 min^{-1}). The relative rapid shallow breathing in this case reflects better synchrony and not distress. *Paw*, airway pressure; *Pdi*, transdiaphragmatic pressure.

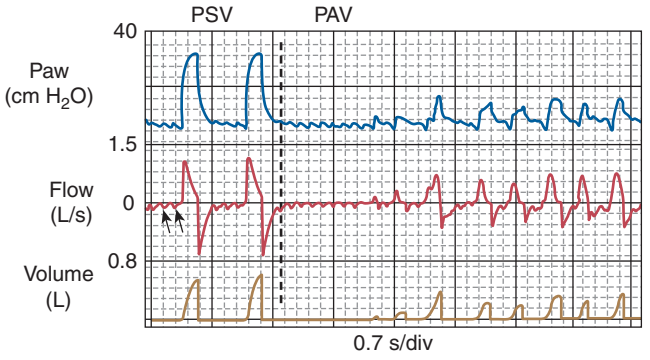

FIGURE 12-25 Example of transition to PAV from PSV in a passive patient in whom large PSV breaths were triggered by cardiac artifacts (*arrows*). Apnea develops upon transition to PAV and continues until Pa_{CO_2} rises above the apneic threshold.

The underlying respiratory rate, however, was 30 min^{-1}, with 20 ineffective efforts per minute. Upon switching to PAV ventilator rate increases to 30 min^{-1}. The highest that V_T can be without apnea is 7/30 or 0.23 L.

Finally, some patients are so over-assisted on conventional assist modes that they are apneic (e.g., Fig. 12-25). The ventilator continues to be triggered either by cardiac flow artifacts (Fig. 12-25) or by a high backup rate. In such cases, the switch to PAV is immediately followed by apnea (Fig. 12-25). The apnea lasts until P_{CO_2} rises above the apneic threshold. This may take a minute or more, depending on how much the patient was overventilated before the switch. Flow artifacts do not trigger significant assist in PAV because the inspiratory phase of the artifact is very brief. When breathing resumes, the breathing pattern will obviously be very different from that observed during apneic ventilation.

For a physician or therapist who is not familiar with the theory of PAV and the fact that patient-selected breathing pattern can be quite different from what is conventionally viewed as desirable, the above two scenarios (rapid shallow breathing or apnea upon transition to PAV) can be disconcerting, if not alarming. Many would, at this point, give up on PAV and return to the previous conventional mode. This is particularly so when respiratory rate is high (e.g., >30 min^{-1}) because these rates are conventionally believed to reflect distress. As indicated earlier (see "Respiratory Rate and Breathing Pattern"), the undistressed respiratory rate, defined as the rate observed with high assist that does not increase further at lower levels of assist (see, e.g., Fig. 12-8), can be up to 46 min^{-1}, or even higher (albeit extremely rarely). An extreme example is shown in Figure 12-26. This patient had a respiratory rate of 59 min^{-1} despite high level PSV and weak efforts. His rate did not change upon switching to PAV despite the increase in effort. Clearly, the high rate observed during PSV was not related to distress. If it had been, it would have increased more as respiratory output increased. This patient remained on PAV for several hours and his rate in fact gradually decreased to 50 min^{-1}.

A particularly useful approach to distinguish between pathologic apnea and overventilation, and between distress-induced tachypnea and undistressed tachypnea in such cases, is to return the patient to his or her previous settings. If the immediate response upon switching to PAV is apnea, the clinician should decrease the backup rate or increase trigger threshold, as the case may be. Apnea will almost always be observed. Reduce the assist until clear triggering efforts appear. A repeat switch to PAV will now not be followed by apnea, thereby establishing that the apnea was related to overventilation at the previous settings. If the immediate response to PAV is tachypnea, return to the previous settings, slow down the monitor speed to be able to observe eight to ten breaths on the same screen. Then, as the tracing is halfway into the screen, suddenly switch to continuous positive airway pressure. The rate observed in the first two to three breaths on continuous positive airway pressure is the patient's real undistressed rate. It is not possible to develop real distress within a few seconds of removing the assist. If this rate is the same rate observed upon switching to PAV, then one should not be concerned unless, of course, respiratory rate increases further later on. Because patient and ventilator rates are the same with PAV, a further increase in ventilator rate clearly reflects an increase in patient rate. In such cases distress must be suspected and dealt with (see "C. Subsequent Management and Troubleshooting" below.

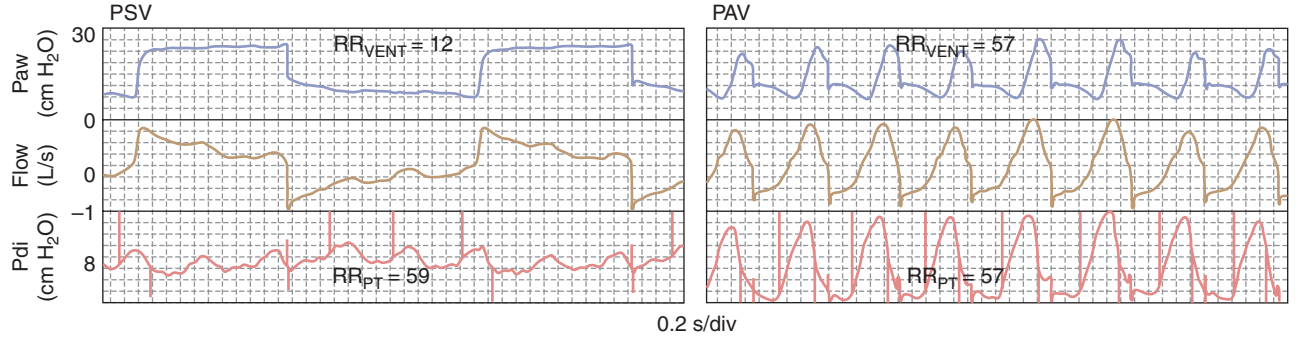

FIGURE 12-26 *Left panel:* Example of extreme tachypnea despite high level of PSV support. Note the efforts are quite small (approximately equal to 4 cm H_2O) and the extreme nonsynchrony (5:1 rhythm). *Right panel:* Upon switching to PAV patient's respiratory rate does not change despite the fact that efforts are now much higher.

In summary, because of the highly variable immediate responses upon switching to PAV, it is reasonable to wait a few minutes, or perform the above check, before concluding that PAV is not appropriate for the patient. Within a few minutes the body's homeostatic mechanisms will have adjusted respiratory output to the level and pattern preferred by the control system. In patients in whom breathing is rapid and shallow during this waiting period, it is advisable to increase PEEP by 2 to 3 cm H_2O to mitigate atelectasis. In addition, in such patients, particularly in those with a prior history of CO_2 retention, it is advisable to obtain an arterial sample for blood gases several minutes after the switch to ensure that the pH is acceptable. Respiratory acidosis (Pa_{CO_2} > 50 mm Hg and pH < 7.35) with no associated clinical distress suggests respiratory depression. Until the cause of respiratory depression is corrected, the patient should not be treated with PAV.

It is highly advisable to record respiratory rate in the first minute after a switch to PAV, as well as the values of estimated compliance and resistance 3 to 4 minutes later, when an adequate number of measurements have been collected. These values will provide important references for subsequent management.

C. SUBSEQUENT MANAGEMENT AND TROUBLESHOOTING

1. Subsequent management depends on whether respiratory distress develops within several minutes after the switch and whether there is a trend for respiratory rate or resistance to go up or for compliance to go down.

   Given the wide range of documented undistressed respiratory rate in ventilated patients (up to 46 min^{-1}),[33,34,96,117] it is my opinion that tachypnea with no other supporting manifestations should not be considered as evidence of distress. In their large study comparing PAV with PSV over a 48-hour interval, Xirouchaki et al[96] defined distress as the presence of at least two of the following: (a) heart rate greater than 120% of the usual rate for longer than 5 minutes and/or systolic arterial blood pressure greater than 180 or less than 90 mm Hg and/or systolic arterial blood pressure changes greater than 20% of the previous value for longer than 5 minutes; (b) respiratory rate greater than 40 breaths/min for longer than 5 minutes; (c) marked use of accessory muscles; (d) diaphoresis; (e) abdominal paradox; and (f) marked complaint of dyspnea. Thus, patients with a respiratory rate greater than 40 breaths/min were maintained on PAV for up to 2 days if there were no other manifestation of distress.

   While a high respiratory rate at a given point is not, per se, indicative of distress, an increase in ventilator rate (or in the respiratory frequency to tidal volume [f/V_T] ratio[127,128]) while the patient is on PAV, provided it is not short-lived, strongly suggests impending failure even in the absence of clinical distress, and even if the absolute rate is modest. Ideally, ventilators should be able to display trends in various physiologic variables (e.g., respiratory rate, compliance, resistance, and so on). In the absence of such a feature one can utilize the respiratory rate obtained immediately after transition to PAV as the reference.

   One advantage of PAV is that it makes it possible to monitor resistance and compliance in real time. At least in COPD patients, a trend of increasing resistance and decreasing compliance heralds frank failure.[1,129] In other patients, the compliance value can be used to derive the Integrative Weaning Index (compliance × arterial oxygen saturation × f/V_T), which shows promise in predicting failure.[130]
2. With the above guidelines, in most patients there will be no clinical distress, and respiratory rate and compliance and resistance will be stable or improving relative to the early measurements (*left blocks* in Fig. 12-22). For these patients, subsequent management is similar to that for other modes and consists of gradual reduction in assist as warranted by clinical condition. So long as there is no clinical distress and respiratory rate and mechanics remain stable or improve, percent assist can be reduced in 10% to 20% decrements every 2 hours until (a) there is no distress or deterioration in respiratory rate and mechanics at 10% to 20% assist. Here, the patient should be considered for extubation as 20% assist represents minimal assist. (b) The patient develops clinical distress or the patient's respiratory rate (or f/V_T) increases or the mechanics deteriorate. In such patients, the assist is increased to the previous level. Such patients are clearly not ready for extubation. Assist should be decreased in smaller steps over longer intervals.
3. A minority of patients will develop distress, or their mechanics will deteriorate, within a few minutes after switching to PAV at 70% assist (*right blocks*, Fig. 12-22). The most common reason for distress at such a high assist (70%) is delayed triggering secondary to severe dynamic hyperinflation or severe respiratory muscle weakness (see "Dynamic Hyperinflation" above). For this reason, the first step is to titrate PEEP up in small increments guided by the results of compliance. Allow 3 minutes between PEEP increases to allow the ventilator to obtain an adequate number of measurements on the new level. If dynamic hyperinflation is in part, or in total, related to expiratory flow limitation, compliance should increase as PEEP is increased. There is no value to increasing PEEP once compliance stabilizes. If distress disappears, the patient is managed with these settings and weaning can then be continued in small steps over long intervals, as tolerated (Fig. 12-22).
4. Distress continues despite PEEP optimization: This scenario is quite uncommon. The caregiver may decide at this point to switch to another mode or to engage in a process of upward titration of percent assist, in 5% steps, with close monitoring of the graphics. In the latter case:

   Ensure that the high inspiratory pressure limit is 40 cm H_2O. Inspect the Paw waveform display for several breaths.

a. If Paw is less than 35 cm H_2O in all breaths, you may continue increasing percent assist. If distress disappears, continue as in the previous groups.

b. If Paw reaches 35 cm H_2O in the latter part of inspiration only in the occasional breath (see Fig. 12-17), there is volume runaway. Here the problem is almost certainly severe dynamic hyperinflation not responsive to PEEP (i.e., high resistance is in the tubing [including the endotracheal tube]) or severe muscle weakness. If distress is still present, such patients cannot be supported adequately with PAV unless triggering is linked to onset of effort (see "Dynamic Hyperinflation" above and Fig. 12-7). This is the maximum that the patient can be supported in the PAV mode. Switch to another mode.

c. If Paw reaches 35 cm H_2O in the latter part of inspiration in most breaths, the patient needs more assist than can be provided by the PAV+ option. This scenario indicates high-end nonlinearity (see "Nonlinearity in the Pressure–Volume Relationship within the Tidal Volume Range" above) in a patient with high ventilatory demand. The patient needs to be sedated. If heavy sedation must be used, consider switching to another mode (e.g., assist control).

d. If Paw reaches 35 cm H_2O *immediately* after triggering and stays there until the cycle ends (i.e., square wave pattern), flow runaway exists. If ATC is concurrently used, it should be discontinued (Fig. 12-19 and related text). If the problem continues and the patient is still in distress, switch to another mode. This problem is occasionally seen in patients with gasping breathing and cannot be corrected by ventilator adjustments.

IMPORTANT UNKNOWNS

Whereas the physiologic advantages of PAV have been proven, it is not clear whether these necessarily translate into clinical benefits. There are reasons to believe that clinical outcome will improve (see "Clinical Outcome" above). This needs to be confirmed, however. Questions may be of a general nature (e.g., Are mortality, length of intubation, and length of ICU stay less with PAV?) or may be directed at specific aspects that we know affect outcome (e.g., by comparison with optimal protocols with other modes):

- If sedation is used on an "as-needed" basis, will patients need less sedation on PAV?
- Will tidal volume over the course of illness be smaller on average?
- Is weaning faster?

I believe that two other questions need to be addressed. These relate to management of tachypnea that is unrelated to distress, a phenomenon that is evident only when PAV is used:

- If a patient decides to breathe in a rapid, shallow manner while on high PAV support (see, e.g., Fig. 12-5B), should the patient be left on PAV or switched to another mode?
- If tachypnea (e.g., >35 breaths/min) with no other signs of distress is present during a weaning trial and does not decrease on high PAV, does the patient need to stay on a ventilator?

THE FUTURE

With the inclusion of automatic mechanics and "smart" alarms, PAV should become the easiest mode to set and use. There is only one variable to adjust: percent assist. The mode adapts automatically to changes in ventilatory demand and respiratory mechanics. A problem will remain, however, in the management of patients with severe DH secondary to very high expiratory resistance and high ventilatory demand. Future PAV delivery systems should include algorithms to begin the assist at the onset of inspiratory effort.

It is also possible that adjustment of percent assist can be automated. PAV offers two features that would facilitate the complete automation of ventilator adjustment. First, ventilator rate, something ventilators can keep track of easily, is an accurate reflection of the patient's respiratory rate. Thus, ventilator rate may be used as one feedback element for automatic adjustment of percent assist. Second, because PAV makes it possible to obtain passive mechanics on an ongoing basis, it is also possible to monitor respiratory muscle output and the work of breathing continuously. These can be used as additional feedback signals to automatically adjust percent assist.

SUMMARY AND CONCLUSION

PAV represents a paradigm shift in mechanical ventilation in that control of ventilator output is shifted from the caregiver to the patient. This shift has several advantages in that the ventilator output is more synchronous with patient efforts, and the support adjusts automatically to changes in ventilatory demand and respiratory mechanics. This mode is also the only mode that makes it possible to monitor respiratory mechanics in real time during assisted ventilation. These features have been all been documented in numerous physiologic studies. Until recently, application of PAV in the clinical setting has been hampered by lack of suitable commercial systems and several technical limitations that made it difficult for any but the sophisticated physiologist to use it, and then only for short periods. A commercial ventilator was introduced a few years ago that, in addition to providing the mode, has addressed several of the technical limitations. Now, it is possible to engage in clinical trials that address the important issue of whether better physiology leads to better clinical outcome? PAV is slowly gaining acceptance among clinicians and the main obstacle remains unfamiliarity with the responses to this mode and long-standing dogmas about

how breathing should be during mechanical ventilation. It is hoped that this latest description will help in this respect.

ACKNOWLEDGMENTS

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13

NEURALLY ADJUSTED VENTILATORY ASSIST

Christer Sinderby
Jennifer C. Beck

RATIONALE

Mechanical ventilation can be delivered with two extreme approaches: (a) by dictating a flow, volume, pressure, or respiratory timing (or some combination), or (b) by delivering assistance synchronized to and regulated by the patient's neural breathing efforts. Whereas the former approach is advantageous in patients who do not breathe, the latter approach is advantageous in spontaneously breathing patients.

Almost 50 years ago, Gunaratna[1] demonstrated that the problem of patients fighting the ventilator during controlled ventilation could be overcome by the use of patient-triggered ventilation. The patient-triggered ventilation was associated with immediate relief of the respiratory distress, apprehension, and agitation.

Since the 1970s, numerous modes of mechanical ventilation that aim to synchronize the ventilator and the patient have been introduced. Patient-triggered or cycled modes of ventilation are controlled by airway pressure,

flow, and/or volume measured in the respiratory circuit. Significant limitations of these signals to trigger and cycle-off the assist have been documented for decades.[2–12] Despite the term *patient-triggered* ventilation, severe patient–ventilator asynchrony occurs in at least 25% of ventilated patients[13–15] and is associated with prolonged duration of ventilation. Patients with frequent ineffective triggering also tend to receive excessive levels of ventilator support[13] and/or sedation.[16] In newborns, compared to controlled ventilation, patient-triggered ventilation is associated with shorter duration of ventilation.[17–20] Excessive assistance can cause muscle fiber injury and atrophy of the diaphragm.[21,22] Conventional ventilation can induce loss of inspiratory muscle force, as much as 75%.[22,23–27] Promoting spontaneous breathing[28–33] and reducing sedation,[34–39] alone or together,[40] shortens the duration of mechanical ventilation.

Last, but not least, regulation of spontaneous breathing constitutes a very complex interaction between motor-nerve output and sensory feedback.

In summary, conventional modes of ventilation have limitations with regards to (a) synchronizing assist delivery to the patient's neural breathing efforts; (b) bedside monitoring of patient respiratory drive and/or interaction with the ventilator; (c) adjusting the level of assist in response to patient demand; and (d) taking advantage of intrinsic lung protective reflexes.

An ideal approach, therefore, is to connect the patient's respiratory centers to the ventilator, as naturally as the respiratory muscles are connected to the brainstem via the phrenic nerves. This notion is what set the spirit for developing the mode known as neurally adjusted ventilatory assist (NAVA).[41]

BASIC PRINCIPLES AND PHYSIOLOGY OF ELECTRICAL ACTIVITY OF THE DIAPHRAGM

From Brain to Breath

Figure 13-1 (*left*) describes schematically the hierarchy of the steps involved in generating a spontaneous breath. Respiratory neurons originating in the brainstem of the central nervous system send their signals to the diaphragm via the phrenic nerves. After neuromuscular transmission, diaphragmatic excitation occurs, where action potentials propagate along the diaphragm muscle fibers. This is the source of the diaphragmatic electrical activity (Edi) (see "Electrical Activity of the Diaphragm" below). The Edi is generated by the neural respiratory output signal and is modulated by input from multiple respiratory reflexes feeding back to the respiratory centers. The Edi signal is the primary signal used to control NAVA (Figure 13-1, *right side*).

The latency time from stimulation of the phrenic nerve in the neck to the onset of the diaphragmatic compound muscle action potential in healthy subjects is approximately 6 to 8 milliseconds.[42–45] Diaphragmatic excitation stimulates contraction of muscle fibers and causes shortening. The result of diaphragmatic contraction is expansion of the thorax, which causes lung distension and lowers pleural and alveolar pressures, thereby lowering airway pressure creating inspiratory flow. These "pneumatic" signals (pressure, flow, and volume) are used today to control conventional patient-triggered ventilation.

The time between central respiratory output to the generation of inspiratory flow in a healthy subject is approximately 26 to 28 milliseconds.[42–44] Factors such as intrinsic positive end-expiratory pressure (PEEP), increased respiratory load, impaired respiratory muscle function, and reduced respiratory drive (secondary to sedation), alone or in combination, will weaken the flow signal. A weakened flow signal is more problematic to detect by the ventilator, increases the time delay to trigger the assist, and, in the worst case, fails to trigger the ventilator.

In summary, an impairment occurring at any of the steps in the hierarchy described in Figure 13-1 may result in delays, dampening, or even full blockage of the signals used to control the ventilator.

Respiratory Reflexes

Figure 13-2 demonstrates a schematic diagram of the major neural feedback systems to the respiratory centers. Neural feedback to the respiratory centers controls respiratory motor output, and hence the Edi.

FEEDBACK FROM THE LUNGS

For a detailed description of the lung reflexes, the reader is referred to Widdicombe[46,47] and Undem and Kollarik.[48]

Important for NAVA is that the lungs host receptors sensitive to stretch and respond to both lung distension and deflation. Based on the response to sustained lung distension these receptors are divided into slowly adapting receptors and rapidly adapting receptors. The classic experiments by Josef Breuer and Ewald Hering in the mid-nineteenth century[49] showed that lung distension shortens inspiration, or prolongs expiration, the so-called Hering-Breuer inspiratory sensitive reflex.[49] They also noted that deflation of the lungs at end-expiration shortens exhalation and stimulates inspiration, the Hering-Breuer deflation-sensitive reflex.[49] These reflexes are caused by slowly adapting receptors, and rapidly adapting receptors, respectively.

The rapidly adapting receptors are also stimulated by chemical stimuli and changes in lung compliance. When stimulated, the rapidly adapting receptors cause tachypnea, cough, and augmented breaths. Pulmonary edema, mediators of inflammation and immune responses, inhaled irritants, and direct tissue damage stimulate the bronchial C-fiber receptors, causing apnea, rapid shallow

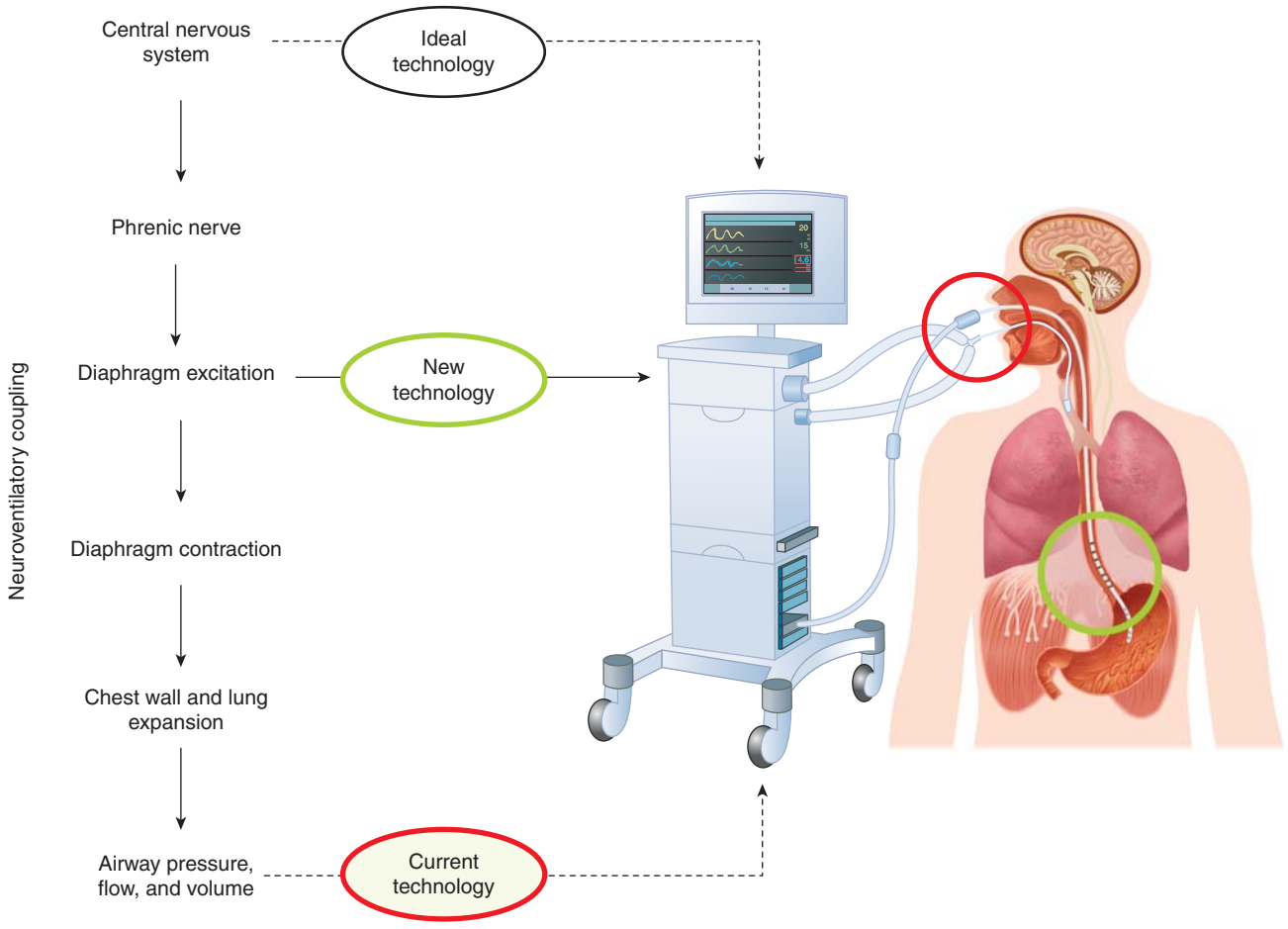

FIGURE 13-1 Overview of neurally adjusted ventilatory assist (NAVA). *Left:* Chain of events involved in spontaneous breathing, beginning with the respiratory centers in the central nervous system, then phrenic-nerve transmission, diaphragmatic electrical activity, diaphragmatic contraction, and ending with airway pressure, flow, and volume (the neuroventilatory coupling). Also indicated are the different levels of signals for ventilator control. During NAVA, electrical activity of the diaphragm is used to control the ventilator. *Right side:* Schematic of setup for NAVA. A feeding catheter equipped with an array of miniaturized electrodes is passed down the esophagus, where the electrical activity of the diaphragm is recorded (*green circle*). Diaphragmatic electrical activity is processed into a waveform, and is used for monitoring neural respiratory drive (in all modes) and for controlling the timing and magnitude of ventilator-delivered pressure during NAVA.

breathing or both, and cough. The above-described reflexes disappear with vagotomy.

FEEDBACK FROM THE RESPIRATORY MUSCLES

Afferent feedback from the respiratory muscles exists and affects neural drive to the different individual muscles.[50–52] Electrical stimulation of the phrenic nerve afferents elicits changes in phrenic efferent activity, breathing pattern, and ventilation, the so-called phrenic-to-phrenic reflex.[53,54] Stimulation of the phrenic afferents can also change neural drive to the intercostal muscles, the so-called phrenic-to-intercostal reflex.[55,56] Golgi tendons and muscle spindles are present in the diaphragm, albeit sparse, and provide feedback related to muscle tension and length, respectively.[57] Respiratory muscle feedback partially controls respiratory drive during unloading[58] and likely influences the sensation of breathing.[59]

JOINT RECEPTORS

Receptors in the costovertebral joints have been suggested as a primary determinant of a load-compensating reflex.[60]

CHEMORECEPTORS

Receptors sensitive to the concentration of oxygen, carbon dioxide, and the pH in the arterial blood are constantly modulating the breathing pattern. Activation of either the hypoxic or hypercapnic chemoreflex elicits hyperpnea (increased respiratory drive and, hence, increased Edi).[61,62]

FEEDBACK FROM THE UPPER AIRWAYS

The larynx contains receptors sensitive to pressure, temperature, and irritants; the laryngeal mucosa also contains C-fiber receptors or J receptors,[46,47] which, when stimulated,

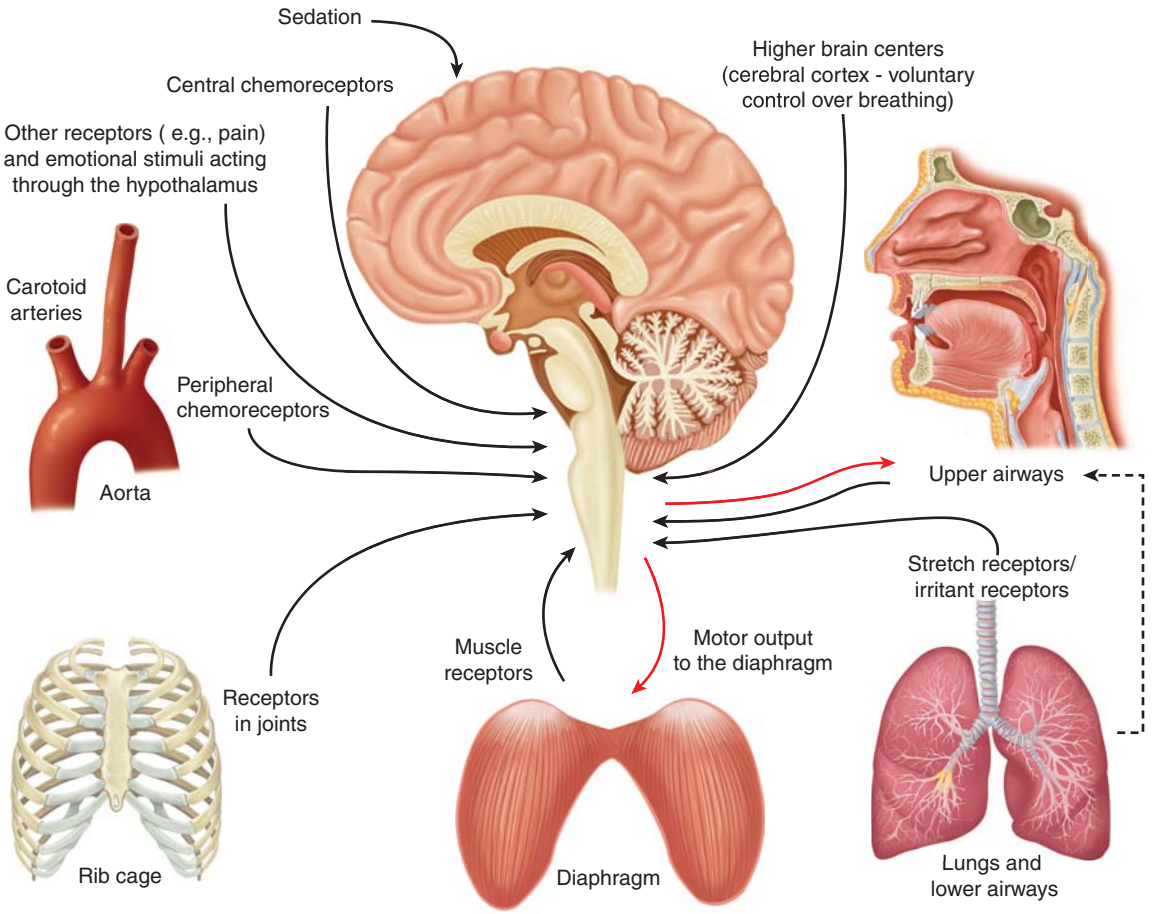

FIGURE 13-2 Respiratory inputs and reflexes important for NAVA. Schematic of the respiratory inputs and reflexes that can affect neural respiratory drive, and hence the motor output to the diaphragm (electrical activity of the diaphragm). The respiratory centers in the brainstem continuously receive information from the peripheral and central chemoreceptors (*upper left side*), receptors in the rib cage and diaphragm (*lower left* and *lower center*), stretch and irritant receptors in the lungs and lower airways (*lower right*), and receptors in the upper airways (*top right*).

cause cough, apnea, bronchoconstriction, and mucus secretion. Recent work by Praud et al[63] suggests that feedback exists from the lungs to the laryngeal muscles.

SEDATION AND ANALGESIA

Increases in sedation and/or analgesia depresses respiratory motor output.[64]

Electrical Activity of the Diaphragm

Petit et al were the first to present, in 1959, a "new technic for the study of functions of the diaphragmatic muscle by means of electromyography in man."[65] Taking advantage of the anatomy of the crural diaphragm, which forms a scarf-like structure around the lower esophageal sphincter, these investigators cleverly obtained the Edi with electrodes on a catheter that was passed down the esophagus.

Considering that nearly all ventilated infants and most intubated adult patients in the intensive care unit are equipped with nasogastric feeding tubes, it was logical to follow up on refining esophageal measurements of Edi for today's clinical use. Some of the obstacles that needed to be overcome included the development of standardized and automated methods to reduce artifacts and filtering effects related to electrode configuration and electrode positioning. Even though Lourenco et al[66] had demonstrated in dogs that the crural electromyogram (EMG) and costal EMG were related to phrenic nerve activity, it was necessary to validate that measurement of Edi with an esophageal electrode relates to global inspiratory effort in ventilated patients.[5]

The Edi signal used for monitoring respiratory drive and for controlling the ventilator during NAVA is an "interference-pattern EMG signal," and constitutes a temporospatial summation of motor-unit action potentials, which, in turn, represent a summation of single-fiber action potentials.

A single-fiber action potential is the extracellular potential generated by movement of ions across the sarcolemma during depolarization of a single muscle-fiber membrane. This current flow can be measured as a voltage difference over time, and when displayed as a waveform, is known as the

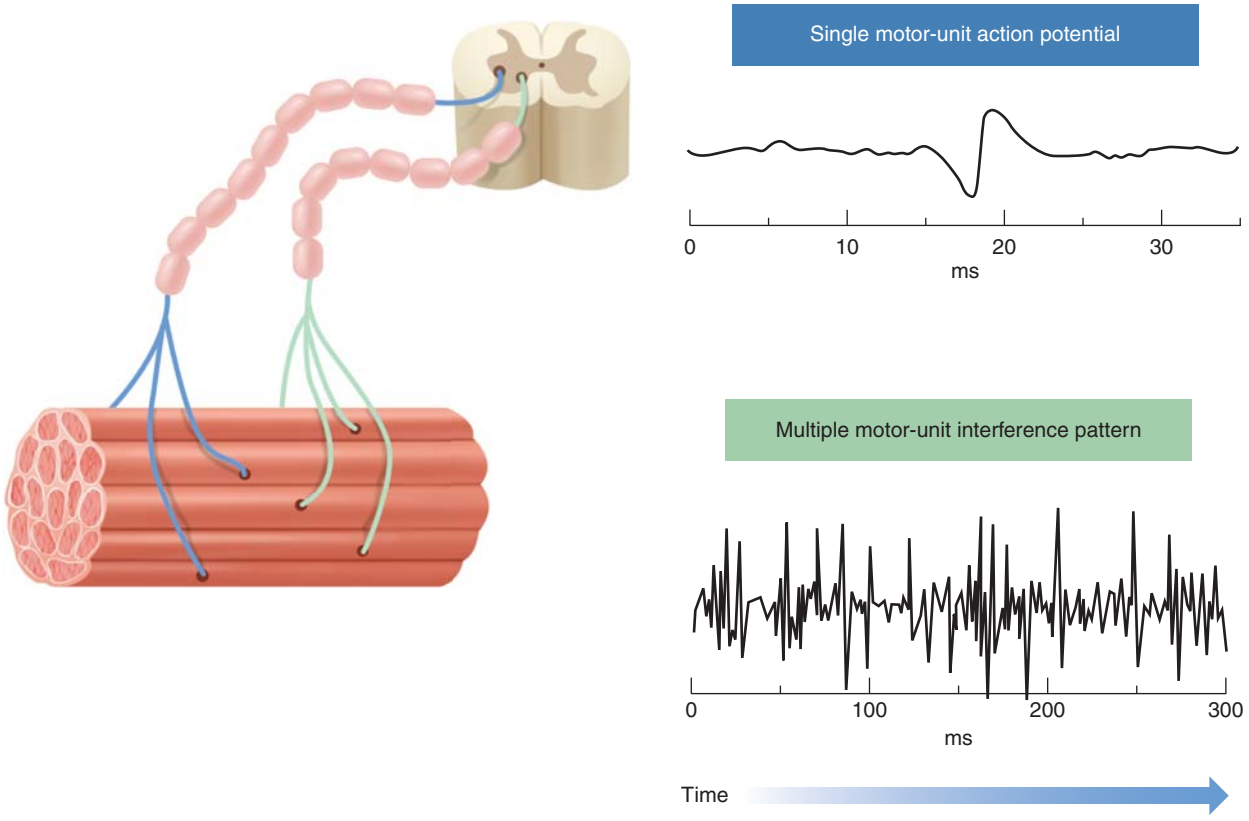

FIGURE 13-3 Skeletal muscle structure and the origin of the interference-pattern EMG. *Left side:* Representation of the structure of skeletal muscle and motor units. Two motor units are demonstrated for simplicity. A motor unit is a single motor neuron and all of the muscle fibers it innervates. Electrical activation of a single motor unit produces a motor unit action potential (*top right*). A spatial and/or temporal summation of the motor-unit action potentials, resulting in an interference-pattern EMG signal (*bottom right*), occurs when several motor units are recruited and/or their firing rate increases. The Edi signal measured during NAVA is an interference-pattern measurement of asynchronously firing diaphragmatic motor units.

action potential. Action potentials are "all or none" in terms of the voltage transient they generate, and they propagate along the muscle-fiber membrane to initiate contraction.

Action potentials occur because of voltage-dependent sodium-potassium channels in the muscle-fiber membrane. In humans, the propagation velocity of an action potential ranges between 2 and 6 meters per second,[67] and depends on the capacitance per unit length (dependent on circumference) and the internal resistance, all passive properties of the muscle fiber. The active properties (e.g., membrane excitability) depend on ion-concentration differences and ion-channel properties, the latter affected by temperature, pH, and electrical field strength. The action potential propagation velocity is dependent on temperature, fiber diameter, pH, fatigue, and ion concentration.[67–71]

Given the muscle innervation scheme, single-fiber action potentials are activated in groups because a single nerve fiber innervates multiple muscle fibers (Fig. 13-3). Thus, a motor-unit action potential represents many single fiber action potentials, which secondary to synchronized initiation, results in mainly a spatial summation of their amplitudes. Motor-unit action potentials are affected by the same factors as single-fiber action potentials, but also the number of muscle fibers within the motor unit, length of the motor unit terminal, fiber-to-fiber differences in action-potential conduction velocity, and dispersion of the motor-unit fibers.[72,73]

Neural breathing effort modulates motor-unit firing rate and recruitment. Hence, when resulting action potentials are summed up in time (temporally) and in space (spatially), the cumulated motor-unit action potential activity (i.e., the interference-pattern EMG) yields a signal where individual motor-unit action potentials can no longer be distinguished (see Fig. 13-3). All factors affecting the individual motor-unit action potentials will influence the interference-pattern EMG, as well as the number of individual motor-unit action potentials, their synchronization, and eventual cancellation of opposite phase potentials.[72,74]

Measurement of Electrical Activity of the Diaphragm

RECORDING ELECTRODES

Optimal Edi signals depend on the use of electrodes with appropriate configuration, maintenance of electrode position and orientation relative to the muscle, and avoidance of signal disturbances.

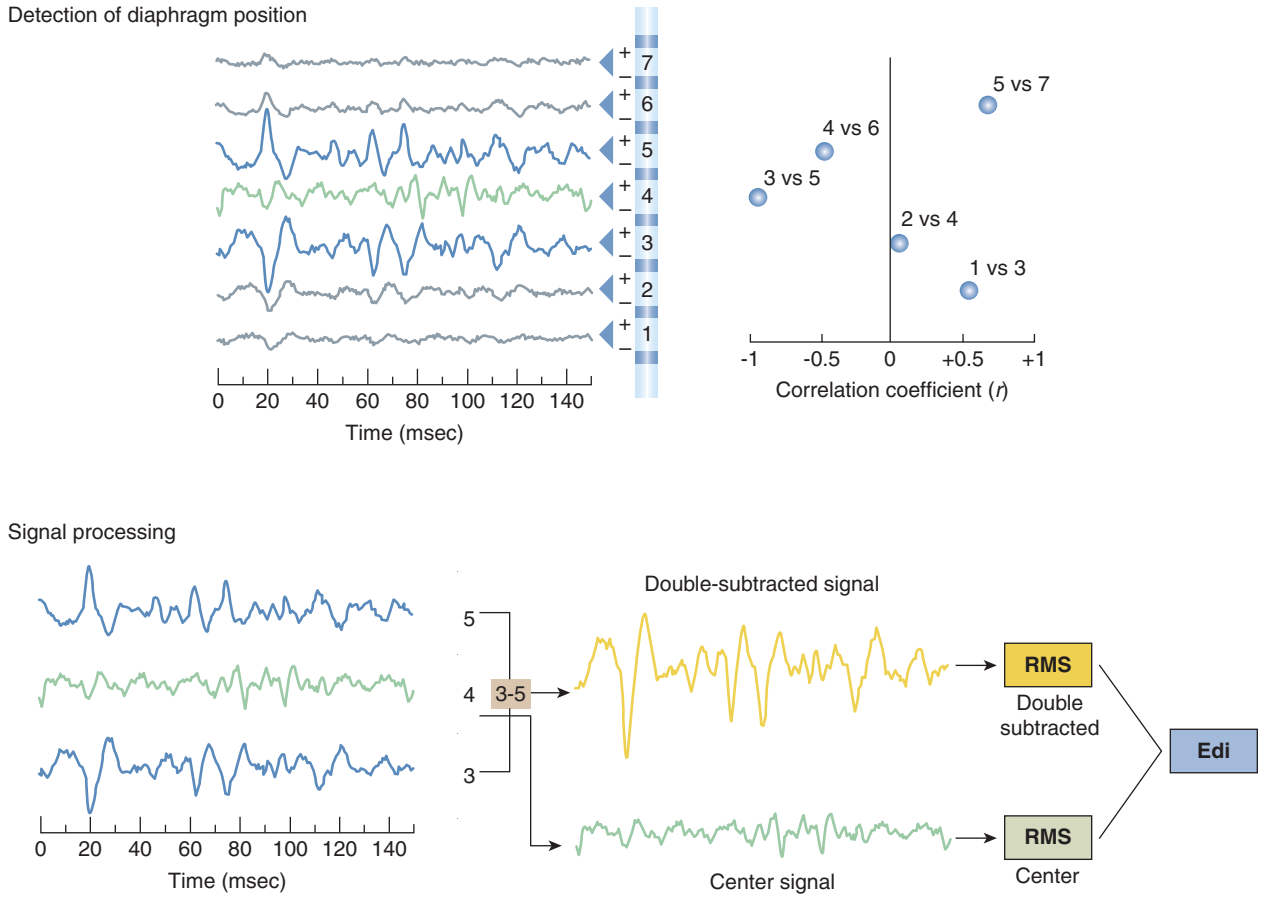

FIGURE 13-4 The double subtraction method. *Top*: Detection of diaphragm position along the array of electrode pairs. *Left:* Raw signals from each electrode pair (electrode array is illustrated in center). *Right*: The electrode pairs closest to the diaphragm are determined by cross-correlating signals from every second pair of electrodes (1 vs. 3, 2 vs. 4, 3 vs. 5, 4 vs. 6, 5 vs. 7, and 6 vs. 8, if eight electrodes are present), and the correlation (*r*) values are plotted (x axis) for each combination (y axis). Today, the cross-correlation algorithm is applied every 16 ms and eight electrode pairs are used. The two most negatively correlated electrode pairs are tagged (in *blue, left side*) for use in the double subtraction (in this example, electrode pairs 3 and 5). The "center signal" is also tagged (in *green*). *Bottom*: Signal processing. *Left:* The same signals that were tagged in the cross-correlation method as being above and below the diaphragm are displayed (*blue*) as well as the center signal (*green*). *Right*: Signal obtained after subtraction of signal from the most negatively correlated signals (electrode pair 5 and 3 in this example) yields the "double-subtracted signal" (*orange tracing*). The root-mean-square is calculated every 16 ms for this signal (*orange*), as well as the waveform at the center (*green*), and the two root-mean-square (RMS) values are summed (double subtracted + center values) to yield the Edi used during NAVA (*grey*). (Adapted, with permission, from Sinderby et al.[77])

In the context of NAVA, the Edi is measured with an array of electrode pairs placed on a nasogastric or orogastric catheter. The catheter is placed in the esophagus at the level of the gastroesophageal junction such that the direction of the electrode array is perpendicular to the crural diaphragmatic muscle fibers.[75]

The Edi is filtered depending on the electrode's position with respect to the diaphragm[75] (Fig. 13-4). If the electrode pair is centered at the level of the diaphragm (both electrodes receive a similar signal), the frequency increases and the power of the Edi decreases because of a cancellation effect (bipolar electrode filtering). If one of the electrodes of the pair is located at the level of the diaphragm and the second is away from the diaphragm (electrode pairs 3 and 5 in Fig. 13-4), the differential recording will be least influenced by bipolar electrode filtering and muscle-to-electrode distance filtering effects.[75] For the electrode pairs even further away in either direction (channels >6 and <2 in Fig. 13-4), there will be lower signal amplitude, because of muscle-to-electrode distance filtering. Given the sequential configuration of electrodes pairs with respect to the differential amplifiers (indicated by + and – signs in Fig. 13-4, top right panel) and the fact that the diaphragm constitutes an electrical sheet with a direction perpendicular to that of the electrode array, signal waveforms obtained above the diaphragm become inversed to those below the diaphragm (Fig. 13-4 top left panel).

Electrical Activity of the Diaphragm Signal Processing

The specific design of the electrode configuration and the signal processing techniques used with NAVA have been developed and tested since the late 1980s so as to overcome

the inherent difficulties associated with EMG measurements in general, as well as anatomical considerations.[76]

The most significant advance in the development of esophageal measurements of Edi was the use of bipolar electrodes in a sequential order and an automated processing technique to track the displacement of the diaphragm.[77] Implementation of a cross-correlation technique (for every second pair of electrodes) every 16 milliseconds determines the position of the diaphragm along the array (Fig. 13-4), and subtraction of opposite phase signals above and below the diaphragm results in a new signal, the "double-subtracted" signal, free from distance filtering, and enhanced signal-to-noise ratio (Fig. 13-4).[77] The root-mean-square (RMS) of this signal is calculated every 16 milliseconds, and added to the RMS of the center signal (i.e., from the electrode pair closest to the muscle[78,79]), as demonstrated in Figure 13-4. The resultant RMS values for every 16 milliseconds sample can be graphically connected, resulting in the Edi waveform (Fig. 13-5).

The RMS is linearly related to how much the muscle is activated, that is, the number of motor units recruited and their firing rate,[80] and under isometric, nonfatiguing conditions, reflects diaphragmatic force (up to 75% of its maximum).

Several artifacts can potentially influence the Edi waveform and need to be controlled for to avoid misinterpretation of the signal, or in the case of NAVA, miscontrolling the ventilator. Today, this is achieved automatically by the processing of the signal, and the user only needs be made aware of the artifacts' potential impact.

As the diaphragm can move as much as 13 centimeters during spontaneous breathing at large tidal volumes,[81] muscle-to-electrode distance filtering could play a role in amplitude measurements of Edi.[82] Signal processing techniques and design of catheter configuration have enabled automatic control over this factor.

Motion artifacts, induced by physical movement of the electrode, are low in frequency but large in amplitude. Signals that are common to both electrodes in the differential recording (e.g., electrical noise) will be suppressed because of the bipolar electrode configuration and the double-subtraction technique.[77] Esophageal recordings of Edi are particularly affected by the electrocardiogram (ECG) and the artifact should be removed from the Edi waveform, especially for the purpose of controlling the ventilator. The ECG is detected with an adaptive threshold level, and replaced by a value predicted from the previous Edi value. To further reduce electrical noise disturbances (e.g., 50 or 60 Hz) and motion artifacts and to minimize ECG and electrical activity from the esophagus, the signal is filtered with a cascade of filters.

The interelectrode distance affects the Edi signal, and hence catheters of different sizes and interelectrode distances are designed to suit different patient ages and sizes.[75]

A long-lived delusion was that changes in diaphragmatic configuration and length affect the Edi waveform.[83] Studies now confirm that diaphragmatic length[71] and chest wall configuration[80,82] do not affect the Edi waveform, or its frequency content, as long as control is achieved over the above-mentioned influences.

ELECTRICAL ACTIVITY OF THE DIAPHRAGM AS A MONITORING TOOL

Interpretation of the Electrical Activity of the Diaphragm Waveform

The Edi waveform, as any other waveform on the ventilator, such as airway pressure or tidal volume, can be characterized by its amplitude and timing, for both the inspiratory phase and the expiratory phase. The Edi waveform has the units of microvolts (μV), generally ranging between a few μV during resting breathing to above 100 μV during maximal inspiratory efforts. Figure 13-6 provides examples of the Edi waveform in a premature infant and in an adult patient.

Increased Edi amplitude on inspiration ("phasic Edi") indicates greater activation of the diaphragm. The amplitude of the Edi waveform has been shown to be related to global diaphragmatic activation[80] and diaphragmatic power output[84] in healthy subjects, outpatients with chronic obstructive pulmonary disease,[78] and ventilated patients.[5] Edi amplitude increases with worsening of respiratory status,[78] reduced ventilator assist,[5] reduced sedation,[85] increased demand for ventilation such as exercise,[79] and increased dead space.[86] The opposite holds true: Edi decreases within a given subject with respiratory improvement, increased sedation, increasing levels of assist, and reducing the partial pressure of arterial carbon dioxide (Pa_{CO_2}).

In a given subject, the amplitude measures of the Edi waveform can be reliably monitored and quantified, for example, during treatment and interventions. Because of anatomical differences (affecting the muscle-to-electrode distance filtering in particular), absolute Edi values can vary between subjects.[78] When trending Edi values over time, it should also be kept in mind that changes in ventilator settings and sedation level influence the magnitude of Edi. The published literature on Edi monitoring and NAVA using the commercially available $Servo_i$ ventilator demonstrates peak Edi values in the range of 8 to 18 μV in adults under a variety of conditions. In one study, values as low as 2 μV and as high as 50 μV were reported when Pa_{CO_2} was manipulated by extracorporeal membrane oxygenation.[87] Only one study to date has reported Edi values in children (mean values of 7 μV during NAVA).[88]

Edi values can be expressed relative to a maximum inspiratory effort (e.g., maximal inspiration without assist) in patients capable of performing the maneuver.[78,89] Sinderby et al[78] demonstrated that patients with impaired respiratory mechanics require a larger fraction of the maximum Edi to achieve the same mechanical output as healthy subjects

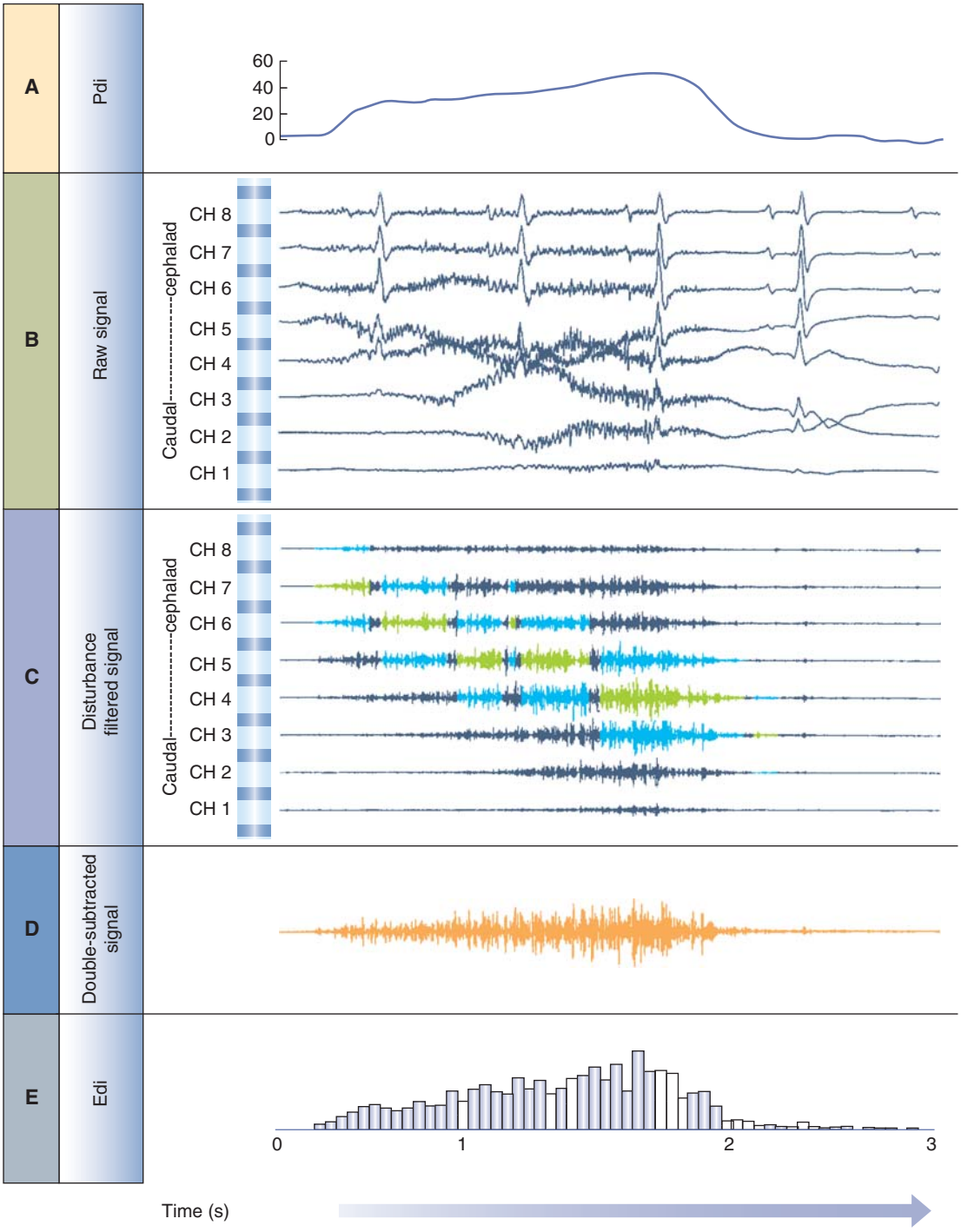

FIGURE 13-5 Edi signal processing during NAVA. **A.** Transdiaphragmatic pressure (Pdi) waveform obtained in a healthy subject performing an inspiration to total lung capacity. **B.** Raw signals obtained from the eight electrode pairs on the esophageal catheter during the same inspiration to total lung capacity. The electrode pair at the top is the most cephalad, whereas the one at the bottom is the most caudal (in the stomach). Note the presence of the electrocardiograms (ECGs) and slow-wave motion artifacts. **C.** Filtered raw signals after processing and removal of ECG and motion artifacts. *Blue* signals show electrode pairs above and below the diaphragm as detected by the cross-correlation algorithm described in Figure 13-4. Signals highlighted in *green* are the center signal as described in Figure 13-4. Note that the intensity of the signals increases throughout inspiration and moves downward with respect to the electrode pairs. **D.** Double-subtracted signal (*orange*) for the same inspiration to total lung capacity. **E.** Root-mean-square (RMS) values from the double-subtracted signal are plotted for every 16-millisecond segment. Note that the RMS values are plotted for the double-subtracted signal in this example from an earlier publication. Presently, the center signal RMS values are also included (as described in Fig. 13-4). (Adapted, with permission, from Sinderby et al.[78])

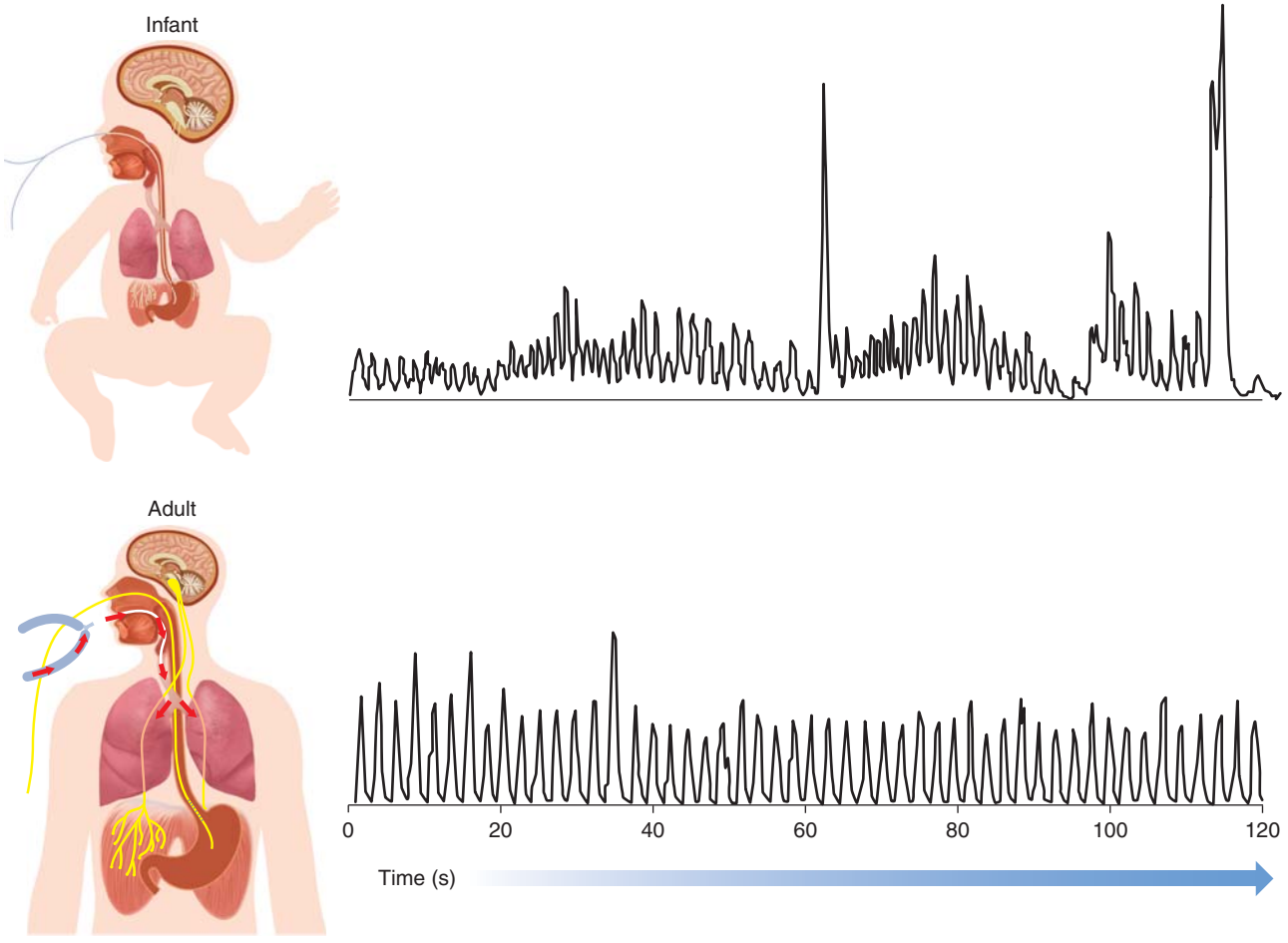

FIGURE 13-6 Examples of the diaphragmatic electrical activity (Edi) waveform in an adult patient and in a premature neonate. *Top panel*: Processed Edi waveform obtained in a nonintubated premature infant. *Bottom panel*: Processed Edi waveform obtained in an intubated adult. The Edi waveform in infants is characterized by larger variability in timing and amplitude, with a distinct amount of changes in the baseline, so-called tonic activity of the diaphragm. The Edi waveform in adults is generally less variable with minimal tonic Edi.

(Fig. 13-7). Statistically, the increase in Edi with respiratory impairment also holds true for absolute values in the same type of patients.[90] In patients with neuromuscular disorders, the Edi during spontaneous breathing, normalized to a maximal effort, can reveal the patient's neural activation reserve, where a ratio at or above 0.5 would indicate extremely little reserve.[78,91] In the same patient group, the absolute Edi observed during a maximal effort can provide information about changes in the total motor-unit pool, that is, a reduced maximal Edi (in μV) as the disorder progresses or vice versa. In patients with late-stage Duchenne muscular dystrophy, the absolute Edi values are low because of a reduced number of available motor units, but in relative terms, they represent approximately 50% of their maximum Edi.[91]

If the Edi persists after the end of an inspiration, the amplitude of the Edi waveform can be quantified (the so-called tonic Edi).[92] The presence of tonic Edi indicates continuous and elevated activation of the diaphragm between respiratory cycles (see Figs. 13-6 and 13-8). Studies in infants and animals suggest that elevated tonic Edi is a reflex response induced by lung derecruitment or removal of PEEP.[92–94] Experimental vagotomy abolishes this reflex.[93,94] Healthy subjects and *adult* mechanically ventilated patients show little, if any, tonic Edi.[78,95,96]

Besides amplitude parameters, the Edi waveform can be used to quantify the timing of the neural breathing pattern, such as neural inspiratory time, neural expiratory time, and neural respiratory rate.

If the catheter position has been deemed appropriate and functioning, a flat Edi waveform at zero μV indicates no diaphragmatic activation. This could be caused by numerous pathologies, including central apnea (no respiratory motor output, or suppressed respiratory drive secondary to mechanical ventilation-induced hyperventilation or sedatives), phrenic nerve damage, or neuromuscular transmission failure.

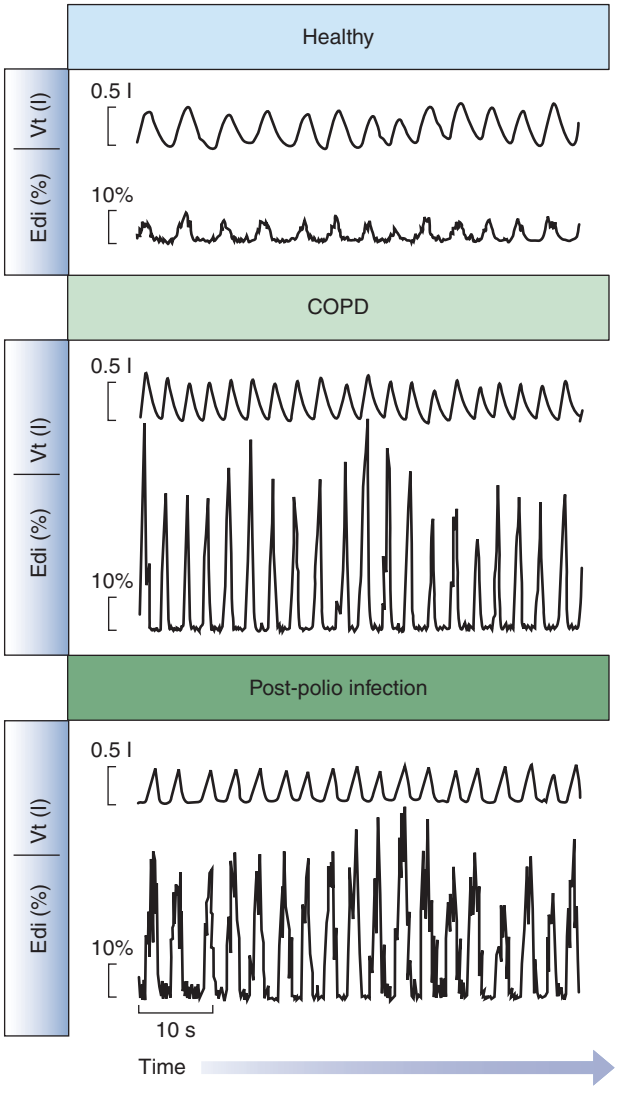

FIGURE 13-7 Examples of the Edi waveform and tidal volume in a healthy subject and in patients. Tidal volume and the Edi waveform are presented for a healthy subject (*top*), a patient with chronic obstructive pulmonary disease (*middle*), and a patient with prior polio infection (*bottom*), all breathing at rest with a mouthpiece (not on a ventilator). Note that all three subjects are breathing with a tidal volume of approximately 500 mL, although diaphragmatic activity required to achieve this tidal volume is eight times higher in the patients than the healthy subject. A higher Edi per milliliter indicates a worsened neuroventilatory efficiency. (Adapted, with permission, from Sinderby et al.[78])

Monitoring Patient–Ventilator Interaction in Conventional Modes of Ventilation Using the Electrical Activity of the Diaphragm

The Edi waveform is considered the reference standard for monitoring patient–ventilator interaction.[4,5,9,15,97,98] During conventional ventilation, when the Edi waveform is simultaneously displayed and superimposed with the airway pressure waveform, it provides immediate bedside information about the interaction between the patient and the ventilator.

An extreme case of poor patient–ventilator interaction is when a patient makes a neural inspiratory effort (Edi waveform starts to increase) and the ventilator does not deliver a breath (Fig. 13-9, *top left*)—often termed "wasted inspiratory efforts." In the example provided, wasted efforts occurred frequently (*red arrows*) during pressure control (PC) ventilation.

At the other extreme of poor interaction is delivery of a ventilator breath when the diaphragm is not active. In Figure 13-9 (*bottom left*), the diaphragm is not activated during the delivery of pressure-support ventilation (PSV). This situation can be a result of too-sensitive trigger settings and too-high levels of assist.

The differences in timing between Edi and ventilator pressure can be quantified for the start (triggering delay) and end (cycling-off delays) of the assisted breaths. Trigger delays are defined as the time interval between the onset of neural inspiratory effort and the onset of the ventilator breath. In Figure 13-9 (*top left*), the assist (*shaded*) can be seen to begin long after the start of neural inspiratory effort. Trigger delays can result from patient characteristics (such as hyperinflation) or ventilator characteristics (trigger sensitivity, trigger algorithms, valve performance).

Cycling-off of a ventilator breath, in healthy subjects, should coincide with the end of neural inspiration. Cycling-off is asynchronous when the ventilator breath terminates while the subject is neurally inspiring (premature cycling-off) or if it cycles-off long after the onset of neural exhalation (delayed cycling-off) (Fig. 13-9, *top left*). In PSV, pneumatic cycling-off algorithms are designed to sense a decrease in flow relative to the peak inspiratory flow. This makes the ventilator cycling-off dependent on the ratio of the time constant of the respiratory system to neural inspiratory time, and the ratio of the pressure support to maximal inspiratory pressure.[99]

Double-triggering can also be detected with the Edi,[98] and can be defined as the delivery of two ventilator breaths for one neural effort. During volume control ventilation or PSV, double-triggering results in the delivery of two full breaths, and could result in "breath stacking" and delivery of higher-than-targeted volumes or pressures.[100]

Monitoring Electrical Activity of the Diaphragm during Weaning from Conventional Ventilation

Monitoring the Edi alone, or in conjunction with other variables, can also be used for decisions about weaning and extubation. The use of daily Edi monitoring during spontaneous breathing trials or during the same fixed level of assist can provide information about changes in

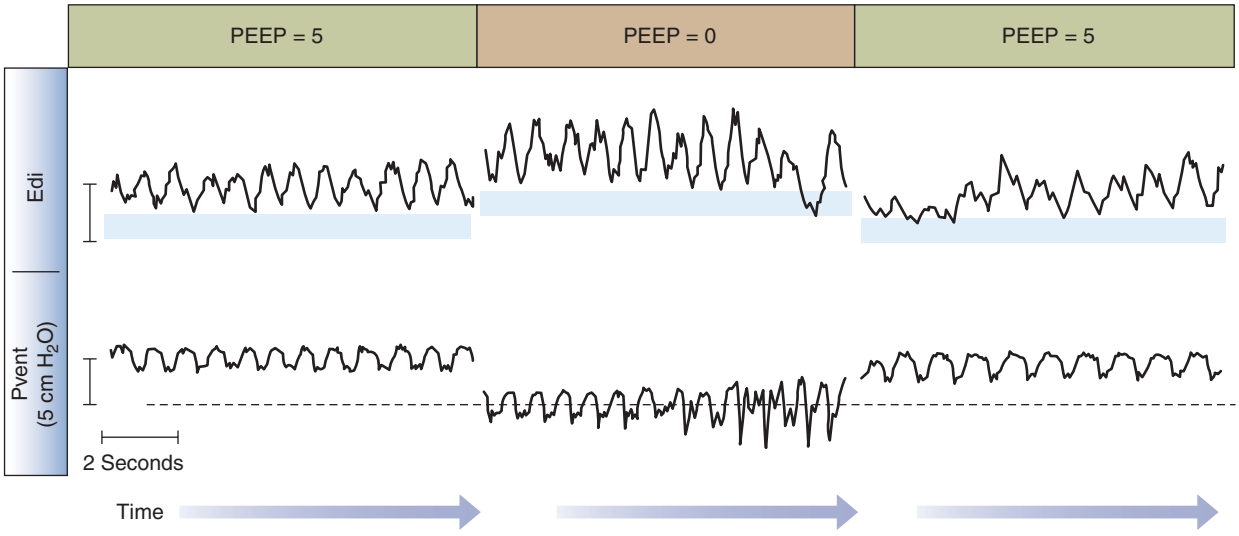

FIGURE 13-8 Impact of removal of positive end-expiratory pressure (PEEP) on tonic Edi. Example of tracings of ventilator-delivered pressure (Pvent) and diaphragmatic electrical activity (Edi) obtained in one intubated and mechanically ventilated infant on synchronized intermittent mandatory ventilation (only the spontaneous breaths in between mandatory breaths are displayed). The amount of tonic Edi (*blue horizontal bars*) increases with brief removal of PEEP (*center*). (Reproduced, with permission, from Emeriaud et al.[92])

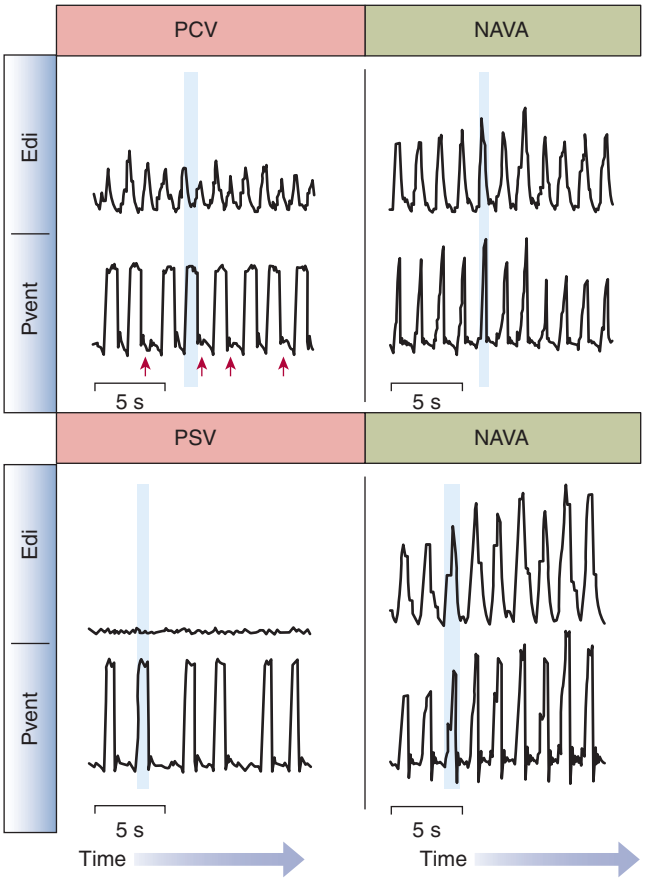

FIGURE 13-9 Patient–ventilator interaction during conventional ventilation and during NAVA. *Top*: Waveforms for Edi and ventilator-delivered pressure (Pvent) for an intubated adult patient breathing on pressure-control ventilation (PCV, *left*) and neurally adjusted ventilatory assist (NAVA, *right*). During PCV, there was a significant amount of wasted efforts (indicated by *red arrows*). During PCV, the delivery of assist (*shaded vertical blue bar*) occurred during neural exhalation, indicating poor patient–ventilator interaction. During NAVA (*right panel*), there were no wasted efforts and the assist was delivered during neural inspiration (*vertical blue shaded bar*). *Bottom*: Waveforms for Edi and ventilator-delivered pressure (Pvent) for an intubated adult patient breathing on pressure-support ventilation (PSV, *left*) and neurally adjusted ventilatory assist (NAVA, *right*). During PSV, too sensitive trigger settings, and too high levels of assist resulted in ventilator-induced hyperventilation and elimination of the Edi. The assist continued to be triggered and delivered (*blue shaded vertical bar*), despite no activation of the diaphragm. During NAVA (*right panel*), Edi controls the ventilator, and cannot be suppressed by ventilator-induced hyperventilation. (Adapted from Sinderby et al,[85] with the kind permission of Springer Science+Business Media.)

respiratory function. If the Edi is referenced to tidal volume during an unassisted breath, the tidal-volume-to-Edi ratio provides an index of the patient's efficiency to generate volume. If an inspiratory occlusion is performed at end-expiration, the ratio of the airway pressure to the Edi expresses the efficiency to generate force. In a recent study, these indices were shown to add important information about extubation failure and success.[101]

BASIC PRINCIPLES AND PHYSIOLOGY OF NEURALLY ADJUSTED VENTILATORY ASSIST

The Edi waveform is today used to control mechanical ventilation in NAVA.[41] NAVA can be delivered by invasive or noninvasive interfaces in all patient ages. Because NAVA uses the Edi waveform to control the assist, the assist is delivered in synchrony and in proportion to the patient's neural respiratory efforts, the latter governed by respiratory demand and reflexes (see Fig. 13-2).

Concept of Neurally Adjusted Ventilatory Assist

NAVA principally works as an artificial respiratory muscle under the same neural control as the patient's respiratory muscles. Figure 13-10 describes how, during NAVA, the patient's respiratory centers serve as the controller for both the patient's diaphragm and the ventilator at the same time. The diaphragm's pressure-generating efficiency depends on its neuromechanical coupling,[80] and is affected by such factors as dynamic hyperinflation and muscle weakness. For the ventilator, the efficiency of pressure generation depends on the NAVA level, a gain factor that controls the amount of pressure for a given Edi. The sum of the patient and ventilator pressures is the transpulmonary pressure, that is, the pressure that distends the lungs.

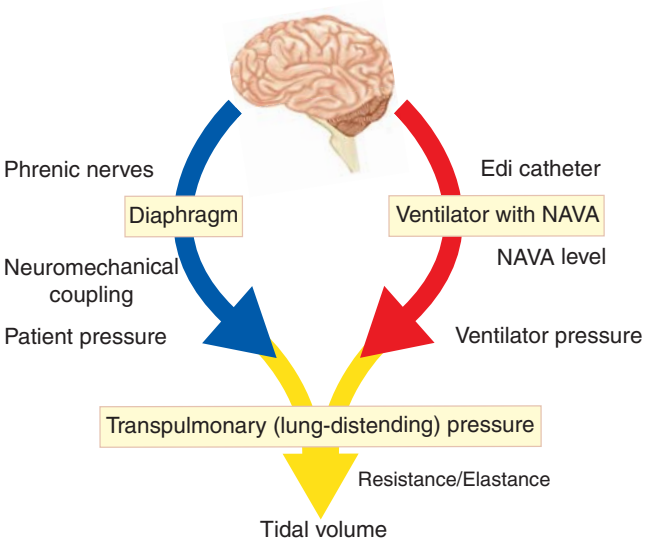

FIGURE 13-10 Concept of NAVA. During NAVA, the respiratory centers control both the patient's own diaphragm (*left*), resulting in a patient pressure, and the ventilator (*right*), creating a ventilator pressure (*right*). Their sum is the transpulmonary (or lung-distending) pressure. Depending on the patient's neuromechanical efficiency (*left*) and on the NAVA level (*right*), the relative contribution of the patient or ventilator to the lung-distending pressure will vary. For a given lung-distending pressure, the tidal volume generated will depend on the elastance and resistance of the patient.

At a fixed NAVA level, the Edi is solely responsible for changes in transpulmonary pressure. If respiratory drive (and hence Edi) is doubled, this doubles the patient pressure *and* doubles the ventilator pressure, therefore doubling transpulmonary pressure. Conversely, reducing the Edi by half reduces the patient pressure by half, *and* the ventilator pressure by half. Therefore, at a constant NAVA level, the patient is in full control of lung-distending pressure.

When the Edi remains constant, an increase in the NAVA level only increases the ventilator's relative contribution to the transpulmonary pressure. Therefore, in relative terms, the patient's contribution to volume is reduced compared to the ventilator.

Triggering

In its current platform, the assist is triggered by the initial increase in Edi (Fig. 13-11). Note that NAVA is triggered by a *deflection* in Edi and not at an absolute level of Edi; the latter would not function when tonic Edi is present. In principle, the Edi signal should precede the airway pressure signal and inspiratory flow signal and trigger on Edi (see Fig. 13-1). There are instances, however, when the filtering of the ECG or artifacts may coincide with the beginning of the Edi, or other inspiratory muscle groups could generate flow first. In this case, the ventilator is triggered by either changes in Edi *or* flow, on a "first-come, first-served" basis. This is to avoid inspiratory occlusions during triggering. If pneumatic triggering occurs (before Edi triggering), a pressure of 2 cm H_2O is delivered until the Edi appears.

Assist Delivery

Throughout neural inspiration, the ventilator delivers pressure in proportion to Edi. The pressure waveform follows the inspiratory portion of the Edi waveform (see Fig. 13-11). This matching of the pressure to the Edi is updated every 16 milliseconds. The Edi is multiplied by a proportionality constant known as the NAVA level, to increase or decrease the assist. The NAVA level has units of cm $H_2O/\mu V$.

The NAVA level is set manually. The range available today is between 0 and 15 cm $H_2O/\mu V$, and can be adjusted in steps of 0.1 cm $H_2O/\mu V$. The response of the ventilator to changes

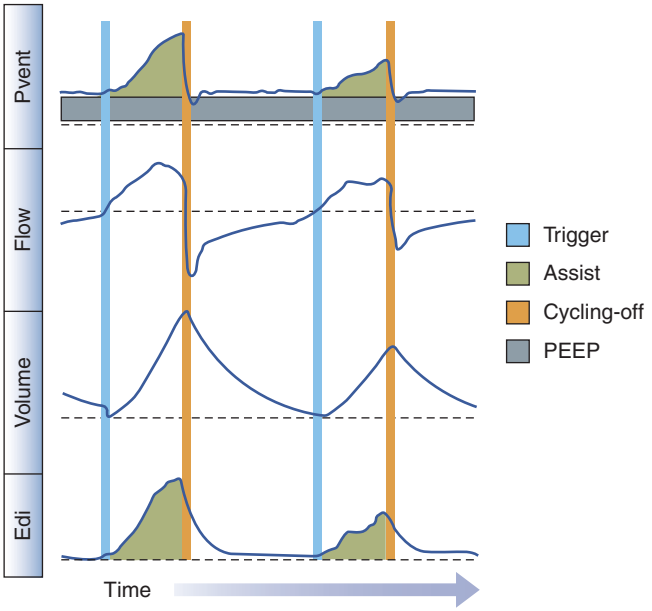

FIGURE 13-11 Features of NAVA. *From top to bottom:* Tracings for ventilator pressure (Pvent), flow, volume, and Edi are displayed for a patient breathing on NAVA. During NAVA, triggering of the ventilator occurs when the Edi exceeds a threshold deflection in Edi, as indicated by the *blue vertical line*. Throughout the inspiration, the ventilator pressure follows the Edi waveform (*green-shaded area*), and the NAVA level determines the proportionality between the ventilator pressure and the Edi. When the Edi waveform has decreased to 70% of the peak, the ventilator cycles off (*orange vertical line*) to a user-defined PEEP (*gray horizontal bar*). During NAVA (and a fixed NAVA level), a larger Edi waveform produces a larger pressure delivery (first breath) and a smaller Edi waveform produces a smaller pressure (second breath).

in the NAVA level is dependent on the absolute level of Edi, which varies between patients. If the Edi is large, it takes only a small change in the NAVA level to produce a large change in ventilator-delivered pressure. For example, an increase in the NAVA level by 1 cm $H_2O/\mu V$ when Edi peak is 10 μV results in an increase in ventilator pressure of 10 cm H_2O, whereas if the Edi is 1 μV, the increase in ventilator pressure is only 1 cm H_2O.

Upper pressure limits are applied during NAVA and can be adjusted. During NAVA the pressure is limited to 5 cm H_2O below the dialed-in limit.

Cycling-Off

During NAVA, the ventilator cycles-off the breath once the Edi drops to 70% of the highest value (see Fig. 13-11). When Edi peak values are low, cycling-off occurs at lower percentages. The breath is cycled off with pressure criteria any time the peak pressure exceeds the predicted NAVA pressure by 3 cm H_2O. In the case of a long neural inspiration, there are time criteria for cycling off: 1.5 seconds in infants and 2.5 seconds in adults.

Physiologic Response to Increasing Neurally Adjusted Ventilatory Assist Levels

If a patient is in respiratory failure, the typical physiologic response to increasing the NAVA level (from zero) is the following (Fig. 13-12).

- "Phase 1": At lowest NAVA levels (see Fig. 13-12, *left*), Edi is highest, indicating a large patient effort with insufficient ventilation. As the NAVA level is progressively increased, ventilator pressure increases, until at some NAVA level, a "patient-desired" transpulmonary pressure (and tidal volume) is reached. This first phase indicates that NAVA supplements the respiratory muscles to restore adequate ventilation.
- "Phase 2": Further increases in the NAVA level result in a constant transpulmonary pressure secondary to a reduction in Edi (see Fig. 13-12).[58,94,96,102,103] This second phase indicates a "comfort zone" where assist levels are adequate to sufficiently unload the respiratory muscles. In this second phase of unloading with NAVA, ventilator pressure, respiratory rate, and tidal volume change minimally.[58,94,96]
- "Phase 3": If the increase in NAVA level continues, the Edi will decrease further until it reaches a plateau (a minimum level). At highest NAVA levels, the Edi is not abolished (see Figs. 13-12 and 13-13),[58,102] but results in an irregular breathing pattern secondary to a too-high loop gain.[96] Even with maximum unloading of the diaphragm, Edi is still present and able to control the ventilator[102] (see Fig. 13-13), without inducing reflex reductions in respiratory rate.[4,15,104–106]

The downregulation of Edi and the avoidance of excessive assist delivery during NAVA have been verified experimentally as preventing ventilator-induced lung injury.[107]

Weaning

Improvement of respiratory function or reduced respiratory demand reduces the Edi waveform. Considering that the pressure delivered during NAVA follows the Edi, as the patient's respiratory status improves and Edi decreases, the pressure delivered will also decrease as long as NAVA levels and sedation management remain constant. Thus, with respiratory improvement, NAVA can—secondary to its close neural integration—be thought of as a "self-weaning" mode.

Noninvasive Neurally Adjusted Ventilatory Assist

The principal difference between invasive and noninvasive NAVA is that the bias flow during PEEP is automatically adjusted (during noninvasive NAVA) and can reach much higher flow levels, ensuring maintained PEEP during the

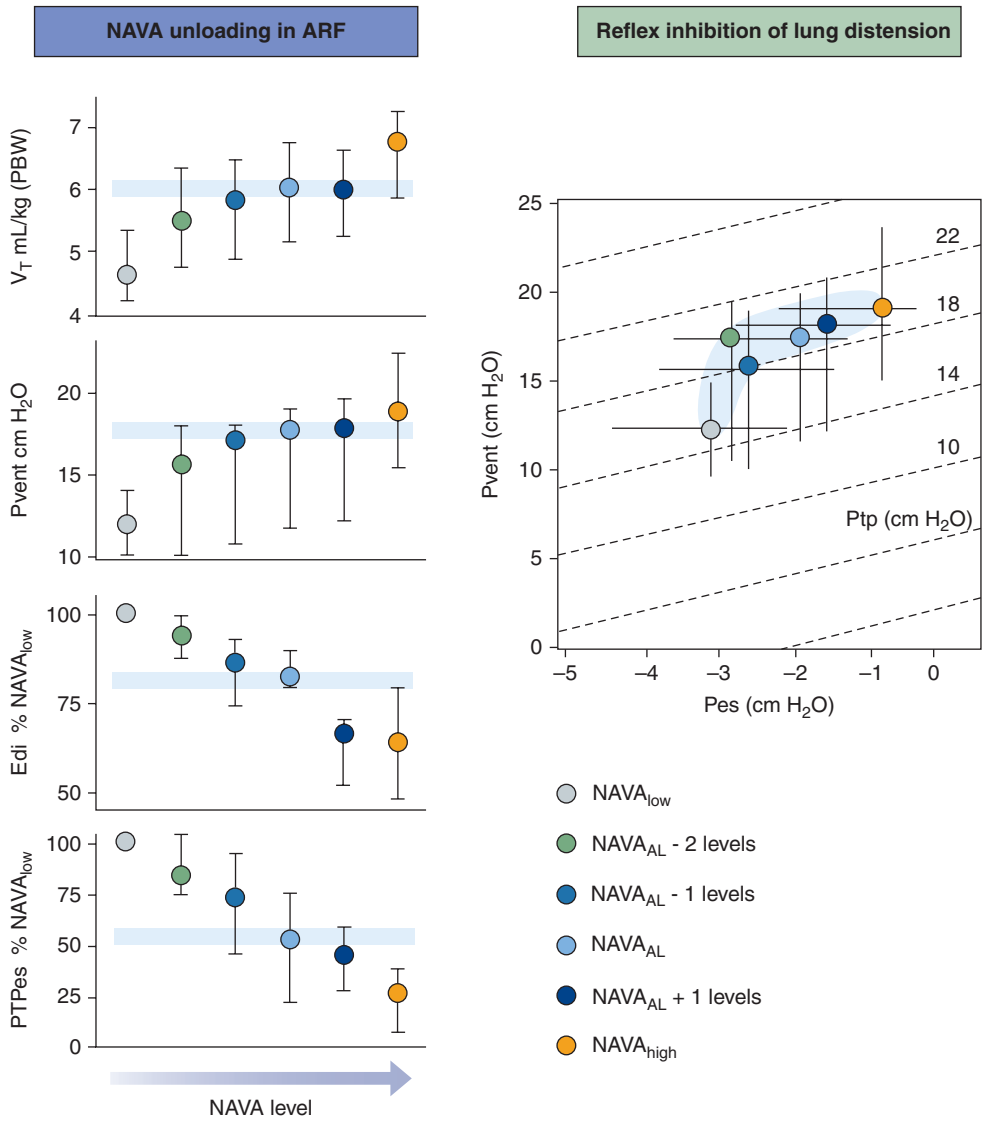

FIGURE 13-12 Physiologic response to increasing NAVA levels. *Left panel:* Changes in tidal volume (V_T) per predicted body weight (PBW), mean inspiratory ventilator pressure (Pvent) including positive end-expiratory pressure (PEEP), electrical activity of the diaphragm (Edi), and esophageal pressure time product (PTPes) for a group of patients during titration of the NAVA level. The initial increase in Pvent and V_T between the lowest NAVA level (*gray dot*, $NAVA_{low}$) and the adequate NAVA level (*royal blue dot*, $NAVA_{AL}$) was associated with a reduction in Edi and PTPes. Thereafter, further increases in the NAVA level did not significantly change either Pvent, V_T, nor minute ventilation (not shown) while the reduction of PTPes and Edi continued from $NAVA_{AL}$ to $NAVA_{high}$ (*orange dot*). *Right:* Interaction between mean inspiratory ventilator pressure (Pvent, *y axis*), esophageal pressure (Pes, *x axis*), and transpulmonary pressure (Ptp, *dashed diagonal lines*) during a NAVA level titration. In this example, from $NAVA_{low}$ (*gray dot*) to one level below $NAVA_{AL}$ ($NAVA_{AL}$–1 level), Pvent increased by 5.0 cm H_2O and reduced the Pes deflection by 0.5 cm H_2O such that transpulmonary pressure increased by 4.5 cm H_2O. Further increasing the NAVA level from $NAVA_{AL}$ to $NAVA_{high}$ resulted in changes of Pvent and Pes that were similar in magnitude and, hence, in an essentially unaltered transpulmonary pressure. PEEP remained unchanged during the NAVA level titration. *ARF*, acute respiratory failure. (Adapted, with permission, from Brander L et al.[96])

neural expiration even in the presence of large leaks. There are also some differences in alarms, which are beyond the scope of this chapter.

In reference to Figure 13-1, Edi precedes inspiratory flow in the chain of events of spontaneous breathing. When a leak is present, Edi is a true indicator of when the breath starts, whereas the flow measurement in itself is affected by the leak. Studies have confirmed that patient–ventilator interaction during NAVA is not affected by severe leaks.[108,109]

Regarding noninvasive ventilation, an important consideration is the anatomical and physiologic consequences of avoiding intubation. Endotracheal intubation conveniently divides the air and food passages such that ventilator assist can be delivered with no interference from upper airway regulation and swallowing. Delivery of assist through the upper respiratory tract using a noninvasive interface, however, introduces a demand to synchronize assist delivery with inspiration for several reasons.

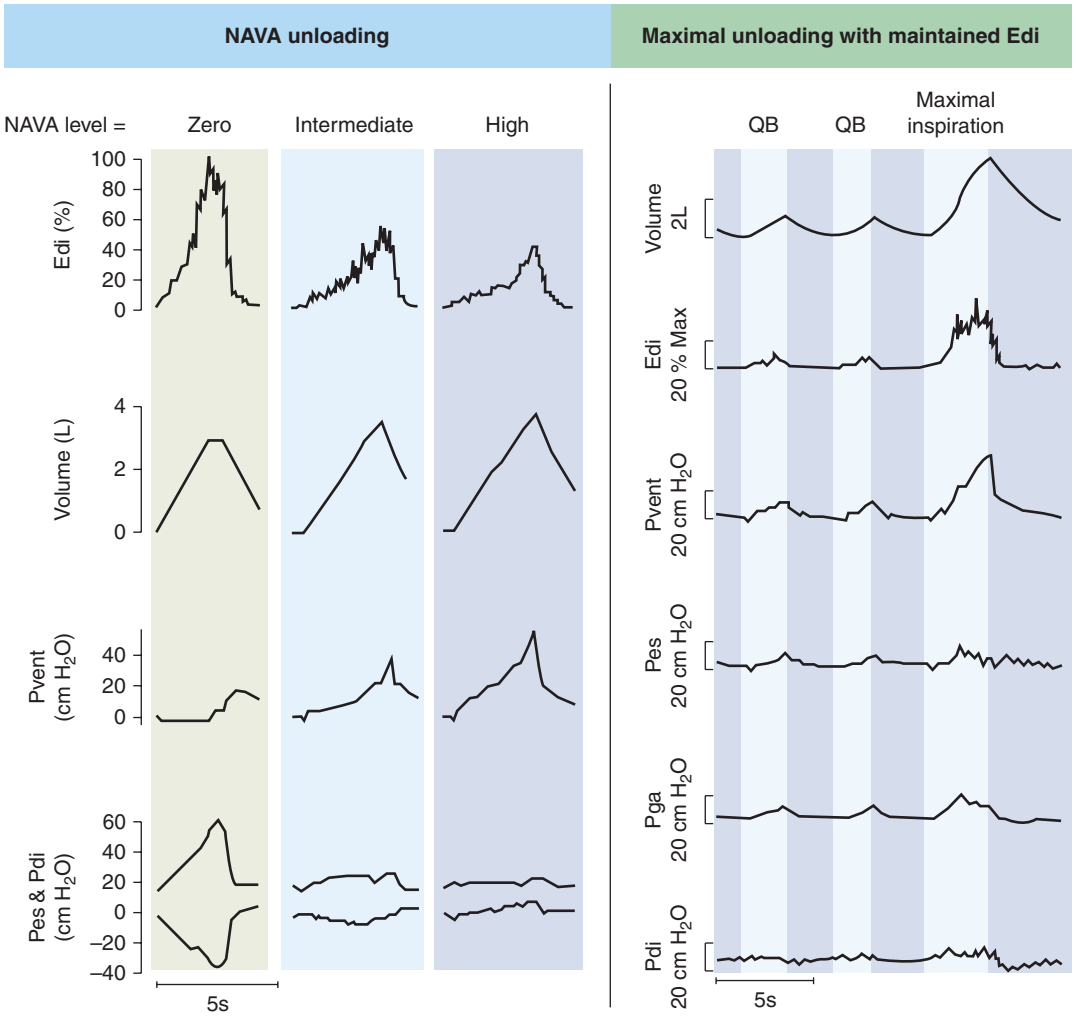

FIGURE 13-13 Respiratory muscle unloading with NAVA. *Left:* Tracings (*from top to bottom*) of electrical activity of the diaphragm (Edi), volume, ventilator pressure (Pvent), and esophageal (Pes) and transdiaphragmatic pressure (Pdi) obtained in one healthy subject performing maximal inspirations with three NAVA levels (zero, intermediate, and high). Increasing the NAVA level resulted in increased ventilator-delivered pressure and deactivation of the diaphragm (by 60%). Note that this was occurring while the Pdi and Pes deflections disappeared, indicating 100% unloading. *Right:* Tracings (*from top to bottom*) of volume, Edi, ventilator pressure (Pvent), esophageal pressure (Pes), gastric pressure (Pga), and transdiaphragmatic pressure (Pdi) obtained in a healthy subject breathing on NAVA at high NAVA levels. The first two breaths were obtained during quiet breathing and the third breath during a maximal inspiration. Note the 100% unloading of the diaphragm (flat Pdi) in all breaths regardless of the level of diaphragm activation, and the remaining Edi, which is still able to control the ventilator at both volumes. (Adapted, with permission, from Sinderby et al.[102])

In humans, the upper airways constitute a common tract allowing ventilation, ingestion, and speech, requiring neural control systems to coordinate respiration with swallowing, speech, cough, and vomiting.[110–113] In 1949, Negus[114] provided the first notation that the glottis opens before inspiration starts. In 1969, Suzuki and Kirchner[115] demonstrated that phasic activity of vocal cord dilators occurs in synchrony with phrenic nerve activity. Kosch et al[116] demonstrated that laryngeal abductors are activated before the diaphragm. The genioglossus is activated and dilates the airway before diaphragmatic activation[117] and airway flow.[118,119] During expiration, activation of, for example, the pharyngeal constrictors also has been suggested to modulate the resistance to airflow.[120,121] Recently, active glottal closure was described during high levels of noninvasive conventional ventilation in nonsedated newborn lambs[122]; active glottal closure is likely mediated by bronchopulmonary receptors.[63]

Another factor complicating the implementation of noninvasive ventilation is swallowing. Swallowing must interact with the inspiratory muscles in a fashion that minimizes disturbances to breathing. In awake human subjects, swallowing is associated with apposed vocal cords and an apneic period,[123] normally followed by expiration.[124] It is suggested that this sequence (swallow followed by expiration) may be protective against aspiration.

The role of the upper-esophageal sphincter is to prevent reflux of food into the airways as well as avoid entry of

air into the digestive tract. During swallowing, the upper-esophageal sphincter is open to accommodate passage of a bolus into the esophagus, and hence delivery of pressure during swallowing increases the risk of gastric distension. During noninvasive NAVA, no gastric distension was observed even at extremely high levels of assist.[108]

Vocal control is achieved by the coordinated efforts of respiratory, laryngeal, and articulatory muscles. Given that speech is an expiratory maneuver, diaphragmatic involvement only occurs on inspirations between phonation, thus assist delivery will be synchronized with NAVA. Abnormal rhythm of the breathing pattern and Edi waveform are anticipated during speech.

In 1937, Coryllos[125] described cough as being composed of three distinct phases: (a) inspiratory, (b) compressive (expiratory pressure generation against a closed glottis), and (c) expulsive (opening of the glottis). The diaphragm is only electrically active during the first two phases and not during the expulsive phase.[121,126] Figure 13-14 illustrates coughing during NAVA.

During the expulsive phase of vomiting, the crural and costal diaphragm dissociate their activities, with the crural diaphragm relaxing (i.e., not triggering NAVA) to allow the ejection of the gastric contents, and the costal diaphragm contracting, to increase the abdominal pressure and thus force the gastric contents outwards.[127–130]

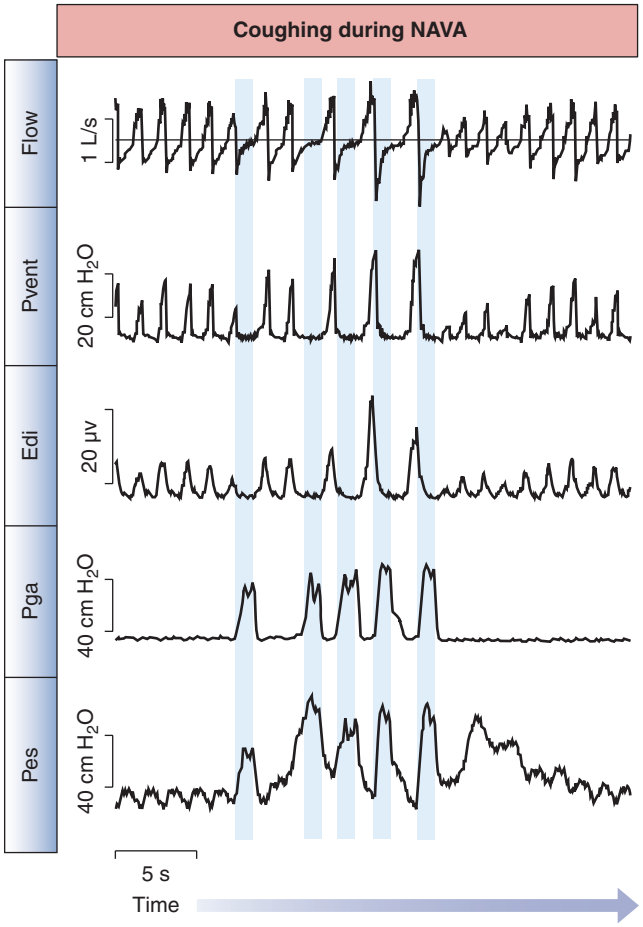

FIGURE 13-14 Coughing during NAVA. Tracings (*from top to bottom*) of flow, ventilator pressure (Pvent), diaphragmatic electrical activity (Edi), gastric pressure (Pga), and esophageal pressure (Pes) in an adult intubated patient ventilated with NAVA who is coughing. The *blue-shaded* vertical areas highlight the coughs (upswing in Pga). The Edi waveform shows termination of Edi during coughs. The functionality of NAVA was not affected by the coughs. (Note that the second compressive phase described in the text is lacking in the intubated patient.)

INDICATIONS AND CONTRAINDICATIONS

Indications

NAVA is indicated for use in patients of all ages who require and qualify for partial ventilator assist, and in whom spontaneous respiratory activity is present. NAVA may prove especially useful in patients at risk for prolonged mechanical ventilation and who fail spontaneous breathing trials.

Monitoring the Edi is indicated in all patients of all ages in any mode of ventilation, invasive or noninvasive, when the goal is to perform bedside evaluation of patient–ventilator interaction and neural breathing pattern, and to ensure that spontaneous breathing is present.

Contraindications

NAVA cannot be applied if (a) Edi is absent, (b) nasogastric and/or orogastric catheters are contraindicated, or (c) ventilatory parameters are unacceptable.

ADJUSTMENTS AT THE BEDSIDE

Implementation of NAVA requires a ventilator with the NAVA option, module, and software, and an Edi catheter.

Electrical Activity of the Diaphragm Catheter Positioning

Catheter positioning is achieved by inserting the tip of the catheter nasally or orally to a predicted distance, and then adjusting the position with feedback from a display showing an Edi curve and four raw signals not filtered for ECG (Fig. 13-15). With the catheter in appropriate position, both P and QRS waveforms should be present at the top and P waves should disappear toward the bottom as illustrated in middle panel of Figure 13-15. The top and bottom panels of Figure 13-15 demonstrate examples of ECG waveforms when the catheter is too far out or too far in, respectively.

A secondary verification method on the same window involves the highlighting of the leads closest to the diaphragm (in blue on the commercially available system), as determined

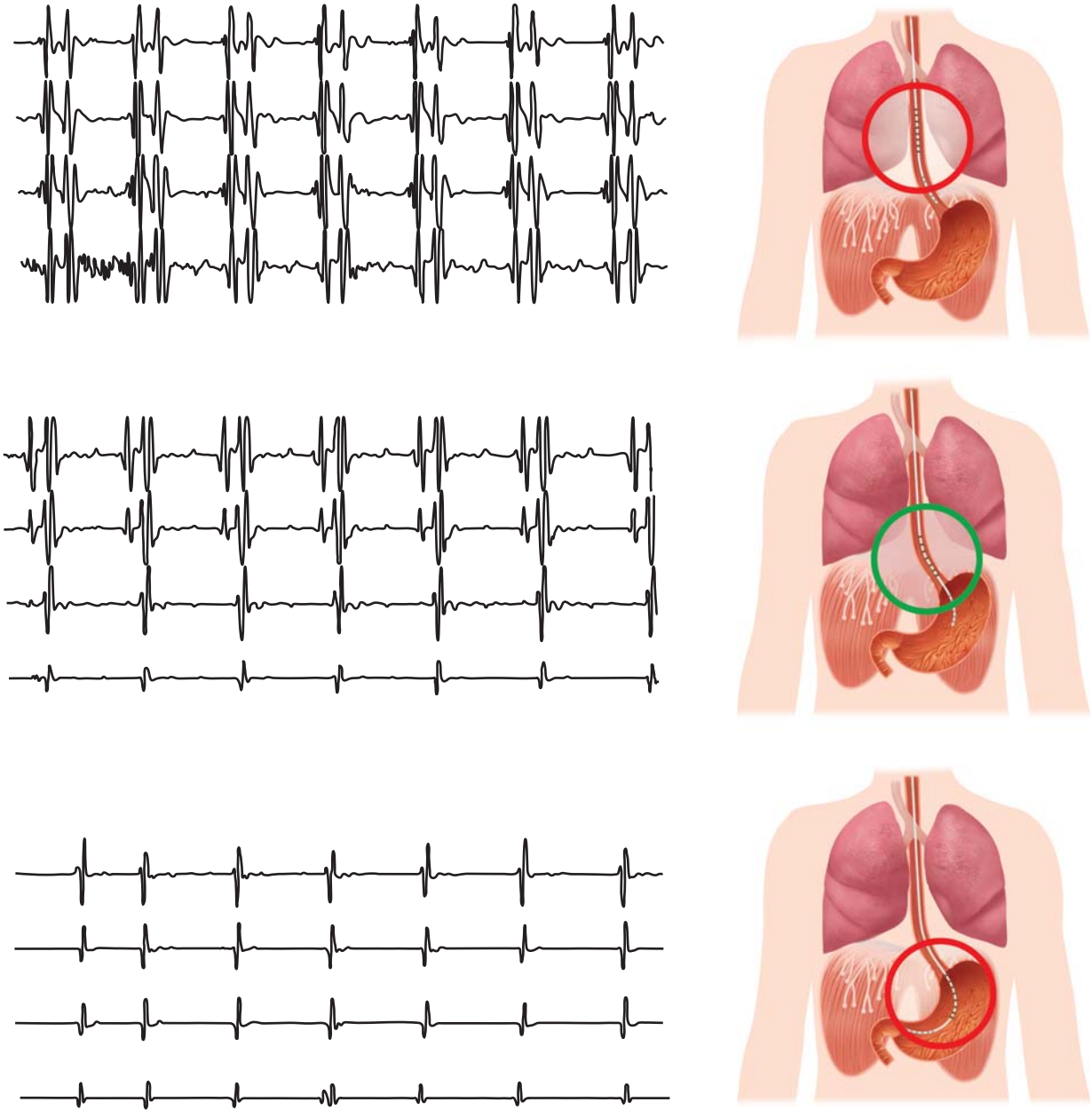

FIGURE 13-15 Electrode positioning during NAVA. Unfiltered tracings obtained from four electrode pairs (top is most cephalad, bottom most caudal) on the Edi catheter when the catheter is too far out (*top*), in good position (*middle*), and too far in (*bottom*). The *middle panels* indicate the correct pattern for the ECG waveforms when the Edi catheter is positioned appropriately (diaphragm located approximately in the middle of the electrode array). This pattern is characterized by distinct P waves and QRS waves whose amplitude is largest at the top, and diminishes more distally. See text for details.

by the cross-correlation method (see Fig. 13-4).[75] Ideally, the two middle leads should be highlighted during inspiration.

The catheter should be fixed after appropriate positioning and the final insertion distance noted. This method has been validated in adult[131] and pediatric[132] patients.

Setting the Neural Trigger

The trigger during NAVA detects a threshold increase in the Edi waveform. The sensitivity of the neural trigger is adjustable, with a default setting of 0.5 μV.

Initial Setting of the Neurally Adjusted Ventilatory Assist Level

To deliver a target pressure, the following formula can be used: Ventilator pressure (above PEEP) in cm H_2O = (peak Edi – min Edi) in μV × NAVA level (cm H_2O/μV). It is possible, that once the NAVA level has been set, and the patient is switched over to the NAVA mode, the Edi waveform might change, and may therefore be different from the targeted pressure.

As an alternative, the NAVA level can be set so that the peak pressure attained during conventional ventilation can be matched. A designated "NAVA preview window" allows feedback for this. It is possible that once the patient is switched over to the NAVA mode, the Edi waveform might change, and may be therefore different from the predicted pressure.

The NAVA level can be titrated by performing stepwise increases in the NAVA level from a minimal level.[58,95,96] It has been suggested that the adequate NAVA level is the one where the increase in ventilator-delivered pressure is slowing—or even plateaus.[96]

Setting Backup Parameters

As in other modes of mechanical ventilation, upper pressure limits and backup parameters should be set for the appropriate patient age and condition.

Setting Positive End-Expiratory Pressure

PEEP should be set as with other modes of mechanical ventilation. In infants, monitoring the tonic Edi may aid with adjustment of PEEP. Emeriaud et al[92] and Allo et al[94] have demonstrated that applying PEEP can reduce tonic Edi (see Fig. 13-8). Monitoring the ratio between tidal volume and Edi (neuroventilatory efficiency) allows identification of an efficient PEEP level.[95] During NAVA, PEEP does not have to be applied to overcome intrinsic PEEP.

Adjustment of the Neurally Adjusted Ventilatory Assist Level during Weaning

NAVA can be combined with any weaning method, for example, daily spontaneous breathing trials, with the advantage that it provides numerical and bedside information about respiratory drive. Any improvement in patient respiratory function (as indicated by a decrease in Edi for the same NAVA level) should be corrected by reducing the NAVA level. The easiest method is to note the Edi value obtained when the patient was comfortable (Edi baseline) and if Edi decreases, reduce the NAVA level until the Edi returns to baseline value. If the patient has undergone a spontaneous breathing trial, another approach is to target an Edi amplitude relative to that observed during a spontaneous breathing trial.[133] Yet another approach is to perform daily titrations of the NAVA level to determine an adequate NAVA level.[96]

TROUBLESHOOTING

The reader is referred to the manufacturer's user manual (Maquet Critical Care AB, Solna, Sweden).

ADVANTAGES AND LIMITATIONS

Table 13-1 lists the advantages and limitations of NAVA.

TABLE 13-1: ADVANTAGES AND LIMITATIONS OF NAVA

Advantages of NAVA
Edi monitoring
Standardized Edi catheter position procedure allows reliable feeding tube placement
Monitoring presence or not of spontaneous breathing during conventional ventilation
Monitoring patient–ventilator interaction during conventional ventilation
NAVA Mode
Improved timing between patient effort and assist delivery independent of
a. Leaks
b. Properties of interface
c. Liquid in respiratory circuit
d. Cardiogenic oscillations in the airway flow
e. Intrinsic PEEP
Neurally integrated with timing of upper airway activity and function
Matching of magnitude assist delivery to patient effort
a. Preservation of respiratory drive
b. No runaway
c. Prevention of excessive assist delivery
d. Responds to changes in respiratory demand
Limitations of NAVA
Cannot use in absence of respiratory drive
Cautious use with uncontrollable respiratory drive
Too-high NAVA levels cause irregular breathing pattern
Cannot be used when feeding tube is contraindicated
Signal disturbances on Edi signal may affect NAVA performance, e.g., ECG leak through

COMPARISON WITH OTHER MODES

Fundamental Differences between Neurally Adjusted Ventilatory Assist and Other Modes

The difference between conventional ventilation (such as PSV, pressure control ventilation, assist-control ventilation, and synchronized intermittent mandatory ventilation) and NAVA lies in the signal used to control the ventilator (see Fig. 13-1). Conventional modes of ventilation control the timing of assist delivery by pneumatic signals (pressure or flow at the airway) or time criteria, and the level of assist is pressure or volume targeted. NAVA, on the other hand, is controlled by the patient's own Edi, occurring at a level proximal to muscle function and respiratory mechanics, and which also responds to respiratory feedback loops.

Neurally Adjusted Ventilatory Assist versus Conventional Ventilation, Impact on Patient–Ventilator Interaction

Compared to conventional modes of ventilation, NAVA improves patient–ventilator synchrony in terms of triggering and cycling-off delays.[4,15,98,103,109] The amount of improved synchrony depends on the disease etiology and the settings in the conventional ventilation arm.

The improvement in trigger delays with NAVA is in the 100 millisecond range.[4,98,103] When expressed as a percentage of the neural inspiratory time, NAVA also shows less relative trigger delay (13% to 14% of neural inspiratory time) than PSV (up to 35% of neural inspiratory time at high levels of PSV).[4] One study recently showed that of their twenty-five patients with mixed etiologies, none had trigger delays greater than 150 milliseconds during NAVA.[98] The trigger delay increases with increasing PSV, but is not affected by increasing NAVA levels.[4,15,103,134] In premature infants, 13% of the breaths during conventional ventilation began *before* the onset of Edi.[109]

Wasted efforts are worsened when the PSV level is increased.[3,4,103,134] In contrast, with NAVA, no wasted efforts have been reported in the literature, even when the NAVA level is increased.[4,15,103,134]

Several investigators have reported shorter cycling-off delays during NAVA compared to PSV in adults[4,98] and in rabbits with lung injury.[103] The cycling-off delays are prolonged with increasing PSV, whereas with increasing NAVA, there is no effect.[4,103,134] In premature infants, cycling-off during PSV or PSV with volume guarantee actually occurs *before* the cycling-off during NAVA.[109]

Some investigators have combined the observed asynchronies (trigger delays, wasted efforts, cycling-off delays) to quantify an "asynchrony index," which was found to be significantly lower during NAVA compared to PSV in adults[4,15,98,137] and neonates,[138] and worsened with increasing levels of PSV.[4,15,137]

One challenge for achieving patient–ventilator synchrony is when leaks are present. Figure 13-16 demonstrates airway pressure tracings obtained during noninvasive PSV and noninvasive NAVA, with increasing leak. The worsening asynchrony with increasing leak was accompanied by an eightfold increase in breathing effort (esophageal pressure-time product, not shown). In premature infants and in rabbits with acute lung injury, trigger delays, and cycling-off delays were equal during invasive NAVA and during noninvasive NAVA.[108,109]

Patient-ventilator interaction is difficult to achieve with pneumatically controlled non-invasive ventilation applied with the helmet interface because of its large volume, high compliance, and sensitivity to leaks.[139] Moerer et al[135] examined patient–ventilator synchrony during neurally and pneumatically triggered and cycled-off PSV with the helmet in healthy subjects. Trigger delays, wasted efforts, and cycling-off delays all increased with increasing PSV when pneumatic control was used. During neural triggering and cycling-off, increasing PSV and breathing frequency did not affect trigger and cycling off delays. The comfort of breathing was significantly better during neurally triggered and cycled-off PSV.

By design, NAVA delivers assist in proportion to the Edi, and a few studies have demonstrated a high correlation between Edi and peak airway pressure delivered,[15,103,109] which was superior to the correlation between Edi and pressure during PSV (Fig. 13-17). The high correlation between Edi and peak ventilator pressure was not affected by the presence of a large leak during noninvasive NAVA in premature babies.[109] During PSV plus volume guarantee, Beck and Sinderby demonstrated a negative correlation between Edi and pressure, indicating a reversed proportionality.[140]

As a result of the improved synchrony with NAVA, the pressure-time product of the diaphragm and the Edi-time product are both less during NAVA than during PSV.[4,103] The diaphragmatic work of breathing during the trigger phase was also found to be less for NAVA compared to PSV, which also showed increased diaphragm work when the PSV level was increased.[4]

Double triggering, delivery of two ventilator breaths back-to-back, occurs during NAVA and PSV; while the prevalence is low,[15,16,98,141] it can sometimes be frequent.[13]

Neurally Adjusted Ventilatory Assist versus Conventional Ventilation, Impact on Breathing Pattern and Gas Exchange

In studies where peak airway pressure was matched, tidal volume was lower during NAVA compared with

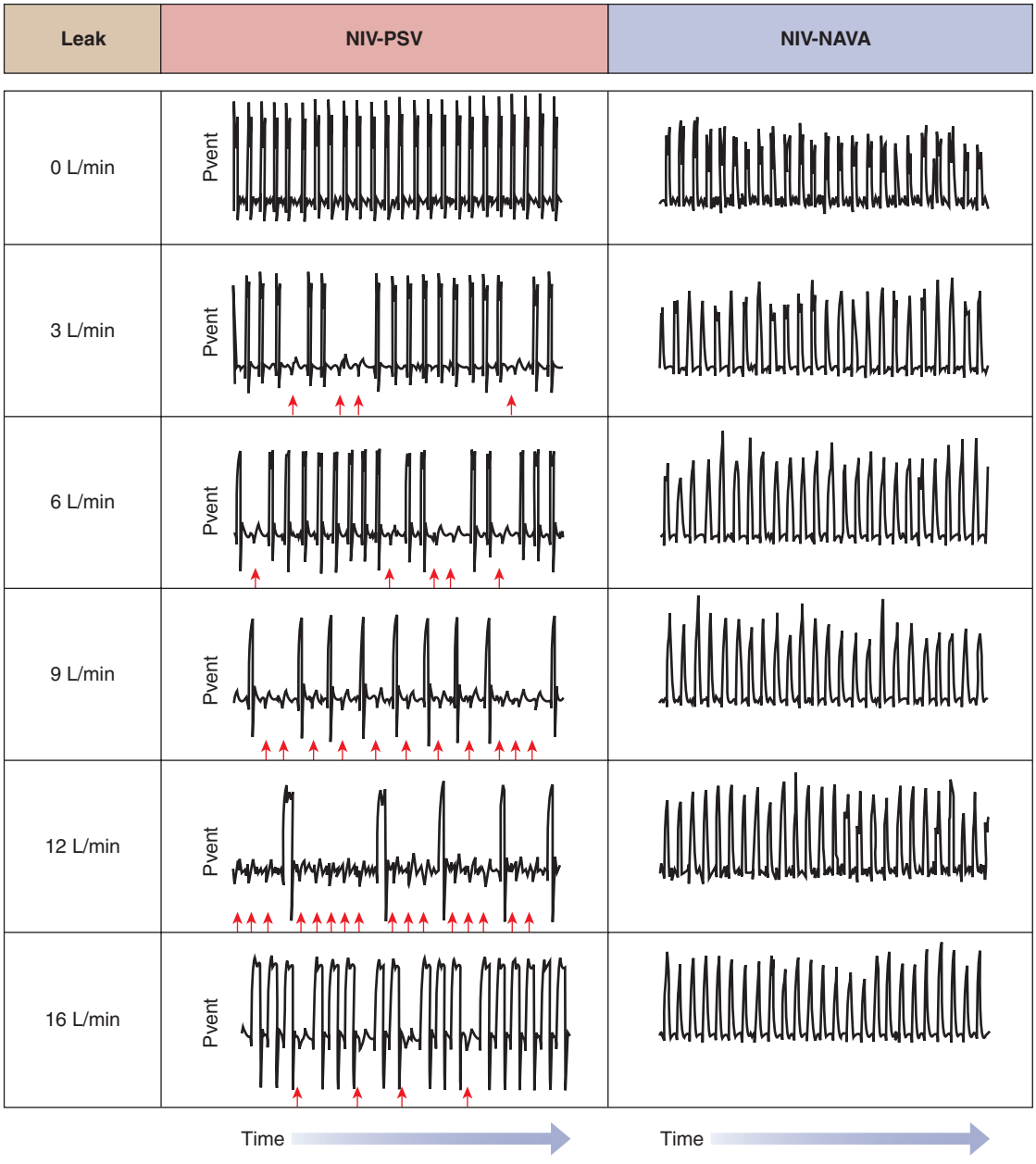

FIGURE 13-16 Patient–ventilator interaction during noninvasive PSV and noninvasive NAVA. Ventilator-delivered pressure (Pvent) is displayed for noninvasive pressure support (NIV-PSV, *left*) and noninvasive NAVA (NIV-NAVA, *right*), for periods of increasing leak (0 to 16 L/min, *top to bottom*). The wasted efforts (*red arrows*) increased with increasing leak during NIV-PSV, whereas wasted efforts were not observed during NIV-NAVA. At the highest leak tested (16 L/min), the ventilator also demonstrated autotriggering and hangup of the ventilator breaths (that were cycled-off by time criteria). During NAVA, synchrony was maintained in terms of timing and proportionality, despite the increasing leak. The increasing asynchrony during NIV-PSV with increasing leak was associated with an eightfold increase in effort (not shown).

PSV,[15,96,137,141] usually 6.5 to 8.5 mL/kg of predicted body weight in adult patients of all illnesses and severities. In animal studies, tidal volume during NAVA is lower than during PSV[103] or volume control set to a lung-protective strategy of 6 mL/kg.[104] When attempts are made to systematically increase PSV and NAVA levels, tidal volume increases during PSV but remains more or less unchanged during NAVA, secondary to downregulation of Edi.[4,103,137] In critically ill postoperative patients, Coisel et al[142] demonstrated no significant differences in tidal volume between NAVA and PSV at baseline, although after 24 hours of each, tidal volume was lower during NAVA.

Some studies report a higher respiratory rate with NAVA compared to PSV.[4,98,137,141,143] The results, however, should be interpreted with caution because the distinction is not always made between neural respiratory rate and ventilator rate. Colombo et al[15] and Spahija et al[4] both reported a reduction in neural respiratory rate with increasing PSV

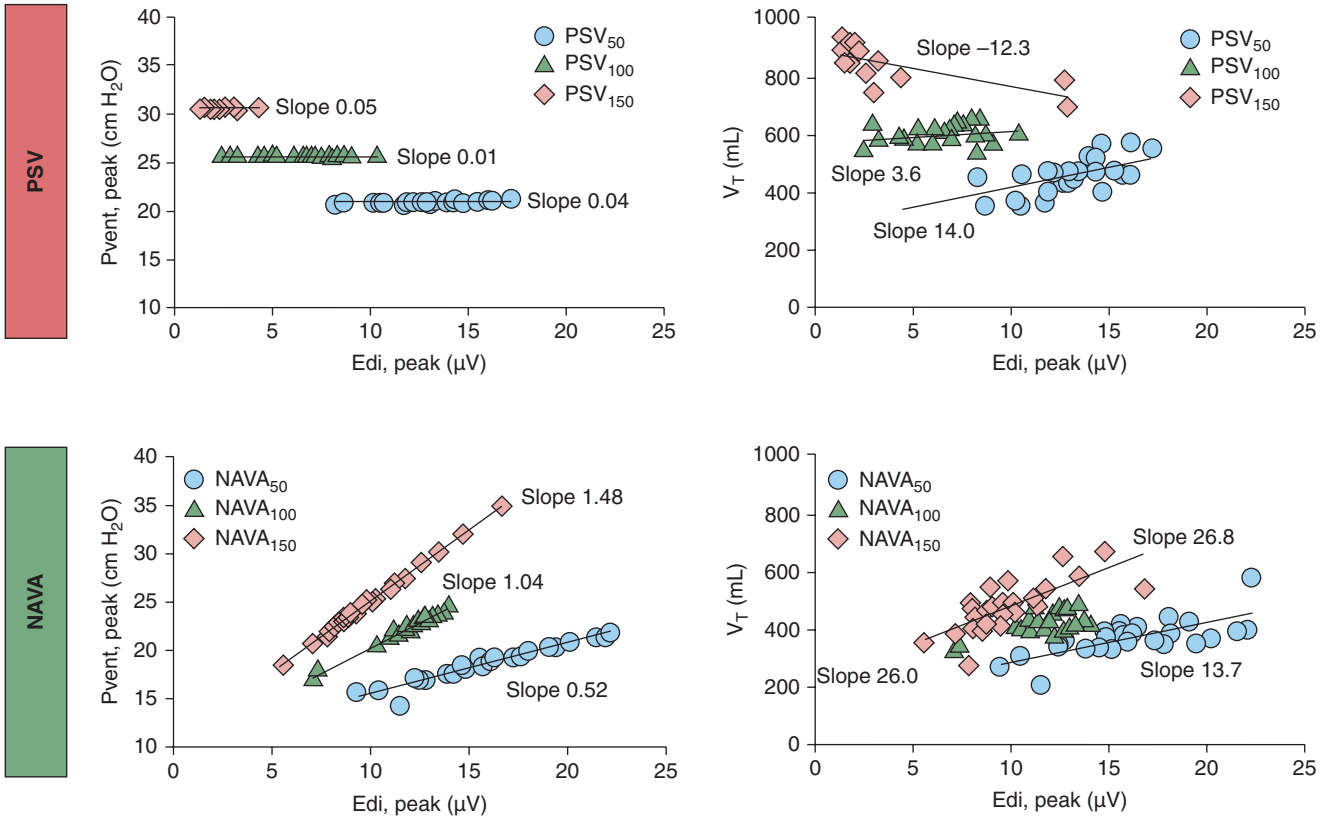

FIGURE 13-17 Proportionality between Edi and ventilator pressure during pressure-support ventilation (PSV) and during NAVA. Relationships between ventilator pressure (Pvent) and Edi (*left panels*), and tidal volume (V_T) and Edi (*right panels*) are depicted for three assist levels with PSV (*upper panels*) and NAVA (*lower panels*), in one patient. The three levels of assist are indicated by different colors. Pvent did not change with varying Edi in PSV. Oppositely, in NAVA, Pvent varied in proportion to Edi. During PSV, V_T slightly rose when increasing Edi only at the lowest level of support. During NAVA, V_T augmented as Edi increased at all levels of assistance. (Adapted, with permission, from Colombo et al.[97])

levels, whereas this was not observed during increasing NAVA levels.[15,96] Another confounding factor in the interpretation of respiratory rate is that, during conventional ventilation, wasted efforts mask the patient's neural respiratory rate. During PSV, the neural respiratory rate can be higher than the ventilator rate.[103] Hence the increased respiratory rate sometimes observed during NAVA may simply be the elimination of wasted efforts. Coisel et al[142] showed no significant differences in ventilator respiratory rate between PSV and NAVA in their group of postoperative patients at baseline or after 24 hours. Beck et al showed a reduced neural respiratory rate during NAVA compared to PSV in preterm infants.[109]

Breathing pattern variability was higher during NAVA compared to PSV[142,143] and was held responsible for improved oxygenation.

All studies comparing NAVA to PSV show maintained clinical stability in terms of heart rate,[109,138] oxygen saturation in both adult[142] and neonatal populations,[109,141,144] minute ventilation,[98,137] and equivalent values of Pa_{CO_2} and partial pressure of arterial oxygen (Pa_{O_2}).[4,15,137,141,143,144] Coisel et al[142] reported an improved Pa_{O_2}/FI_{O_2} (fractional inspired oxygen concentration) ratio after 24 hours of NAVA in postoperative patients. In one pediatric study that measured hemodynamics, NAVA and PSV were equivalent.[138]

Neurally Adjusted Ventilatory Assist versus Conventional Ventilation, Limitation of Excessive-Assist

In rabbits with lung injury, Beck et al[103] demonstrated that a fourfold increase in PSV generated four times as much airway pressure, whereas, a fourfold increase in NAVA level resulted only in an increase from 3.5 cm H_2O to 7 cm H_2O, secondary to downregulation of Edi at higher NAVA levels. In adult and critically ill patients, progressively increasing the NAVA level is associated with a deactivation of the diaphragm at higher levels, such that delivered pressure and tidal volume do not increase excessively.[4,15,96,134,137,143] This is in clear contrast to studies with increasing PSV where the targeted pressure (and volume) increases as directed.

In general, the shape of the waveform during PSV is squarer than the triangular shape observed with NAVA.[4] Thus, for matched peak airway pressures, NAVA resulted in lower mean airway pressure as compared with NAVA.[4,15,98,103,143]

Breatnach et al[144] used NAVA for several hours in infants, and found, similar to what Allo et al[94] found in rabbits, that mean airway pressures decreased over time. In premature infants weighing <1500 g, Stein et al[145] also demonstrated reduced mean airway pressures over time when ventilated on NAVA.

High levels of PSV in association with involuntary triggering can produce hyperventilation, and may even eliminate the Edi completely (see Fig. 13-9). In contrast, high levels of NAVA do not eliminate the Edi (see Fig. 13-13).[102]

Neurally Adjusted Ventilatory Assist and Proportional-Assist Ventilation

NAVA and proportional-assist ventilation have not been directly compared. Both modes strive to improve assist delivery in spontaneously breathing patients and both have been found to improve synchrony and physiological variables compared to conventional modes.[140]

SUMMARY AND CONCLUSION

Many patients receiving conventional modes of ventilation receive substandard treatment, which has been associated with prolonged ventilator time. This is secondary to the limitations of conventional ventilators to detect and correct inappropriate timing and delivery of pressure.

Diaphragmatic electrical activity represents the neural output from respiratory centers, a signal which responds to respiratory demand. Diaphragmatic electrical activity is modulated by chemo, muscle, lung and other receptors, which act to ensure adequate ventilation while protecting the lungs. Simply monitoring the diaphragmatic electrical activity waveform is suitable for clinical monitoring of respiratory drive, neural breathing pattern, as well as patient–ventilator synchrony.

NAVA is a mode of ventilator assistance for spontaneously breathing patients, and uses the diaphragmatic electrical activity to trigger, to deliver assist, and to cycle-off the ventilator. Neural triggering and cycling-off improve patient–ventilator synchrony and are unaffected by leaks in the respiratory circuit. Because NAVA is modulated by neural feedback, assist is adjusted instantaneously in response to changes in patient respiratory demand.

NAVA introduces a new avenue for mechanical ventilation, and, different from the conventional deterministic approach of delivering static quantities of assistance, encourages personalized care that takes into account patient's individual differences and needs for every breath.

ACKNOWLEDGMENTS

Drs. Beck and Sinderby have made inventions related to neural control of mechanical ventilation that are patented. The license for these patents belongs to Maquet Critical Care. Future commercial uses of this technology may provide financial benefit to Drs. Beck and Sinderby through royalties. Dr. Beck and Dr. Sinderby each own 50% of Neurovent Research Inc. (NVR). NVR is a research and development company that builds equipment and catheters for research studies. NVR has a consulting agreement with Maquet Critical Care.

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PERMISSIVE HYPERCAPNIA

John G. Laffey
Brian P. Kavanagh

Carbon dioxide (CO_2) is the "waste product" of aerobic respiration. In health, arterial carbon dioxide tension (Pa_{CO_2}) is tightly regulated, with minute ventilation potently enhanced in response to small elevations in CO_2 tension. In critical illness its role is becoming better understood; indeed, in survivors of cardiac arrest, elevated CO_2 is associated with a higher incidence of reported near-death experiences.[1] Although usually well tolerated, hypercapnia traditionally has been considered to be an adverse event. In fact, the extent and severity of acidosis are predictive of adverse outcome in diverse clinical contexts, including cardiac arrest,[2,3] sepsis,[4–6] and in neonatal practice.[7] Traditional approaches to CO_2 management in the operating room and for patients with acute respiratory failure generally focused on the deleterious effects of hypercapnia, traditionally targeting therefore normocapnia or even hypocapnia.

This approach, however, has been increasingly questioned. The potential for high tidal volumes to injure the lung directly, a phenomenon termed *ventilator-induced lung injury,* is clear from experimental[8,9] and clinical[10–14]

studies. Current "protective" ventilator strategies mandate lower tidal volumes (V_T), and generally necessitate hypoventilation and tolerance of hypercapnia. This "permissive hypercapnia" has been accepted progressively in critical care for adult, pediatric, and neonatal patients requiring mechanical ventilation.

RATIONALE

The potential for mechanical ventilation to contribute to lung and systemic organ injury and to worsen outcome in patients with the acute respiratory distress syndrome (ARDS) is clear. The use of high V_T may cause injury via several mechanisms.[8,9] Increased mechanical stress may activate the cellular and humoral immune response directly in the lung.[8,15–17] Intrapulmonary mediators and pathogens, such as prostaglandins,[18] cytokines,[19] endotoxins,[20] and bacteria,[21] have been demonstrated to access the systemic circulation following high-stretch mechanical ventilation. The demonstration that mechanical ventilation may cause systemic organ dysfunction in animal models could explain in part the high rate of multiorgan failure in ARDS.[22] In current practice, hypercapnia is tolerated as the lesser of two evils so as to realize the benefits of lower tidal volumes.[23,24]

BASIC PRINCIPLES

Permissive Hypercapnia

Conventionally, the protective effect of ventilator strategies incorporating permissive hypercapnia is solely secondary to lower tidal volume, with hypercapnia being permitted so as to achieve this goal. Protective ventilator strategies that involve hypoventilation cause both limitation of lung stretch and elevation of arterial P_{CO_2}; thus, low tidal volume is distinct from elevated P_{CO_2} and, by manipulation of respiratory variables (frequency, V_T, dead space, and inspired CO_2), can to some extent be controlled separately.

Therapeutic Hypercapnia

If hypercapnia were proven to have independent benefit, then deliberately elevating Pa_{CO_2}, termed *therapeutic hypercapnia*, might provide an additional advantage over reducing V_T alone. Conversely, in patients managed with conventional permissive hypercapnia, adverse effects of elevated Pa_{CO_2} may be concealed by the benefits of lessened lung stretch. These issues are underscored by the fact that hypercapnia has adverse effects in some clinical settings, such as critically elevated intracranial pressure or pulmonary vascular resistance. Because patient outcome from critical illness may be related to systemic rather than lung injury, the clinician also must consider the effects on the brain and cardiovascular systems.

These issues have led several investigators to study the direct effects of induced hypercapnia per se in models of lung and systemic organ injury. These studies raise the potential that hypercapnia may exert active roles—beneficial or adverse—in the pathogenesis of inflammation and tissue injury. Thus, therapeutic hypercapnia may someday become a testable clinical approach to critically ill patients.[25]

Accidental Hypercapnia

This is reported most commonly in the context of errors in mechanical ventilation, such as circuit disconnects (or malconnections that permit rebreathing of exhaled gases).[26] A second cause is hypoventilation secondary to drug-induced respiratory depression,[27] severe respiratory failure (e.g., status asthmaticus),[28] or massive aspiration (e.g., grain inhalation).[29]

Determinants of Hypercapnia

The determinants of hypercapnia can be described as the balance of CO_2 production versus elimination.

$$Pa_{CO_2} \propto \frac{CO_2 \text{ production}}{CO_2 \text{ elimination}} + \text{inspired } [CO_2] \qquad (1)$$

Inspired CO_2 (FI_{O_2}) usually is negligible. Increased CO_2 production is a potential contributor to hypercapnia, particularly in hypermetabolic disease states such as hyperpyrexia. Therefore, for practical purposes, Pa_{CO_2} reflects the rate of elimination of CO_2; there are no common "physiologic" causes of hypercapnia. Hypercapnia is seen most commonly in the context of acute or chronic respiratory failure associated with reduced minute ventilation or increased dead space.

Effects on Alveolar Gas Exchange

The effects of hypercapnia on systemic oxygenation are discussed below. It is often forgotten that decreasing V_T can reduce oxygenation of pulmonary venous blood. This has two contributing elements: the composition of the alveolar gas and the increase in intrapulmonary shunt. Decreased V_T increases propensity to atelectasis, which increases intrapulmonary shunt.[30] In addition, when V_T is decreased, there is a proportionate decrease in alveolar ventilation ($\dot{V}_A$), resulting in an elevated alveolar CO_2 tension (Pa_{CO_2}). As pointed out by Bidani et al,[31] the alveolar gas equation

$$PA_{O_2} = FI_{O_2}(P_B - 47) - (Pa_{CO_2}/R) \qquad (2)$$

where PA_{O_2} is the alveolar oxygen tension, P_B is the barometric pressure, and R is the respiratory quotient, can be combined with the following relationship:

$$Pa_{CO_2} = (\dot{V}_{CO_2}/\dot{V}_A) \times P_B \qquad (3)$$

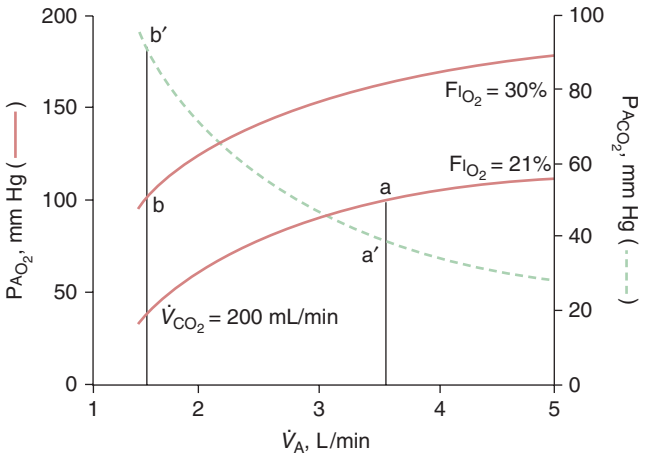

FIGURE 14-1 Relationship of alveolar oxygen tension ($P_{A_{O_2}}$) and alveolar ventilation ($\dot{V}_A$) at $F_{I_{O_2}}$ (0.21 and 0.30), calculated assuming a constant carbon dioxide production ($\dot{V}_{CO_2}$ of 200 mL/min). At either $F_{I_{O_2}}$, decreasing $\dot{V}_A$ to low values significantly reduces $P_{A_{O_2}}$, especially with very low levels of $\dot{V}_A$. A small increase in $F_{I_{O_2}}$ (21% to 30%) easily compensates for the fall in $P_{A_{O_2}}$ resulting from hypoventilation. *Solid line*, relationship between $P_{A_{O_2}}$ and $\dot{V}_A$; *dotted line*, relationship between Pa_{CO_2} and $\dot{V}_A$. (Modified, from Bidani A, Tzouanakis AE, Cardenas VJ Jr, Zwischenberger JB. Permissive hypercapnia in acute respiratory failure. *JAMA*. 1994;272: 957–962.)

where $\dot{V}_{CO_2}$ is CO_2 production, to express alveolar O_2 as a function of $F_{I_{O_2}}$ and $\dot{V}_A$:

$$P_{A_{O_2}} = F_{I_{O_2}}(P_B - 47) - (\dot{V}_{CO_2}/\dot{V}_A) \times (P_B/R) \qquad (4)$$

Thus, with the exception of very low levels of minute ventilation, increases in $\dot{V}_A$ have minor impact on alveolar—and consequently pulmonary venous—oxygenation. In contrast, modest increases in $F_{I_{O_2}}$ can have a far more significant impact on oxygenation and can compensate easily for reduced V_A (Fig. 14-1).[31]

PHYSIOLOGIC EFFECTS

The physiologic effects of hypercapnia are complex and incompletely understood, with direct effects often counterbalanced by indirect effects. To understand hypercaponia in critically ill patients, the effects of pH and Pa_{CO_2} need to be considered together.

Carbon Dioxide versus Hydrogen Ion

Hypercapnia generally results in acidosis (greater H^+ concentration) via its spontaneous and carbonic anhydrase–catalyzed combination with water to form carbonic acid. The protons thus generated can react with titratable groups in certain amino acids, resulting in structural changes in many proteins and enzymes in cell membranes and cellular aqueous environments.[32] Because acidosis suppresses most cellular functions, the body uses a number of strategies to defend its intracellular and extracellular pH within remarkably narrow limits.[25] The intracellular acidosis produced by hypercapnia may be corrected within a few hours, as opposed to 1 to 2 days for renal compensation.[33] This buffering occurs via active cell-membrane ion transporters that extrude protons and exchange them for extracellular sodium.

During hypercapnia, CO_2 per se may react directly with some free amine groups in proteins to form carbamate residues.[34–36] This binding of CO_2 also modifies protein structure and function and may explain some of the differences in the observed effects of CO_2 and H^+ when both lead to equal changes in pH. A good example is the Bohr effect, where increased Pa_{CO_2} results in a rightward shift of the hemoglobin (Hb)-O_2 dissociation curve, reflecting a lowered affinity of hemoglobin for O_2.

Effects of Hypercapnia on the Lung

PULMONARY VASCULAR EFFECTS

In contrast to the systemic circulation, hypercapnic acidosis produces vasoconstriction and increased resistance in the pulmonary circulation;[37] such effects are exacerbated in the setting of preexisting pulmonary hypertension.[37] Hypercapnic vasoconstriction generally is weaker than hypoxic pulmonary vasoconstriction; its more important effect may be in augmenting hypoxic vasoconstriction.[32] Little is understood about how CO_2 acts on pulmonary vascular smooth muscle.

PULMONARY GAS EXCHANGE

Acute respiratory acidosis can alter shunt via autonomic or direct effects on pulmonary vasculature and on the airways. Acidosis enhances hypoxic pulmonary vasoconstriction and therefore usually reduces shunt and increases partial pressure of arterial oxygen (Pa_{O_2}), whereas alkalosis has the opposite effect.[38] CO_2 administration improves matching of ventilation and perfusion and increases arterial oxygenation by this mechanism in both health[39–41] and disease.[42] A dose–response relationship exists wherein increased $F_{I_{CO_2}}$ results in progressive augmentation of Pa_{O_2}.[40,43] In fact, administration of CO_2 during late inspiration—limiting its exposure to the conducting airways—results in most of the beneficial pulmonary effects (i.e., $\dot{V}_A/\dot{Q}$ matching and oxygenation) and less systemic acidosis (Fig. 14-2).[44] Permissive hypercapnia in patients with ARDS appears to increase shunt secondary to a reduction in V_T and airway closure rather than from elevated CO_2 levels.[45]

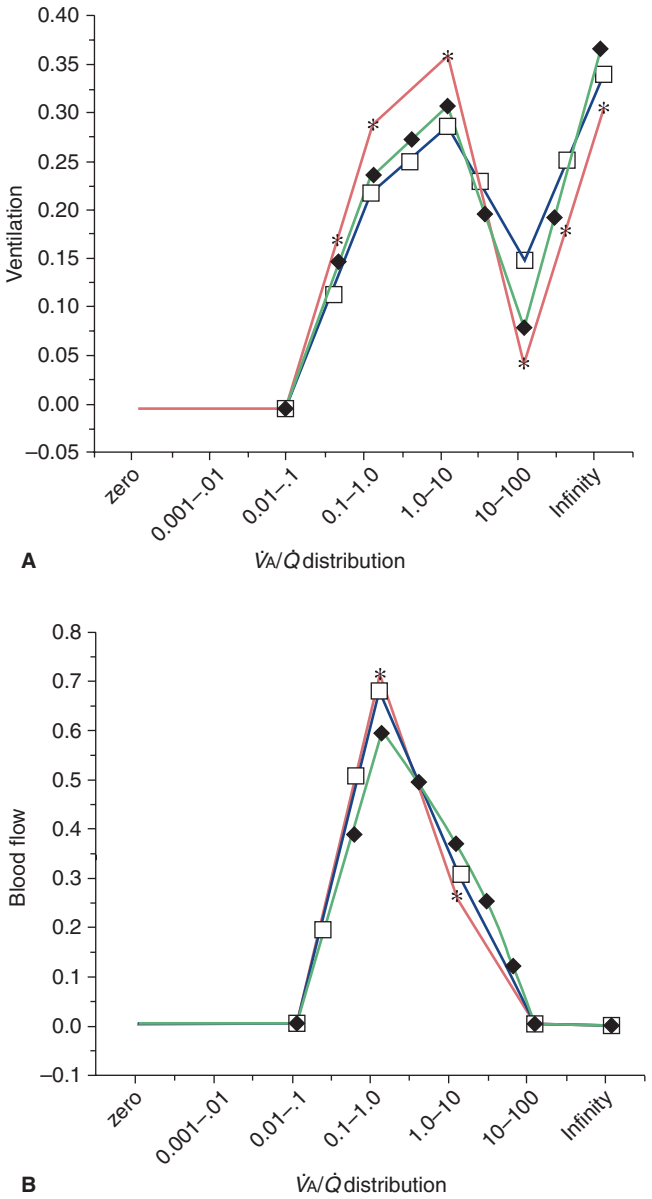

FIGURE 14-2 Effects of room air and inspired CO_2 on the distribution of ventilation (**A**) and of perfusion (**B**). The lowest values of $\dot{V}_A/\dot{Q}$ correspond to regions of intrapulmonary shunt and the highest to regions of alveolar dead space. Addition of CO_2 to inspired gas (throughout the respiratory cycle, *; restricted to late inspiration, □) resulted in more homogeneous ventilation and perfusion compared to no added CO_2 (room air ♦). $\dot{V}_A/\dot{Q}$, ratio of ventilation to perfusion. (Reproduced, with permission, from Brogan TV, Robertson HT, Lamm WJ, Souders JE, Swenson ER. Carbon dioxide added late in inspiration reduces ventilation–perfusion heterogeneity without causing respiratory acidosis. *J Appl Physiol.* 2004;96:1894–1898.)

AIRWAY TONE

Hypercapnia has been reported to either increase[46] or decrease[47] airway resistance. These effects may be explained the direct dilation of small airways and the indirect (i.e., vagally mediated) large airway constriction.[32] These opposing but balanced actions may produce little net alteration in airway resistance.[48]

LUNG COMPLIANCE

Parenchymal lung compliance increases in response to hypercapnic acidosis. This may be secondary to increased surfactant secretion or more effective surface tension–lowering properties under acidic conditions.[49]

PHYSIOLOGIC ROLE OF HYPERCAPNIA IN THE LUNG

In health, CO_2 alters lung compliance as well as pulmonary vascular and airway tone.[32] The combined effect of small airways constriction and decreased compliance explains the phenomenon of hypocapnic bronchoconstriction and pneumoconstriction that occurs following acute regional pulmonary artery occlusions.[50,51] These effects either may alter regional ventilation to keep pace with a primary change in perfusion or may alter regional perfusion to match a primary change in ventilation.[32]

Central Nervous System Effects of Hypercapnia

NEUROVASCULAR REGULATION

Hypercapnic acidosis causes cerebral vasodilation. The increase in cerebral blood flow and blood volume must be considered carefully in any patient at risk for raised intracranial pressure.[25] The mechanism of cerebral vasodilation depends on the arterial bed and type of artery. Nakahata et al[52] demonstrated that hypercapnic acidosis induced cerebral precapillary arteriolar vasodilation, which depended on acidosis rather than CO_2. They demonstrated that the adenosine triphosphate (ATP)-sensitive potassium channel plays a major role. Others have suggested roles for both ATP-sensitive and calcium-activated potassium channels[53] and the neuronal isoform of nitric oxide synthase.[54]

REGULATION OF VENTILATION

Hypercapnia is a potent regulator of ventilation. Mild hypercapnia (increase in end-tidal pressure of carbon dioxide [P_{CO_2}] of 8 mm Hg) in healthy volunteers resulted in a compensatory metabolic alkalosis over 24 to 48 hours that was maintained over the course of exposure.[55] Although there was a modest increase in ventilatory chemosensitivity to acute hypoxia, no change occurred in response to acute elevations in CO_2.

CEREBRAL TISSUE OXYGENATION

Hare et al[40] demonstrated that hypercapnic acidosis increases cerebral tissue partial pressure of oxygen (P_{O_2}) through augmentation of Pa_{O_2} and increased cerebral blood flow (Fig. 14-3), although, studies in patients suggest that in the presence of sepsis, hypercapnia may impair cerebral

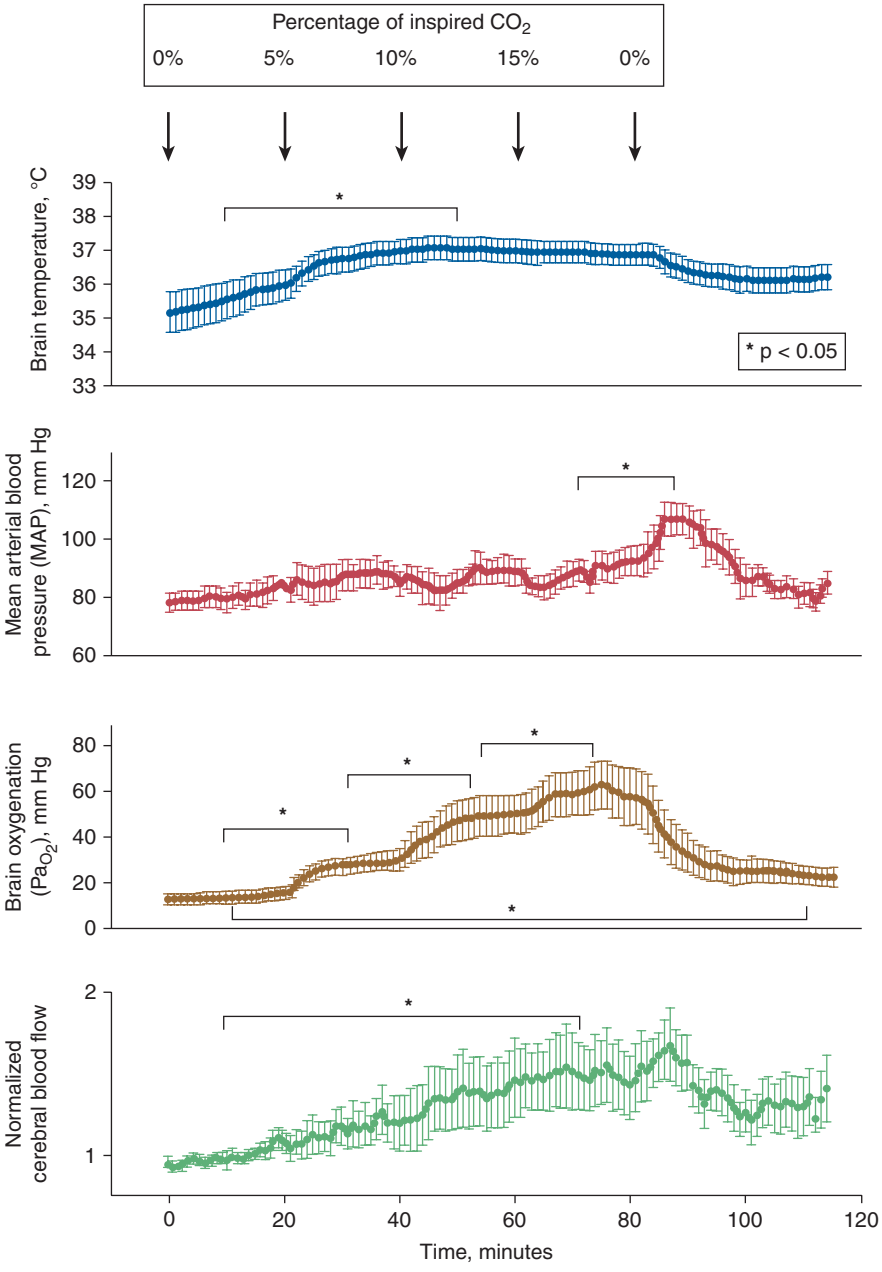

FIGURE 14-3 Increases in inspired CO_2 concentration produce progressive increases in brain tissue O_2 tension and cerebral perfusion. (Reproduced, with permission, from Hare GM, Kavanagh BP, Mazer CD, et al. Hypercapnia increases cerebral tissue oxygen tension in anesthetized rats. *Can J Anaesth.* 2003;50:1061–1068.)

autoregulation.[56] The faster recovery times associated with administered CO_2 in animals[57] and patients[58] following general anesthesia may reflect increased perfusion and anesthetic washout.

Neuromuscular Effects of Hypercapnia

DIAPHRAGMATIC FUNCTION

Recent studies highlight the potential for hypercapnia to exert deleterious neuromuscular effects. Rat diaphragms exposed to prolonged hypercapnia (7.5% CO_2 for 6 weeks) undergo significant changes,[59] including depressed diaphragmatic tension and time to contraction and relaxation, and altered diaphragmatic composition (i.e., increased slow-twitch and decreased fast-twitch fibers). In fact, even short-term exposure (7% inspired CO_2) may impair neuromuscular function transiently through effects on afferent transmission or synaptic integrity in healthy volunteers.[60] Relatively brief exposures to hypercapnia may also cause reversible impairment of diaphragmatic muscle contractility.[61]

Cardiovascular Effects of Hypercapnia

HEMODYNAMIC EFFECTS

Hypercapnic acidosis directly reduces the contractility of cardiac and vascular smooth muscle.[32] This is counterbalanced by the hypercapnic-mediated sympathoadrenal effects causing increased preload, increased heart rate, and decreased afterload, which lead to a net increase in cardiac output.[32] In intact animals and human subjects, myocardial contractility and cardiac output increase during hypercapnia because of increased sympathetic activity.[62]

EFFECTS ON TISSUE OXYGENATION

Hypercapnia results in a complex interaction of altered cardiac output, hypoxic pulmonary vasoconstriction, and intrapulmonary shunt, with a net increase in Pa_{O_2}. Because hypercapnia generally elevates cardiac output, global O_2 delivery is increased.[63] Regional (including mesenteric) blood flow also is increased,[64] thereby increasing organ oxygen delivery. Because hypercapnia and acidosis shift the Hb-O_2 dissociation curve rightward and may cause an elevation in hematocrit,[65] tissue oxygen delivery is further facilitated. Acidosis may reduce cellular respiration and oxygen consumption,[66] which further correct supply–demand imbalance, in addition to enhancing O_2 delivery. Acidosis may protect against ongoing tissue production of *further* organic acids by a negative-feedback loop, providing a mechanism of cellular metabolic shutdown at times of nutrient shortage (e.g., ischemia).[67] In addition, hypercapnic acidosis increases P_{O_2} in subcutaneous tissues and in the intestinal wall.[68]

Hypercapnia and Development

Hypercapnia may exert complex effects on development,[69] such as inhibition of embryonic morphogenesis, as well as egg laying and hatching in the *Drosophila*.[70] It induces aberrant motility and slows development, decreases fertility, and increases life span in *Caenorhabditis elegans*.[71] Tissue effects in neonates may differ from those in adults as exposure to hypercapnia for 2 weeks reduced expression of several matrix proteins in infant, but not in adult, lungs,[72] and sustained exposure in the neonate may cause microvascular injury and impair brain growth via induction of nitrative stress.[73] In the neonatal lung, hypercapnia may increase alveolar budding, but may also increase central nervous system apoptosis.[74]

CELLULAR AND MOLECULAR EFFECTS OF HYPERCAPNIA

A clear understanding of cellular and biochemical mechanisms underlying the effects of hypercapnia is essential for successful translation of laboratory findings to the bedside, as well as for prediction of potential side effects.

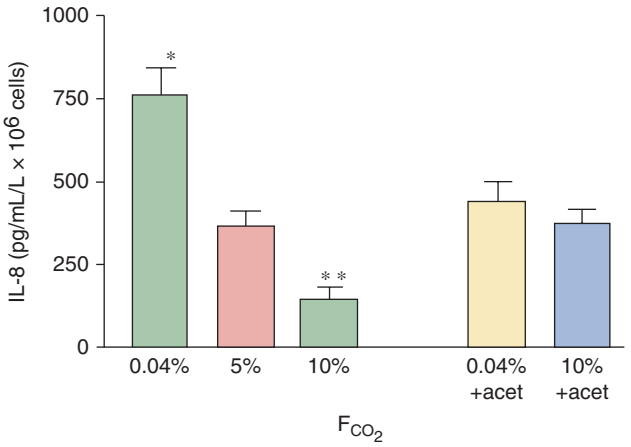

FIGURE 14-4 Hypercapnia (10% CO_2) inhibits, whereas hypocapnia (0.04% CO_2) potentiates, the release of interleukin (IL)-8 from endotoxin-stimulated neutrophils. Incubation with acetazolamide, which impairs the effect of extracellular CO_2 on intracellular pH, abolished the influence of extracellular CO_2. (Reproduced, with permission, from Coakley RJ, Taggart C, Greene C, McElvaney NG, O'Neill SJ. Ambient pCO_2 modulates intracellular pH, intracellular oxidant generation, and interleukin-8 secretion in human neutrophils. *J Leukoc Biol.* 2002;71:603–610.)

Effects on the Immune Response

Hypercapnia and acidosis modulate diverse components of the host immune response, particularly cytokine and chemokine signaling, as well as neutrophil and macrophage function.

CHEMOKINE AND CYTOKINE SIGNALING

Hypercapnia interferes with coordination of the immune response by modulating signaling among immune effector cells. Hypercapnic acidosis inhibits neutrophil release of interleukin (IL)-8 following endotoxin stimulation[75] (Fig. 14-4), reduces release of tumor necrosis factor-α (TNF-α) and IL-1 from stimulated macrophages in vitro,[76] and inhibits IL-6 and TNF-α in macrophages[77] as well as in whole (human) blood.[78] Hypercapnic acidosis reduces TNF-α concentrations in the bronchoalveolar fluid following in vivo pulmonary ischemia-reperfusion.[79] Such effects on cytokines and chemokines may be sustained; for example, intraperitoneal macrophages demonstrate impaired TNF-α production for up to 3 days following exposure to hypercapnia.[80,81] These actions appear to be mediated, at least in part by inhibition of the transcriptional regulator nuclear factor kappa B (NF-κB).[82]

THE CELLULAR IMMUNE RESPONSE

Hypercapnia may impact the cellular immune response via several mechanisms, including impaired coordination of cytokine signaling as well as inhibition of neutrophil expression of key inflammatory and adhesion molecules (e.g., chemokines, selectins, and intercellular adhesion molecules).[75] Neutrophil chemotaxis may be directly impaired.[83] These

effects also occur in vivo as lung neutrophil recruitment is inhibited during ventilator-induced[84] and endotoxin-induced[85] lung injury. Hypercapnic acidosis directly impairs neutrophil[86] and macrophage[70] phagocytosis, effects that appear to be a function of the acidosis rather than the CO_2 tension.[87]

The cellular and molecular mechanisms underlying the inhibitory effects of hypercapnic acidosis in the neutrophil and macrophage are increasingly understood. Both hypercapnia and acidosis impair neutrophil intracellular pH regulation. Intracellular pH decreases when neutrophils are activated by immune stimuli[75] and, where pH is normal, there tends to be a recovery in neutrophil intracellular pH (toward normal). Hypercapnia decreases extracellular and intracellular pH in the local milieu, resulting in a rapid fall in neutrophil cytosolic pH,[88] potentially overwhelming the capacity of phagocytes—especially when activated[89]—to regulate cytosolic pH.

Free Radical Generation and Activity

In common with many biologic systems, the enzymes that produce oxidizing free radicals function optimally at physiologic pH. Oxidant generation by both basal and stimulated neutrophils appears to be regulated by ambient CO_2 levels, with oxidant generation reduced by hypercapnia and increased by hypocapnia.[75] Production of superoxide by stimulated neutrophils in vitro is decreased at acidic pH.[90] Hypercapnic acidosis inhibits the generation of oxidants such as superoxide by neutrophils[75] and by macrophages.[91] Although free radicals such as superoxide have been implicated in the pathogenesis of injury in acute lung injury and/or ARDS, effective phagocyte generation of free radicals is necessary for killing of ingested bacteria. The finding that hypercapnia reduces endotoxin-induced pulmonary oxidant production[92] reinforces concerns that neutrophil-mediated bacterial killing might be critically inhibited.

In the brain, hypercapnic acidosis attenuates glutathione depletion and lipid peroxidation,[93] which reflect free-radical activity and tissue damage, respectively. In the lung, hypercapnic acidosis reduces free-radical tissue injury following ischemia–reperfusion[79] and attenuates the production of the higher oxides of nitric oxide, such as nitrate and nitrite, following both ventilator-induced[94] and endotoxin-induced[85] injury. Hypercapnic acidosis inhibits injury mediated by xanthine oxidase and directly inhibits the enzyme.[95] Interactions between CO_2 and free radicals may also have fundamental effects as recent work indicates that hypercapnia may cause signaling, in part, by cellular oxidation.[96]

PEROXYNITRITE-MEDIATED TISSUE NITRATION

Specific concerns exist regarding the potential for hypercapnia to potentiate tissue nitration by peroxynitrite, a potent free radical. Peroxynitrite is produced in vivo largely by the reaction of nitric oxide with superoxide radical and causes tissue damage by oxidizing a variety of biomolecules and by nitrating phenolic amino acid residues in proteins.[97] The potential for buffered hypercapnia to promote the formation of nitration products from peroxynitrite has been clearly demonstrated in vitro.[98,99] The potential, however, for hypercapnic acidosis to promote nitration of lung tissue in vivo depends on the injury. For example, hypercapnic acidosis decreased tissue nitration following pulmonary ischemia–reperfusion,[79] but increased nitration following endotoxin exposure[85,98,100] (Fig. 14-5).

Regulation of Gene Expression

Some effects of hypercapnia may be mediated by regulation of gene expression. Several unidentified proteins are upregulated by hypercapnia in the normal lung,[101] and hypercapnia may regulate this process at the level of gene transcription via altering the half-life of messenger RNA or by modulating protein synthesis. Molecular mechanisms underlying hypercapnic acidosis–mediated control of gene transcription include membrane acid-sensing ion channels and acid-responsive gene promoter regions.[102–104] Furthermore, the coding for certain proteins for messenger RNA has pH-sensitive regions.[103]

Hypercapnic acidosis has been demonstrated to regulate the expression of genes central to the inflammatory response in models of cell injury. NF-κB is a key regulator of the expression of multiple genes involved in inflammatory response, and its activation represents a pivotal early step in activation of the inflammatory response.[105] NF-κB is found in the cytoplasm in an inactive form bound to inhibitory proteins called *inhibitory protein* κB (IκB). The important isoforms are IκB-α and IκB-β. IκB proteins are phosphorylated by the IκB kinase complex and subsequently degraded, thus allowing NF-κB to translocate into the nucleus, bind to specific promoter sites, and activate target genes.[105] Hypercapnic acidosis inhibits endotoxin-induced NF-κB activation and DNA binding in pulmonary endothelial cells by decreasing IκB-α degradation[82] (Fig. 14-6). Hypercapnic acidosis also suppressed endothelial production of intercellular adhesion molecule-1 and IL-8, which are critically regulated by the NF-κB pathway.[82] Importantly, although inhibition of NF-κB may have important antiinflammatory effects, it may also reduce repair following injury.[106]

Effects on Recovery and Repair Mechanisms

EXTRACELLULAR FLUID CLEARANCE

Hypercapnia appears to inhibit epithelial fluid transport, a potentially important mechanism by which alveolar edema is cleared during lung injury.[107] The effect appears to be mediated via hypercapnia per se and seems to be independent of

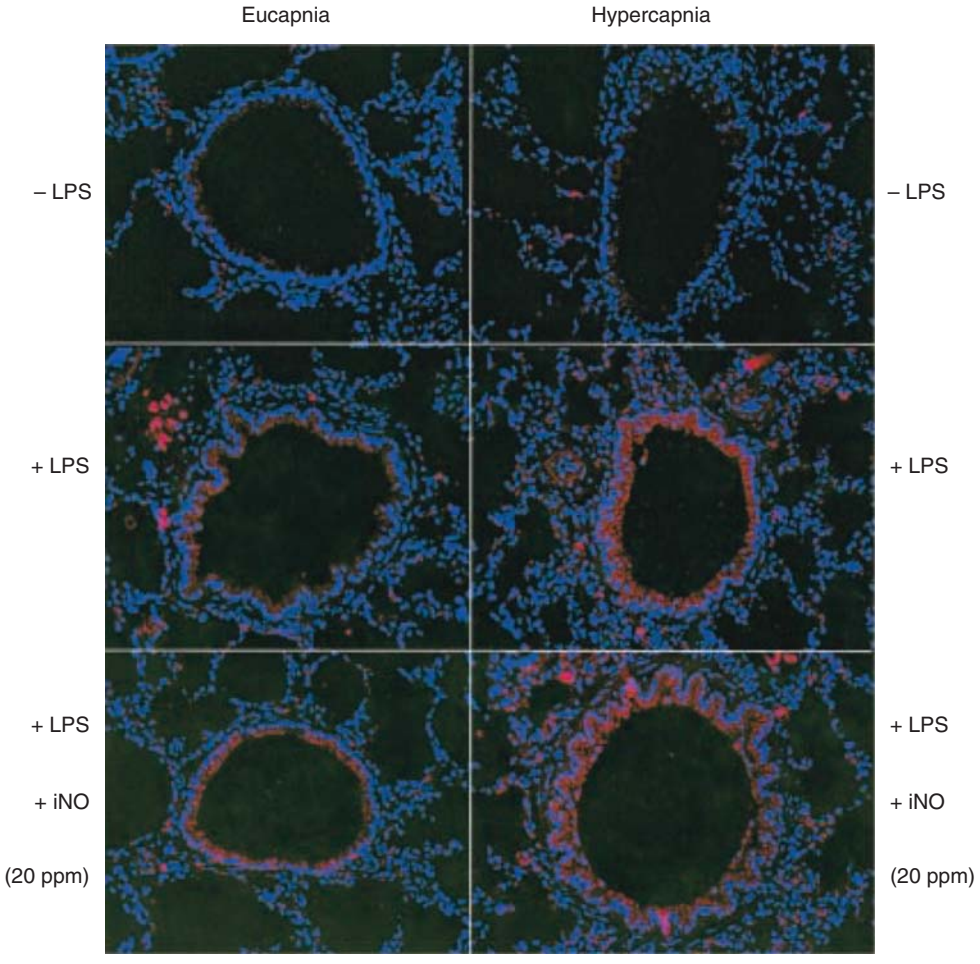

FIGURE 14-5 Hypercapnia and inhaled nitric oxide significantly increased the formation of 3-nitrotyrosine following lipopolysaccharide pretreatment. *HC*, Hypercapnia; *iNO*, inhaled nitric oxide; *LPS*, lipopolysaccharide. (Reproduced, with permission, from Lang JD, Figueroa M, Sanders KD, Aslan M, Liu Y, Chumley P, Freeman BA. Hypercapnia via reduced rate and tidal volume contributes to lipopolysaccharide-induced lung injury. *Am J Respir Crit Care Med.* 2005;171:147–157.)

ambient pH.[107] The mechanism of action involves adenosine monophosphate (AMP)-activated protein kinase, which, when activated by hypercapnia, promotes Na, K-ATPase endocytosis.[108] The decrement in alveolar fluid clearance can be prevented by β-adrenergic agonists or cyclic adenosine monophosphate.[108] More recent studies have also implicated extracellular signal-regulated kinase in the activation of AMP-activated protein kinase by hypercapnia, leading to Na, K-ATPase endocytosis.[109]

EPITHELIAL WOUND REPAIR

Hyercapnia appears to inhibit pulmonary epithelial-cell resealing[110] following ventilator-induced lung injury via a pH-dependent mechanism,[111] and also inhibits the closure of pulmonary epithelial wounds via a mechanism that involves reduced activation of NF-κB, which, in turn, inhibits cellular migration.[106] These effects of hypercapnia on wound healing appear to be a function of CO_2 tension rather than acidosis.

EFFECTS IN THE SETTING OF ORGAN INJURY

Hypercapnia and the Injured Lung

INSIGHTS FROM LABORATORY DATA

Ischemia–Reperfusion Injury. Hypercapnic acidosis attenuates the increased lung permeability consequent to free-radical-mediated lung injury (Fig. 14-7).[95] Although hypercapnic acidosis reduces xanthine oxidase activity,[95] this does not account for all its protective effects.[112] Subsequent in vivo studies confirmed and further characterized the protective effects of hypercapnic acidosis in ischemia–reperfusion lung injury. Hypercapnic acidosis preserved lung mechanics, attenuated protein leakage and reduced pulmonary edema in addition to preserving oxygenation in comparison with control conditions following in vivo pulmonary ischemia–reperfusion,[79] as well as in lung injury secondary to splanchnic reperfusion.[43] Such protective

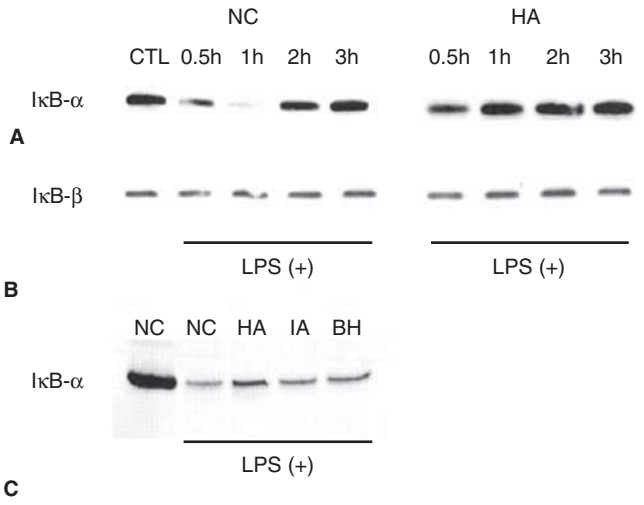

FIGURE 14-6 Hypercapnia suppresses the degradation of IκB-α (**A**) but not IκB-β (**B**) following exposure to lipopolysaccharide, thereby inhibiting the nuclear translocation of NF-κB and downstream cytokine production. The effects of isocapnic acidosis and buffered hypercapnia (**C**) on IκB-α degradation were intermediate between normocapnic control and hypercapnic acidosis conditions. *BH*, buffered hypercapnia; *HA*, hypercapnic acidosis; *IA*, isocapnic acidosis; *LPS*, lipopolysaccharide; *NC*, normocapnia; *NF-κB*, nuclear factor κB. (Reproduced, with permission, from Takeshita K, Suzuki Y, Nishio K, et al. Hypercapnic acidosis attenuates endotoxin-induced nuclear factor-[kappa]B activation. *Am J Respir Cell Mol Biol*. 2003;29:124–132.)

effects of hypercapnic acidosis are not mediated via decreases in pulmonary artery resistance; on the contrary, protection occurred despite elevated pulmonary artery pressures.[43]

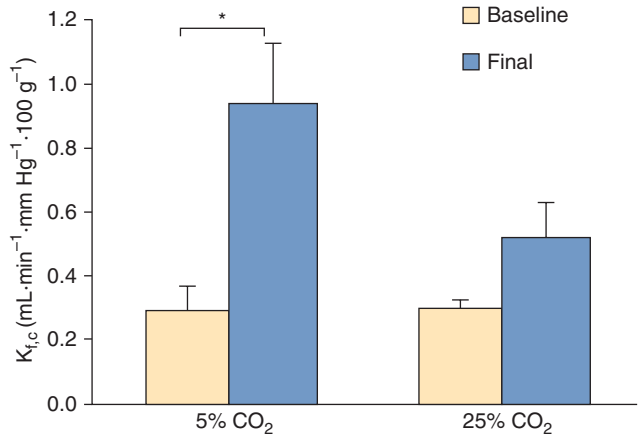

FIGURE 14-7 Effects of CO_2 on ischemia–reperfusion in the isolated perfused lung. Pulmonary microvascular permeability is significantly less following reperfusion in the presence of hypercapnia (25% CO_2) compared with normocapnia (5% CO_2). $K_{f,c}$, pulmonary microvascular filtration coefficient. (Reproduced, with permission, from Shibata K, Cregg N, Engelberts D, et al. Hypercapnic acidosis may attenuate acute lung injury by inhibition of endogenous xanthine oxidase. *Am J Respir Crit Care Med.* 1998;158(5 Pt 1):1578–1584.)

Ventilation-Induced Lung Injury. The direct effects of hypercapnic acidosis in ventilator-induced lung injury have been examined in both ex vivo and in vivo models. The addition of inspired CO_2 decreased ventilator-induced lung injury in the isolated rabbit lung,[94] the in vivo rabbit[84] (Fig. 14-8), and in the in vivo mouse.[113] Not all the data are positive. Supplemental CO_2 exhibits more modest protective effects in the setting of more clinically relevant tidal stretch. Strand et al[114] demonstrated that significant hypercapnic acidosis (mean Pa_{CO_2} of 95 mm Hg) was well tolerated in preterm lambs and also appeared to reduce lung injury. In the context of a clinically relevant high V_T adult model (V_T 12 mL/kg, positive end-expiratory pressure 0 cm H_2O), Laffey et al[43] reported that hypocapnia was deleterious and conversely that hypercapnic acidosis was protective. In contrast, inspired CO_2 did not attenuate lung injury in an atelectasis-prone model that mimics neonatal respiratory distress syndrome.[115] Taken together, these findings suggest that while hypercapnic acidosis substantially attenuates injury secondary to excessive stretch, its effects in the context

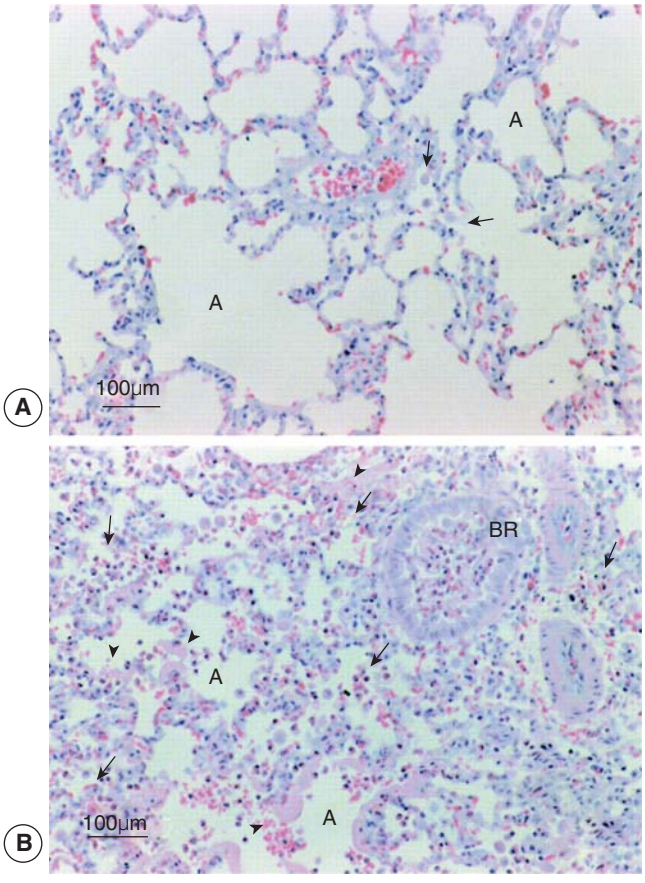

FIGURE 14-8 Lung histology following high tidal volume ventilation in the in vivo rabbit. The extent of histologic injury is far less with addition of inspired CO_2 (Pa_{CO_2} of 80 to 100 mm Hg) (**A**) than with a Pa_{CO_2} of 40 mm Hg (**B**). (Sinclair SE, Kregenow DA, Lamm WJ, Starr IR, Chi EY, & Hlastala MP. Hypercapnic acidosis is protective in an in vivo model of ventilator-induced lung injury. *Am J Respir Crit Care Med. 2002*;166:403–408.)

of more clinically relevant lung stretch or, with extensive atelectasis, may be more modest.

Pulmonary Hypertension. In neonatal models, chronic hypercapnia attenuates the development of hypoxia-induced pulmonary hypertension[116,117] in part via augmentation of L-arginase expression resulting in increased local nitric oxide[117] and in part via inhibition of endothelin expression.[118] Although no mechanism was established, comparable effects were described wherein chronic hypercapnia attenuated the development of long-term hypoxia-induced pulmonary hypertension in the rat.[119]

Pulmonary Sepsis. The mechanisms of lung injury in sepsis-induced ARDS are quite distinct from those in "sterile" experimental models. Lipopolysaccharide, a key endotoxin of gram-negative bacteria, initiates lung injury by activating a specific receptor, the Toll-like receptor-4.[120] Hypercapnic acidosis can reduce the severity of lung injury induced by local administration of endotoxin.[85] Mechanisms of sepsis-induced injury, however, include damage to host tissue from the inflammatory response, as well as damage caused by direct bacterial invasion.[24,85] In preclinical sepsis models, the effects of hypercapnia appear to depend also on the severity—and phase—of the injury. Although hypercapnic acidosis did not alter the severity of mild injury induced by instilled *Escherichia coli*,[121] it did reduce the severity of more severe lung injury induced by the same organism.[122] In the setting of established *E. coli* pneumonia, short-term hypercapnia reduced lung injury, particularly when effective antimicrobial therapy was used.[122] In contrast, in the setting of prolonged *E. coli*-induced pneumonia (i.e., 72 hours), ongoing environmental hypercapnia worsened the severity of the lung injury.[86] Here, prolonged hypercapnia reduced bacterial killing, in part by reduced neutrophil phagocytic activity (Fig. 14-9).[86] Subsequent studies confirmed that these effects in prolonged infection appear to be a function of the hypercapnia and not acidosis, as buffered hypercapnia also worsened infection-induced injury.[87] Nonetheless, deleterious effects of hypercapnia in the setting of prolonged pneumonia were completely ablated by antimicrobial therapy.[86]

Concerns regarding harm caused by hypercapnia in prolonged lung infection are reflected in an elegant series of studies in the *Drosophilia*[70] demonstrating an increased mortality in infections with multiple different bacterial pathogens, including *Staphylococcus aureus*, *Enterococcus faecalis*,

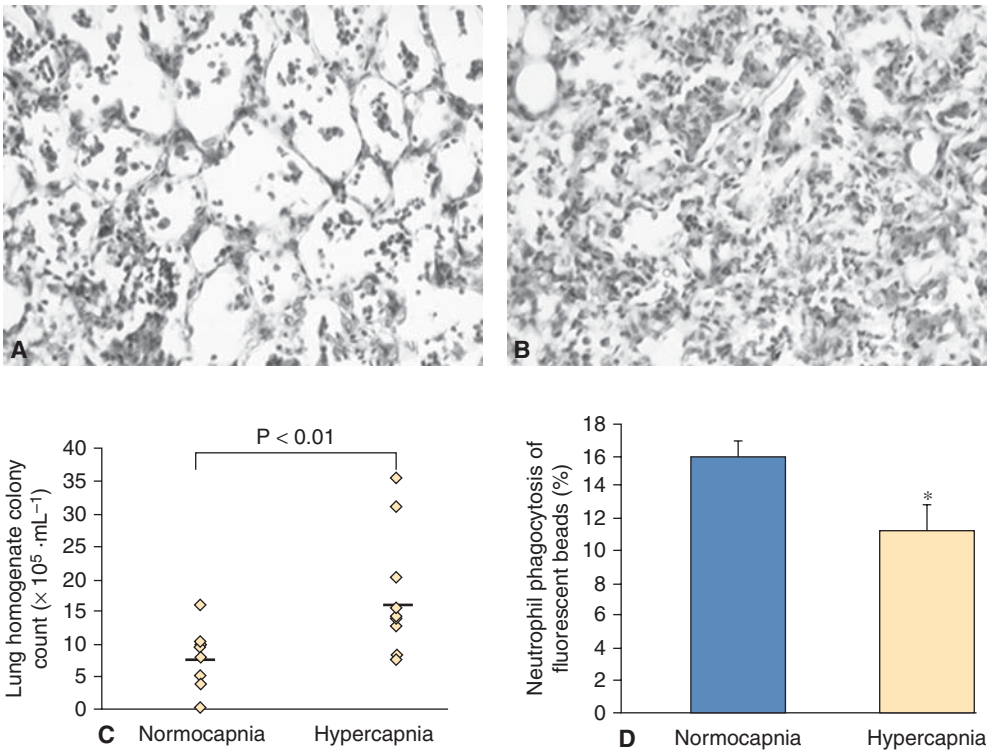

FIGURE 14-9 Sustained hypercapnic acidosis worsens pneumonia-induced lung injury and increases bacterial load. *Panels A* and *B* represent photomicrographs of section of lung tissue from a lung exposed to normocapnia and hypercapnia respectively, 2 days after intratracheal infection with *E. coli*. Animals exposed to environmental hypercapnia (inspired CO_2 5%) sustained a more severe lung injury. *Panel C* demonstrates greater bacterial load in lungs from *E. coli* infected groups exposed to hypercapnia compared to normocapnia. *Panel D* demonstrates that neutrophils from rats exposed to hypercapnia have a reduced ability to phagocytose fluorescent latex beads compared to neutrophils from normocapnic rats. (Modified, with permission, from O'Croinin DF, Nichol AD, Hopkins N, et al. Sustained hypercapnic acidosis during pulmonary infection increases bacterial load and worsens lung injury. *Crit Care Med*. 2008;36:2128–2135.)

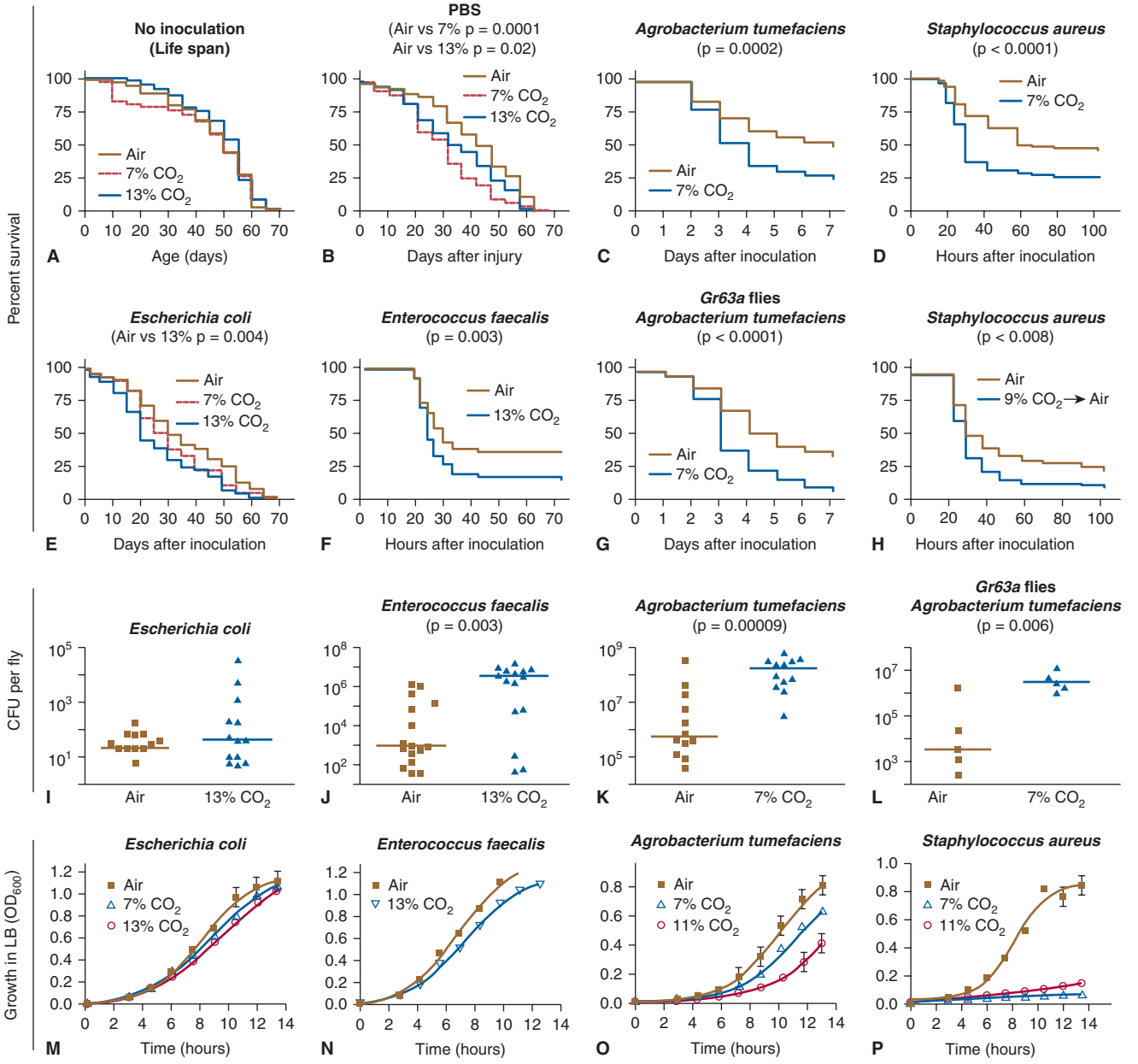

FIGURE 14-10 Prolonged hypercapnia decreases resistance of *Drosophila* to specific bacterial infections. *Panel A.* Hypercapnia does not affect *Drosophila* life span. *Panels B* to *H.* Hypercapnia slightly increases death of flies inoculated with sterile phosphate-buffered saline (*PBS*) (*Panel B*) or with *E. coli* (*Panel E*), but significantly increases mortality at CO_2 levels as low as 7% after inoculation with *A. tumefaciens* (*Panel C*), the human pathogen *S. aureus* (*Panel D*), and the *Drosophila* natural pathogen *E. faecalis* (*Panel F*). Immune suppression does not require the neuronal CO_2 receptor Gr63a (*Panel G*). *Panel H.* Pretreatment of flies with 9% CO_2 before *S. aureus* infection in air is sufficient to increase mortality, even when flies are cultured in air after inoculation. For *Panels A* to *H*, unless otherwise noted, flies were exposed to indicated CO_2 level for 24 hours before inoculation and returned to hypercapnia until end of assay. We show representative results for the lowest CO_2 levels at which significant effects on mortality were consistently observed. *Panels I* to *L.* Hypercapnia increases the bacterial load for strains causing increased mortality during hypercapnia. *Horizontal lines* show medians. *Panels M* to *P.* Effects of hypercapnia on bacterial growth. Note that *S. aureus* growth is dramatically reduced in 7% CO_2 even though hypercapnia increases mortality of flies infected with *S. aureus*. (Reproduced, with permission, from Helenius IT, Krupinski T, Turnbull DW, et al. Elevated CO_2 suppresses specific *Drosophila* innate immune responses and resistance to bacterial infection. *Proc Natl Acad Sci U S A*. 2009;106(44):18710–18715.)

and *E. coli*.[70] The effects appear to be a function of the elevated CO_2 (not lowered pH) and are mediated in part via suppression of Rel/NF-κB, an important conserved pathway (Fig. 14-10).[70]

Systemic Sepsis. In a sheep model of established sepsis, hypercapnia augmented hemodynamics (comparably to dopamine) and resulted in increased systemic oxygenation.[123] In a small animal model of established systemic sepsis

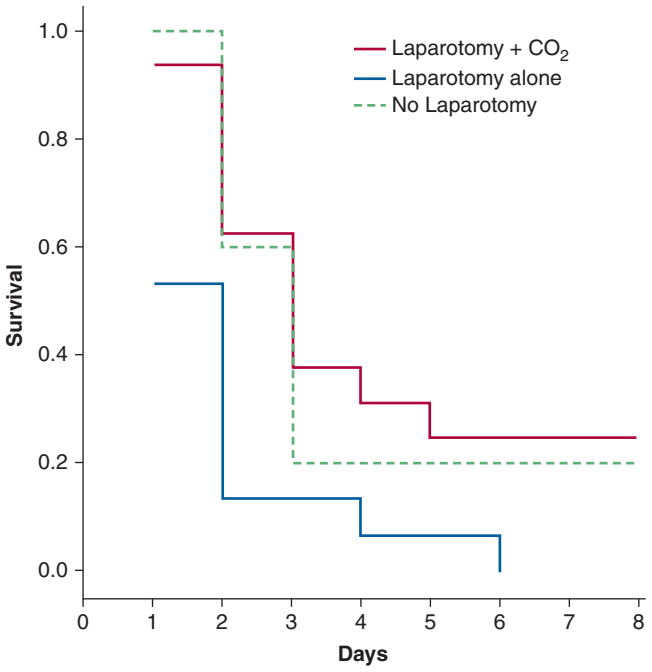

FIGURE 14-11 Insufflation of CO_2 into the peritoneal cavity improves survival following cecal ligation and puncture-induced systemic sepsis. Animals were first subjected to cecal ligation and puncture. Four hours later, animals underwent a laparotomy and induction of a CO_2 pneumoperitoneum (laparotomy + CO_2), laparotomy alone, or no laparotomy, and survival was determined over the following 8 days. (Modified, with permission, from Metzelder M, Kuebler JF, Shimotakahara A, et al. CO_2 pneumoperitoneum increases survival in mice with polymicrobial peritonitis. *Eur J Pediatr Surg.* 2008;18:171–175.)

induced by cecal ligation and perforation, hypercapnia had similar effects on hemodynamics.[124] In contrast to established pulmonary sepsis,[86] hypercapnia reduced the lung injury—in terms of histology and lung mechanics—associated with cecal ligation and perforation[124]; importantly, in this setting, hypercapnia did not increase bacterial load in the lung, bloodstream, or peritoneal cavity.[124] Buffering the hypercapnic acidosis maintained the hemodynamic benefits, but ablated the lung protection.[125] Direct intraabdominal administration of carbon dioxide—by introducing operative pneumoperitoneum—may reduce the severity of abdominal sepsis. In experimental endotoxin sepsis, CO_2 pneumoperitoneum reduced mortality following laparotomy,[126] and insufflation before laparotomy also increased survival.[127] These protective effects are seen also in polymicrobial sepsis (Fig. 14-11),[128,129] and may be secondary to the immunomodulatory effects of hypercapnia,[127,130] which appear to be mediated by the localized peritoneal acidosis.[131,132]

Insights from Other Models. Inhaled CO_2 protects against hyperoxic lung injury in the neonatal rat.[116] In lung injury induced by oleic acid, metabolic alkalosis increased intrapulmonary shunt.[133] Whereas metabolic acidosis decreased shunt and increased arterial oxygen saturation (SaO_2) and mixed venous oxygen tension (PvO_2), hypercapnic acidosis did not affect intrapulmonary shunt fraction ($\dot{Q}_S/\dot{Q}_T$), Sa_{O_2} or mixed venous oxygen saturation (SvO_2). Both Pa_{O_2} and PvO_2, however, increased with hypercapnic acidosis possibly in part because of a rightward shift of the Hb-O_2 dissociation curve and/or increased cardiac output. When the hypercapnia was buffered with bicarbonate, gas exchange deteriorated during hypercapnia, shunt increased, and Sa_{O_2} was reduced.[133] The direct vasodilator effect of hypercapnia in hypoxic lung regions may be opposed by acidosis with little overall net effect on shunt from respiratory acidosis. With buffering however, the vasodilator effect of CO_2 may be unopposed, hypoxic pulmonary vasoconstriction inhibited, and shunt increased.[133]

Therapeutic versus Permissive Hypercapnia. The effects of hypercapnia may also depend on the means of achieving it. The effects of hypercapnia in preclinical models described earlier were generally obtained by increasing CO_2 in the inspired gas. Hypercapnia, however, can be induced by reducing V_T and/or respiratory rate; achieved this way, hypercapnia appears to worsen lung damage induced by systemic endotoxin administration.[100] Inspired CO_2 is distributed uniformly through all ventilated regions, whereas hypercapnia caused by reducing alveolar ventilation may not be.[134] These issues underline the need to consider the means of achieving hypercapnia, as well as the diversity of experimental models.[135]

INSIGHTS FROM CLINICAL DATA

Reduction of V_T results in permissive hypercapnia. The lung alterations, however, involve the reduced V_T, the ensuing hypercapnic acidosis, and the potential influence of altered respiratory frequency. No clinical studies to date have dissected out these changes; it is difficult to conceive of how this would be done. Nonetheless, conventional application of permissive hypercapnia involves reduction of V_T, some increase in respiratory frequency, and tolerance of hypercapnic acidosis.

Pulmonary Vascular Effects. Pulmonary hypertension is almost invariable in ARDS. While protective ventilation may augment pulmonary vascular flow, the net effect of hypercapnic acidosis is usually to increase pulmonary vascular resistance. Inhaled nitric oxide usually can overcome such hypercapnia-induced pulmonary hypertension and may increase cardiac output.[136] Pulmonary hypertension may result in high capillary wall stress; therefore, worsening of such stress by hypercapnia theoretically could exacerbate stretch-induced lung injury.[33,137]

Pulmonary Gas Exchange in Acute Respiratory Distress Syndrome. In ARDS, hypercapnia usually results in a slight increase in Pa_{O_2} and a somewhat larger increase in venous and tissue P_{O_2}.[138] The increase in Pa_{O_2} occurs partly because of an increase in cardiac output and partly because of a rightward shift of the Hb-O_2 dissociation curve, which

facilitates oxygen unloading to the tissues.[25,139] The overall effect, therefore, is likely to enhance tissue oxygen uptake. In patients with ARDS, the reduction in mean airway pressure after initiation of pressure-limited ventilation (without high positive end-expiratory pressure [PEEP]) may result in lung derecruitment and increased shunt.[140] Three clinical studies shed light on these mechanisms.

Feihl et al[45] provided a detailed assessment of pulmonary physiology associated with a large reduction in V_T (mean: from 10 to 6 mL/kg). Induction of permissive hypercapnia markedly increased intrapulmonary shunt, although there was no effect on dispersion of $\dot{V}_A/\dot{Q}$ (Fig. 14-12).[45] Permissive hypercapnia increased cardiac output and decreased Pa_{O_2} from 109 to 92 mm Hg apparently owing to a combined effect of reduced V_T, increased shunt fraction, and decreased alveolar ventilation.[45] Thorens et al[138] studied the rapid induction of hypercapnia in eleven patients with ARDS, where V_T was reduced such that Pa_{CO_2} rose from approximately 40 to 60 mm Hg, and pH correspondingly decreased from 7.4 to 7.26.[138] There were significant increases in venous mixture, cardiac index, and mean pulmonary artery pressure, prompting the authors to caution against rapid induction of permissive hypercapnia. Pfeiffer et al[141] studied the effect of permissive hypercapnia consequent to V_T reduction in twenty-two patients with ARDS categorized into septic (i.e., hyperdynamic) or nonseptic groups. Multiple inert gas uptake measurements revealed an increase in intrapulmonary shunt but maintained—or increased—Pa_{O_2}.[141]

Overall, these data suggest two opposing sets of effects on oxygenation: reduced V_T worsens atelectasis and increases intrapulmonary shunt, but these effects are countered by elevated cardiac output (and perhaps reduced O_2 consumption), which increases mixed venous O_2 content.[141] These concepts have been supported by mathematical models of oxygen kinetics in ARDS.[139]

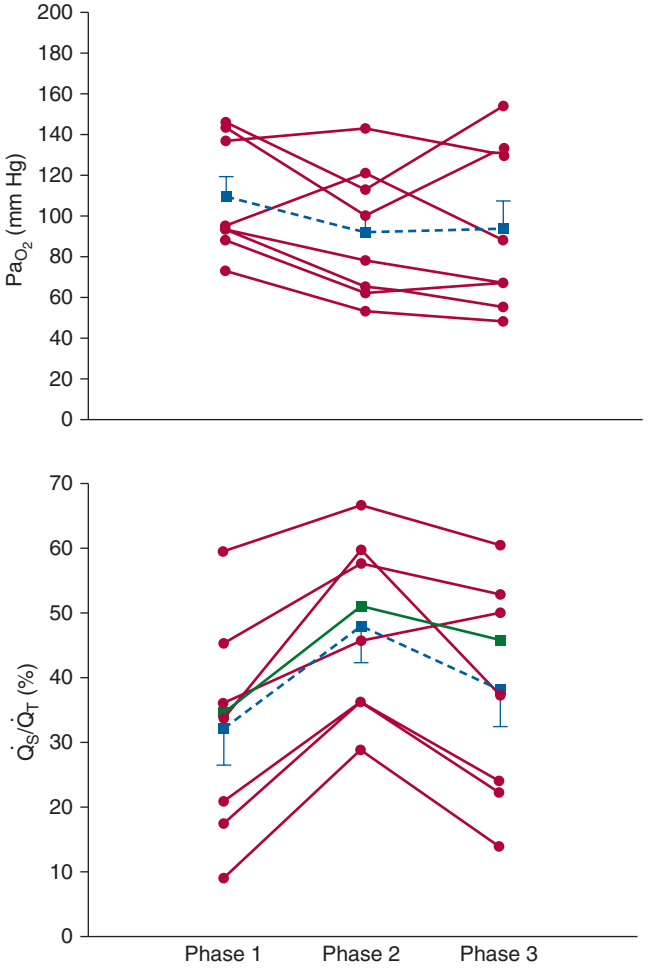

FIGURE 14-12 The effects of permissive hypercapnia and dobutamine on arterial oxygen tension (Pa_{O_2}) and venous admixture $\dot{Q}_S/\dot{Q}_T$. Phase 1 (high V_T, 10.3 mL/kg) represents baseline conditions. Phase 2 (low V_T, 6.5 mL/kg) represents a change to permissive hypercapnia, which was associated with a slight decrease in mean Pa_{O_2} and a large increase in $\dot{Q}_S/\dot{Q}_T$. Phase 3 represents resumption of baseline high V_T (10.3 mL/kg) plus infusion of dobutamine; it resulted in stabilization of Pa_{O_2} despite residual elevation of intrapulmonary shunt. (Reproduced, with permission, from Feihl F, Eckert P, Brimioulle S, et al. Permissive hypercapnia impairs pulmonary gas exchange in the acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2000;162:209–215.)

Hypercapnia and the Injured Brain

INSIGHTS FROM LABORATORY DATA

Several studies have demonstrated protective effects of hypercapnia in brain injury. Hypercapnic acidosis attenuates hypoxic-ischemic brain injury in the immature rat. Vannucci et al[142,143] developed a model of hypoxic-ischemic injury in the immature rat consisting of unilateral common carotid artery ligation, exposure to hypoxia (FI_{O_2} of 0.8%), and thereafter exposure to varying concentrations of inspired CO_2 (0%, 3%, 6%, or 9%) for 2 hours.[142,143] Neuropathologic assessment at 30 days of age demonstrated that hypocapnia was harmful and that elevated CO_2 was protective.[143] The experimental model caused hyperventilation. Without supplemental CO_2, the animals were frankly hypocapnic, which caused harm. Therefore, exposure to supplemental CO_2 may have provided protection by preventing hypocapnia rather than by producing hypercapnia. The investigators subsequently demonstrated that cerebral blood flow was better preserved during hypercapnia, and the higher oxygen delivery promoted cerebral glucose utilization and oxidative metabolism for optimal maintenance of tissue high-energy phosphate reserves.[142] Cerebrospinal fluid glutamate levels were also lowest with hypercapnia, and it is possible that inhibition of excitatory amino acid neuro-transmitter secretion may contribute to neural protection.[142] Additional mechanisms of neural protection may involve inhibition of free radicals[93,144] or attenuation of neuronal apoptosis.[145]

INSIGHTS FROM CLINICAL DATA

Hypercapnia greatly increases cerebral blood flow and, if critical, may raise intracranial pressure, resulting in

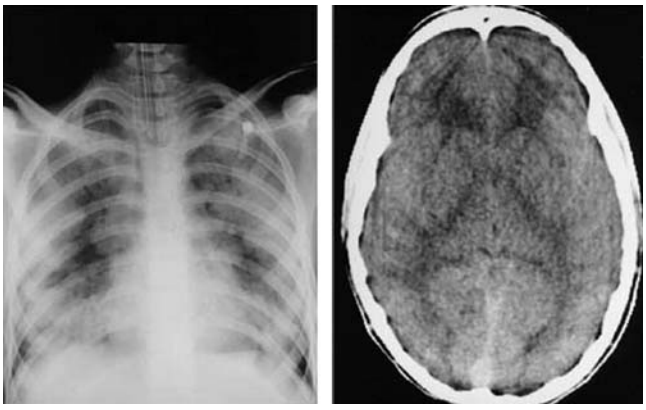

FIGURE 14-13 A chest radiograph and brain computed tomographic scan of a child with both ARDS and cerebral edema illustrating the trade-off that occurs when permissive hypercapnia is instituted to protect against ventilator-associated lung injury. (Reproduced, with permission, from Tasker RC, Peters MJ. Combined lung injury, meningitis and cerebral edema: how permissive can hypercapnia be? *Intensive Care Med*. 1998;24:616–619.)

papilledema and headache. In the clinical setting, cerebral effects of hypercapnia often overlap with the effects of hypoxemia.[146] The resulting abnormalities include restlessness, tremor, slurred speech, and fluctuations of mood. Very high levels of Pa_{CO_2} cause narcosis.[146] Raised intracranial pressure, however, is not an absolute contraindication to permissive hypercapnia; in fact, with careful management it has been used successfully in a patient suffering from acute lung injury and meningoencephalitis with cerebral edema (Fig. 14-13).[147]

Hypercapnia and the Cardiovascular System

INSIGHTS FROM LABORATORY DATA

Effects on the Myocardium. Hypercapnic acidosis protects the heart against ischemia–reperfusion injury. This has been demonstrated in isolated perfused neonatal lamb hearts, where greater degrees of hypercapnic acidosis were associated with progressively greater protection,[148] as well as in myocardial cells.[149] Although hypercapnia directly reduces contractility, it may also provide preconditioning protection.[150] Exposure to comparable metabolic acidemia (pH 6.8), however, followed by buffering to normal pH with bicarbonate and tris-hydroxymethyl aminomethane (THAM), is not protective.[148] In contrast, metabolic acidosis (pH 6.6) prevented myocardial stunning following global ischemia.[151] The latter investigators have since demonstrated that both hypercapnic and metabolic acidosis were equally effective in reducing infarct size in an in vivo canine model of coronary artery ischemia–reperfusion.[152] Possible mechanisms for the protective effects of acidosis include reduction of calcium loading to the myocardium through H^+ inhibition of calcium uptake and, in the case of hypercapnic acidosis, induction of coronary vasodilation. Nomura et al[148] found that the greatest coronary artery flow occurred with maximal hypercapnia. In contrast, increases in regional coronary artery flow do not contribute to the protective effects of normocapnic acidosis.[153]

Effects on the Vascular System. Hypercapnic acidosis attenuates the development of septic shock following cecal ligation and puncture.[24,123,125] The hemodynamic effect of hypercapnia in an ovine model was comparable to that seen with dobutamine,[108] and appears to be an effect of hypercapnia and not acidosis.[125] Hypercapnic acidosis improves microcirculation in the anesthetized rabbit,[154] which corresponds to the improvement in tissue oxygenation observed during surgery.[155,156] The absence of improved oxygenation during cardiopulmonary bypass[157] may reflect fixed aortic flow and suggest that hypercapnia-induced increases in oxygenation are a function of modulation of flow—and not vascular tone—in the perioperative setting.

INSIGHTS FROM CLINICAL DATA

Critical Illness The potential for hypercapnia to exert detrimental effects on cardiac output[158] and the peripheral circulation[159] may be overstated, particularly when hypercapnia develops gradually. As discussed earlier, the net hemodynamic effect is probably beneficial.[45,63] Nevertheless, hypercapnic acidosis may exert adverse hemodynamic effects in critically ill patients, particularly where myocardial function is already depressed. In addition, acute hypercapnia may cause hypotension where endogenous catecholamine production has been maximized or where β-blocking drugs reduce the potential for sympathetic activation to overcome the direct depressive effects of hypercapnia. Even in critically ill patients requiring inotropic drug infusions, cardiac output increases almost invariably after an acute rise in Pa_{CO_2}, although the mean arterial pressure may fall because of direct hypercapnia-induced systemic vasodilation.[136]

In patients with ARDS, the rapid induction of hypercapnia to a target Pa_{CO_2} of 80 mm Hg for 2 hours resulted in decreased systemic vascular resistance and increased cardiac output.[160] In addition, myocardial contractility was decreased, and mean pulmonary artery pressure was increased.[160] In stable patients with ARDS, reduction of V_T (from 10 to 7.7 mL/kg) associated with an increase in Pa_{CO_2} (from 37.9 to 56.7 mm Hg) was not associated with changes in hemodynamics or measures of oxygen delivery or consumption.[161]

Renal, Hepatic, and Splanchnic Effects

In isolated hepatocytes exposed to anoxia[162] or chemical hypoxia,[163] acidosis delays the onset of cell death; correction of pH accelerated cell death. This phenomenon

may represent a protective adaptation against hypoxic and ischemic stress. Isolated renal cortical tubules exposed to anoxia have improved ATP levels on reoxygenation at a pH of 6.9 when compared with tubules incubated at pH 7.5.[162] Elevated CO_2 preserves tissue oxygenation of the gastrointestinal mucosa during hemorrhagic shock[164,165] and has been reported to reverse sepsis-induced reductions in gastrointestinal cellular ATP[166] (and the reciprocal rise in lactate) and can prevent increases in mucosal permeability[167] triggered by endotoxemia.

The marked sympathetic activation associated with hypercapnic acidosis, particularly when combined with arterial hypoxemia, can lead to intense renal vasoconstriction and tubular sodium reabsorption, causing depressed glomerular filtration and increased fluid retention.[168] In a clinical study of ARDS, hypercapnia resulted in no important alterations in splanchnic circulation, although in this case CO_2 was increased by increasing apparatus dead space (and not by reduction of V_T).[169]

Effects of Acidosis versus Hypercapnia

EFFECTS MEDIATED VIA pH CHANGES

The protective effects of hypercapnic acidosis in experimental lung and systemic organ injury appear to be primarily a function of the acidosis generated.[98,112] The effects of buffering may depend on the model and the pathogenesis of the injury. In the isolated lung hypercapnic acidosis attenuated ventilator-induced lung injury, whereas in cultured cells buffering reduced cell resealing[111] and pulmonary epithelial repair[106] following physical injury. In the isolated lung, the protective effect of hypercapnic acidosis in ischemia–reperfusion was greatly attenuated when the pH was buffered,[112] and although metabolic acidosis attenuated reperfusion injury, it was less effective than hypercapnic acidosis.[112] The myocardial protective effects of hypercapnic acidosis are also seen with metabolic acidosis in ex vivo[151] and in vivo[152,153] models. Metabolic acidosis exerts protective effects in other models of organ injury; it delays cell death following caused by anoxia[162] or chemical hypoxia,[163] and reoxygenation at acidotic (compared with alkalotic) pH is associated with better preservation of cellular ATP.[162] In contrast to the lung, the type of acidosis (i.e., hypercapnic versus metabolic) appears to be of importance in the renal tubule.

EFFECTS MEDIATED VIA CARBON DIOXIDE

Certain effects of hypercapnia, including the inhibitory effects of hypercapnia on pulmonary epithelial wound healing,[106] and the deleterious effects in prolonged pulmonary sepsis,[86,87]appear to be a function of CO_2 and not pH. The effects of hypercapnia on the NF-κB pathway may also relate to CO_2 rather than acidosis,[70,106] and the developmental effects of hypercapnia, at least in *Drosophila* and in *C. elegans*, appear to be mostly independent of the pH.[70,71]

USE IN SPECIFIC CLINICAL SETTINGS

Acute Severe Asthma

Although much current work on ventilator strategies involving permissive hypercapnia concentrates on lung injury, its use was first described in status asthmaticus by Darioli and Pettet.[170] Permissive hypercapnia decreases dynamic hyperinflation in ventilated patients with acute severe asthma by increasing expiratory time and decreasing V_T, and this reduces end-inspiratory lung volume and lessens auto-PEEP. Other investigators have confirmed that morbidity and mortality are reduced with the use of permissive hypercapnia in ventilated patients with acute severe asthma.[171] Modest levels of permissive hypercapnia (approximately 60 mm Hg) are employed widely in ventilated patients with acute severe asthma.[81]

Acute Respiratory Distress Syndrome

The potential for protective lung ventilation strategies with varying degrees of permissive hypercapnia to improve survival in patients with acute lung injury and ARDS was suggested initially by Hickling et al.[12,13] Two studies by this group, one retrospective[12] and one prospective,[13] strongly indicated that use of low V_T was beneficial. In the retrospective study, fifty patients with severe ARDS (lung injury score ≥2.5; mean Pa_{O_2}/FI_{O_2} = 94) were managed with limitation of peak airway pressure to less than 30 cm H_2O.[12] The mean maximum Pa_{CO_2} was 62 mm Hg, and the hospital mortality (16%) was less than predicted by Acute Physiology and Chronic Health Evaluation (APACHE) II score (39.6%). Importantly, the authors reported no differences between survivors and nonsurvivors in terms of lung injury score, ventilator score, Pa_{O_2}/FI_{O_2}, or maximum Pa_{CO_2}.[12] The prospective study[13] investigated comparable patients and also limited peak airway pressures to less than 30 cm H_2O, did not buffer hypercapnic acidosis, and commenced with a V_T of 7 mL/kg (as opposed to 12 mL/kg in the retrospective study). Again, hospital mortality rates were lower than predicted by APACHE II score (26.4% vs. 53.3%).[13]

The five prospective, randomized, controlled trials[10,11,172–174] that measured survival in ARDS are discussed in detail elsewhere (see Chapter 42). Two were positive (the ventilator strategy had an impact on mortality),[10,11] and three were not.[172–174] To some extent, permissive hypercapnia developed in all the trials, although there was much variability. Among the four major trials, the postrandomization Pa_{CO_2} values (mean ± standard deviation [SD]) in the control (higher V_T) trial groups were 35.8 ± 8.0 mm Hg,[10] 36.0 ± 1.5 mm Hg,[11] 41.0 ± 7.5 mm Hg,[172] and 46.0 ± 10 mm Hg.[174] The postrandomization Pa_{CO_2} values in the protective (lower V_T) trial groups were 40.0 ± 10,[10] 58.0 ± 3.0,[11] 59.5 ± 15,[172] and 54.5 ± 19[174] mm Hg. It is clear that ventilation strategy can have an impact on mortality (in the positive trials), yet there was no discernible relationship between levels

of hypercapnia and survival. Also, there was no controlled approach to the administration of buffers. Finally, one of the reports mentioned (without supportive analysis) that the permissive hypercapnia might have increased the incidence of renal failure.[174]

The database of the largest of these studies[10] was subsequently analyzed to determine whether, in addition to the effect of V_T, there might be an independent effect of hypercapnic acidosis.[175] Mortality was examined as a function of permissive hypercapnia on the day of enrollment using multivariate analysis and controlling for other comorbidities and severity of lung injury. It was found that permissive hypercapnia reduced mortality in patients randomized to the higher V_T but not in those receiving lower V_T.[175] If these data are confirmed, there may be a good case for testing hypercapnic acidosis as an adjunct to attenuate ventilator-associated lung injury.

Neonatal and Pediatric Practice

Use of permissive hypercapnia in neonatology has been recognized since the study by Wung et al in 1985.[14] They described lower than previous mortality and lower incidence of chronic lung disease in neonates suffering from persistent fetal circulation who were treated with low V_T entailing a high Pa_{CO_2}.[14]

NEONATAL RESPIRATORY DISTRESS SYNDROME

Infants with neonatal respiratory distress syndrome have been studied in a randomized, controlled trial.[176] Although not powered to detect differences in survival, the duration of mechanical ventilation was shorter in the permissive hypercapnia group; and, no obvious adverse effects were seen (Fig. 14-14). Although encouraging, such a small study would not detect a subtle increase in adverse effects. More recently, a prospective multicenter study of extremely premature neonates in Denmark (1994 to 1995) reported that a ventilator strategy incorporating permissive hypercapnia and early use of nasal continuous positive airway pressure and surfactant reduced the incidence of chronic lung disease significantly.[177]

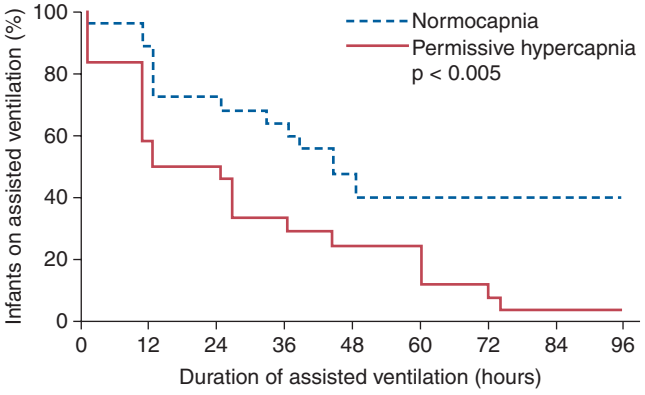

FIGURE 14-14 Duration of mechanical ventilation in neonates with respiratory failure randomized to conventional therapy or permissive hypercapnia. (Reproduced, with permission, from Mariani G, Cifuentes J, Carlo WA. Randomized trial of permissive hypercapnia in preterm infants. *Pediatrics*. 1999;104(5 Pt 1):1082–1088.)

CONGENITAL DIAPHRAGMATIC HERNIA

Permissive hypercapnia plays an increasing role in the ventilator management of infants with congenital diaphragmatic hernia.[178] This contrasts sharply with traditional management, which involved aggressive hyperventilation with the aim of producing systemic alkalinization. High levels of barotrauma, poor long-term respiratory outcomes, and poor survival rates, however, have prompted the recognition that the hypoplastic lung is the major pathophysiologic defect. Accordingly, avoidance of barotrauma has assumed increasing importance, and ventilator strategies involving permissive hypercapnia are used increasingly. A retrospective analysis of three treatment protocols in high-risk infants with congenital diaphragmatic hernia reported that permissive hypercapnia was associated with a substantial increase in survival, decreased barotrauma, and decreased morbidity at 6 months. In contrast, the earlier introduction of high-frequency oscillatory ventilation (which readily controls Pa_{CO_2}) had minimal impact. Despite limitations, the increased survival associated with the use of permissive hypercapnia is persuasive.[179]

CONGENITAL HEART DISEASE

Four studies of patients with congenital heart disease are relevant.[180–183] In the context of single-ventricle physiology, pulmonary vascular resistance can be controlled by inducing alveolar hypoxia or alveolar hypercapnia. Two studies documented that the addition of inspired CO_2 increased cerebral oxygenation and mean arterial pressure compared with reducing FI_{O_2} in hypoplastic left-heart syndrome[183] and following cavopulmonary connection.[182] Hypoventilation also improves systemic oxygenation after bidirectional superior cavopulmonary connection, potentially via a hypercarbia-induced decrease in cerebral vascular resistance, thus increasing cerebral, superior vena caval, and pulmonary blood flow.[180] Finally, a detailed recent study demonstrated that without altering V_T or mean airway pressure, the addition of CO_2 to inspired gas resulted in improved cerebral blood flow and systemic oxygenation following cavopulmonary connection.[181]

COMPLICATIONS

The complications of hypercapnia relate primarily to those caused by hypercapnic acidosis per se and those caused by the use of low V_T.

Complications Associated with Hypercapnic Acidosis

Although many physiologic effects are associated with hypercapnic acidosis, there are few complications. The most notable complications include intracranial and pulmonary hypertension. Complications are of most concern in patients with specific risk factors, especially where acidosis is acute, severe, or not buffered.

Complications Associated with Low Tidal Volumes

Reduced V_T may lead to increased intrapulmonary shunt, reducing Pa_{O_2}.[45] This is generally not a difficult problem and can be countered by a recruitment maneuver, elevation of PEEP or mean airway pressure, prone positioning, or other strategies. A more serious issue is whether small V_T values increase mortality, a source of significant controversy and a major issue in the meta-analysis by Eichacker et al.[184] They suggested that not only were very high V_T values dangerous, but so too were very small V_T values. This was the basis of a U-shaped curve depicting a relationship between V_T and mortality; the investigators suggested that the ARDS Network 6 mL/kg V_T protocol was potentially dangerous, should not be used, and should not be considered the standard of care.[184] Considerable controversy ensued. Another group published an abbreviated meta-analysis pooling the results of important clinical trials.[185] They countered the analysis of Eichacker et al and concluded that there was no statistical basis for the assertion that low V_T values are harmful.

LIMITATIONS AND CONTRAINDICATIONS

Limitations

A substantial body of literature emphasizes the potential for full recovery following exposure to extreme levels of hypercapnia, termed *supercarbia,* in both adults and children. Several children exposed to extremes of Pa_{CO_2} (155 to 269 mm Hg)[186] and one patient with asthma with a Pa_{CO_2} of 293 mm Hg (pH 6.77)[28] have been described, with excellent recovery and no long-term sequelae. In adults, in the early 1950s, the accidental development of severe respiratory acidosis was not uncommon in patients undergoing certain surgical procedures; Pa_{CO_2} as high as 200 mm Hg was reported during thoracotomy without apparent adverse effects.[187] More recently, reports exist of survival without sequelae following exposure to Pa_{CO_2} values of up to 375 mm Hg (pH 6.6).[188,189] Indeed, a case report indicates complete recovery following a pH of 6.46 secondary to ethylene glycol poisoning.[190] These numbers, impressive though they are, do not suggest that all patients—certainly not those who are already critically ill—would survive such exposure without incident or even survive at all. Nonetheless, they do indicate that severe hypercapnic acidosis per se is not *invariably* harmful.

Contraindications

As with almost any situation, there are few absolute contraindications and many relative contraindications. Some authorities suggest that intracranial hypertension is an absolute contraindication,[191] although this is disputed.[147] In any case, the risks and benefits of hypercapnia in the setting of intracranial hypertension must be weighed and monitored carefully. Additional relative contraindications include pulmonary hypertension, significant hypovolemia, or uncontrolled severe metabolic acidosis.[191]

ADJUNCTIVE THERAPIES

Buffering Hypercapnic Acidosis

Buffering of the acidosis induced by hypercapnia in patients with ARDS remains a common, albeit controversial, clinical practice.[192,193] The effects of buffering hypercapnic acidosis need to be considered because both hypercapnia—and acidosis—exert distinct biologic effects. As discussed above (Basic Principles), there is evidence that the protective effects of hypercapnic acidosis in ARDS are a function of the acidosis rather than the elevated CO_2 per se.[98,112] In contrast, some of the potentially harmful effects of hypercapnia, such as delayed wound healing[106] and worsening of lung injury as a result of prolonged pneumonia,[87] occur despite buffering.

SODIUM BICARBONATE

Buffering with sodium bicarbonate was permitted in the ARDS Network study.[10] Concerns with its use, however, have caused its removal from routine use in cardiac arrest algorithms.[194,195] The effectiveness of bicarbonate as a buffer depends on the ability to excrete CO_2, rendering it less effective in buffering hypercapnic acidosis. In fact, bicarbonate may further raise Pa_{CO_2} where alveolar ventilation is limited, as in ARDS.[196] Bicarbonate may correct arterial pH but worsen intracellular acidosis[197] because the CO_2 produced when bicarbonate reacts with metabolic acids diffuses readily across cell membranes, whereas bicarbonate cannot.[198]

In metabolic acidosis, the situation is also complex. Bicarbonate infusion can augment the production of lactic acid.[199–205] In ketoacidosis it can slow the clearance of ketoacids.[206] Of greater concern, bicarbonate administration is associated with a fourfold increase in risk of cerebral edema in children with diabetic ketoacidosis.[207] When compared with an equimolar dose of sodium chloride, bicarbonate administration does not improve the hemodynamic status of critically ill patients who have lactic acidosis.[208]

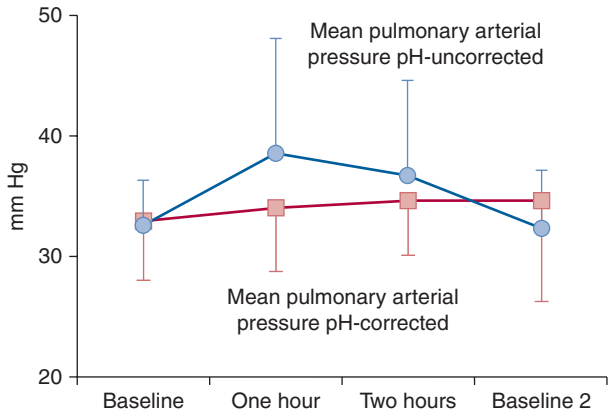

FIGURE 14-15 Pulmonary artery pressure is elevated by rapid institution (over 2 hours) of permissive hypercapnia (*blue line*) in patients with ARDS. Institution of a comparable degree of permissive hypercapnia buffered with tromethamine (THAM, *red line*) attenuated the effects. (Reproduced, with permission, from Weber T, Tschernich H, Sitzwohl C, Ullrich R, Germann P, Zimpfer M, Sladen RN, Huemer G. Tromethamine buffer modifies the depressant effect of permissive hypercapnia on myocardial contractility in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2000;162:1361–1365.)

TROMETHAMINE

There may be a role for the amino alcohol tromethamine (THAM) in hypercapnic acidosis. THAM penetrates cells easily and can buffer pH changes and simultaneously reduce P_{CO_2}.[209] Unlike bicarbonate, which requires an open system for CO_2 elimination in order to exert its buffering effect, THAM is effective in a closed or semiclosed system.[209] THAM rapidly restores pH and acid–base regulation in acidemia caused by CO_2 retention.[209] In a small but carefully performed clinical study of twelve patients with ARDS, rapid induction of a hypercapnic acidosis resulted in decreased systemic vascular resistance, increased cardiac output, decreased myocardial contractility, decreased mean arterial pressure, and increased mean pulmonary arterial pressure.[160] Buffering of the hypercapnic acidosis with THAM rapidly attenuated but did not fully reverse these changes (Fig. 14-15).[160] Thus, it could be argued that although permissive hypercapnia generally is well tolerated in patients with ARDS, buffering with THAM[160] might be a useful cotherapy where hemodynamic instability supervenes.

CARBICARB

Carbicarb is an equimolar mixture of sodium carbonate (Na_2CO_3 0.33 M) and sodium bicarbonate ($NaHCO_3$ 0.33 M) and may have advantages over the latter. Carbicarb has been studied in mixed respiratory and metabolic acidosis and has proved effective in raising arterial pH and preventing lactate elevation;[196] in contrast to sodium bicarbonate,[197] it corrects the systemic and intracellular acidosis seen with hypercapnia[210] without elevating Pa_{CO_2}. Carbicarb, however, did not appear to possess any advantages in terms of restoration of hemodynamic stability over isoosmolar amounts of hypertonic saline or sodium bicarbonate in a canine shock model.[201] The similar responses may relate to their identical sodium content, with no additional benefit attributable to correction of pH.[201]

In summary, although common clinical practice, no outcome data (e.g., survival or duration of hospital stay) support the buffering of hypercapnic acidosis in patients. In the absence of correcting the primary problem, buffering hypercapnic acidosis with bicarbonate is not likely to be of benefit. If the clinician elects to buffer a hypercapnic acidosis, the rationale should be clear (e.g., to ameliorate potentially deleterious hemodynamic consequences) and the responses measured. THAM and Carbicarb may have a role in these clinical situations.

Augmenting Carbon Dioxide Clearance

DEAD SPACE GAS REPLACEMENT

At the end of expiration, the ventilator circuit distal to the Y-piece and the anatomic dead space both contain alveolar gas. This CO_2-rich gas then constitutes the first part of the next breath delivered to the distal lung. The contribution of this dead space gas to ventilation increases with decreased V_T, given that dead space is relatively fixed. Techniques that aim to replace dead space gas with fresh gas have been advocated as an adjunct to protective ventilator strategies. These techniques may increase effective alveolar ventilation and facilitate further reductions in V_T, minimizing transpulmonary pressures.

Tracheal gas insufflation (TGI) delivers fresh gas into the central airways either continuously or in a phasic fashion during expiration (see Chapter 22). Experimental studies in animal models of ARDS and in lung models highlight the potential role of TGI in clinical practice.[211] Zhu et al[99] reported that TGI, either alone or in combination with partial liquid ventilation, attenuated the development of lung injury resulting from mechanical ventilation of surfactant-depleted lungs. Use of expiratory TGI can help clear CO_2 and facilitate V_T (and plateau pressure) reduction in patients with combined brain and lung injury, and it has also been demonstrated to augment CO_2 clearance when combined with high frequency oscillation. Despite extensive investigation, however, concerns persist with regard to the safety and monitoring of TGI that have impeded its introduction into clinical practice.[212]

Aspiration of dead space gas during expiration and controlled replacement with fresh gas is a related technique designed to minimize dead space. A feasibility study of eight patients with chronic obstructive pulmonary disease who were managed with permissive hypercapnia demonstrated that aspiration of dead space gas resulted in a similar decrease in Pa_{CO_2} but with less intrinsic PEEP compared to TGI.[213]

Coaxial double-lumen endotracheal tubes, which eliminate the contribution to dead space from the ventilator circuit distal to the Y-piece, may improve the efficiency of ventilation. No adverse hemodynamic effects or auto-PEEP

has been detected with use of the coaxial tube.[214] Reduction in Pa_{CO_2} is inversely proportional to V_T. Initial safety and efficacy evaluations of this promising adjunct in patients with ARDS are required.

ADDITIONAL TECHNIQUES

High-frequency oscillatory ventilation and extracorporeal CO_2 removal are discussed in Chapters 19 and 21, respectively.

ADJUSTMENTS AT THE BEDSIDE

Adjustments at the bedside are specific to the patient and the clinical context. The following principles may guide therapy, although in the end the physician must individualize the risks and benefits for each patient.

First, in a patient who is being mechanically ventilated, confirm correct placement of the endotracheal tube and the ventilation of both lungs. Consider and (where possible) correct reversible conditions that might have an impact on oxygenation or CO_2 removal (e.g., pleural effusion, atelectasis, and/or pneumothorax). Next, decide whether the patient is comfortable and whether there is patient–ventilator dyssynchrony. Then note the ventilator settings (i.e., plateau pressure, V_T, and rate) and the arterial blood-gas values, and consider whether these are appropriate. Concurrent with these considerations, evaluate the patient for causes of high Pa_{CO_2}, and reduce or eliminate any that are present. Such conditions include increased production of CO_2 (e.g., fever, sepsis, shivering, or more rarely, thyroid storm, malignant hyperthermia, or neuroleptic malignant syndrome) or decreased CO_2 elimination (e.g., increased dead-space-to-tidal-volume ratio [V_D/V_T]).

The next step involves arbitrary decisions made by the clinician at the bedside on the target tidal distension (V_T, or plateau pressure). It is important to recognize that optimal values are unknown, which is not to say that the values are unimportant; they are definitely important. Across populations, adverse effects are associated with very high V_T.[10,11] We do not advise on the ideal V_T or plateau pressure for any specific patient, recognizing that these issues can be both difficult and controversial. After clinicians select an appropriate V_T for the patient in question, they next consider the "maximal" allowable Pa_{CO_2} and the degree of acidosis that they believe the patient can tolerate. This is empirical. Although some authors suggest arbitrary limits, in the end, the decision is based on patient comfort, presence of contraindications, and clinician "comfort." When considering ventilator settings, consider the relative values of V_T, plateau pressure, and rate, and estimate the relative contributions of changes in each. For example, if the rate is inappropriately low, then increasing it will allow further reduction in V_T with less elevation in Pa_{CO_2}. Conversely, increasing the rate may induce a degree of hyperinflation (auto-PEEP),[215] which, although potentially protective, can complicate ventilator management and could induce elevation of the Pa_{CO_2}.

Finally, having decided on the desired ventilator settings and the permissible limits of toleration, decide on the trade-offs involved and the time scale. One trades the benefits of the approach—reduction of ventilator-associated lung injury—against the cost—conditions caused or exacerbated by permissive hypercapnia. Such trade-offs are inherent in the practice of medicine[216] but are seldom addressed by clinical trials. Finally, the clinician decides on the rate of introducing permissive hypercapnia. In some situations, there is little choice. For example, in acute severe asthma, hypercapnia occurs immediately, for otherwise, the patient would be subjected to incredibly high airway pressures. Having decided on the target V_T or plateau pressure, increase the rate and slowly decrease the V_T. There is no formula. Extremes of V_T or plateau pressure should be reduced immediately, and less extreme elevations should be reduced more gradually. For example, in ARDS, a V_T of 15 mL/kg could be reduced immediately to 10 mL/kg and further reduced over several hours with a concomitant increase in rate. Obviously, if ideal ventilator settings are tolerated by the patient and the Pa_{CO_2} and pH are normal, then the clinician would not do anything to elevate the Pa_{CO_2}.

TROUBLESHOOTING

To address problems that develop, it is key to understand the pathophysiology. This amounts to management of dyspnea, intracranial hypertension, pulmonary hypertension, and sometimes, hypoxemia. Troubleshooting follows logically the principles used in initiating permissive hypercapnia. In reality, it represents a work in progress, wherein the clinician considers risks versus benefits (real and potential) for each patient at the bedside.

Tidal Volume and Respiratory Rate

The first issue is to determine whether the V_T (or perhaps plateau pressure) is actually in the range desired by the clinician. If V_T is far lower than desired, increasing it will alleviate "unnecessary" hypercapnic acidosis. If the respiratory rate is too low, increasing it also will lower the Pa_{CO_2}.

Rate of Change

Was the permissive hypercapnia introduced too quickly? Overly rapid introduction of hypercapnia results in a greater degree of acidosis because the physiologic buffering systems are unable to cope. Most unfavorable effects of hypercapnic acidosis (e.g., dyspnea and intracranial hypertension) are more pronounced where acidosis is greater. More gradual introduction of permissive hypercapnia may prevent these problems.

Adjuvant Therapies: Control of Metabolic Acidosis

Buffering sometimes can be appropriate for modifying the adverse effects of significant acidosis. The clinician needs to identify conditions other than ventilator settings and Pa_{CO_2} per se that have an impact on acid–base status. Hyperchloremic acidosis may have developed consequent to high volumes of intravenous saline, total parental nutrition, or renal tubular acidosis, and can be buffered easily or possibly prevented. Renal impairment, which slows the generation of endogenous bicarbonate or excretion of hydrogen ion, or generates endogenous organic acids, can be alleviated by renal replacement therapy.

Adjuvant Therapies: Alternative Elimination of Carbon Dioxide

Adjuvant therapies can be directed at the elevated Pa_{CO_2}. Examples include high-frequency oscillation, TGI, and extracorporeal techniques.

Specific Evaluation of the Complication

In some circumstances, clinicians suspect a problem, such as pulmonary or intracranial hypertension, that leads them to completely avoid permissive hypercapnia. Such an approach may not be appropriate in the absence of clear proof of the feared condition because the patient may be at a far greater risk of ventilator-associated lung injury than of the feared condition or potential complication. In such a setting, the clinician should consider appropriate monitoring. For example, insertion of an intracranial pressure monitor or jugular oximetry catheter may provide evidence that allows the clinician to gradually introduce, titrate, or clearly avoid hypercapnia in a patient with head injury. Such an approach has been described when managing children suffering from meningococcal septicemia complicated by elevated intracranial pressure and severe acute lung injury (see Fig. 14-13).[147] Concerns about pulmonary hypertension can be addressed by measuring, and monitoring the degree of pulmonary hypertension or its sequelae (e.g., right-ventricular failure, tricuspid regurgitation, or right-to-left shunting). In this case, transthoracic echocardiography or pulmonary artery catheterization may be indicated. The clinician will recognize that adverse effects (e.g., epithelial fluid reabsorption) may exist, which may not be detected by conventional monitoring.

Specific Treatment of the Complication

Direct testing for a feared complication may enable early detection. It also permits the direct "independent" treatment if permissive hypercapnia is still deemed necessary to tolerate specific ventilator settings. Specific treatment might include inhaled nitric oxide for pulmonary hypertension[136] or sedation, osmotherapy, or hypothermia for intracranial hypertension. Of course, the most common complaint, dyspnea, can be treated directly with sedatives and opioids[217]; neuromuscular blockade, while paralyzing respiratory muscle contraction, of course, does not alter the perception of dyspnea.

IMPORTANT UNKNOWNS

Although much is known about hypercapnia, much remains unknown. The principles underlying the approach to permissive hypercapnia have been established.[25,31,33,191,218–220] Such principles are inherently limited by the state of our knowledge. The unknowns relating to permissive hypercapnia can be grouped as follows.

Hypercapnia versus Acidosis

Most of the acute physiologic effects of hypercapnic acidosis can be attributed to the effects of pH. CO_2 itself, however, has significant biochemical effects, especially on tissue nitration. In the context of endogenous or exogenous buffering, the effects of elevated CO_2 are not understood.

Therapeutic Hypercapnia

The role of the deliberate elevation of CO_2, as opposed to passive elevation of CO_2 resulting from reduced V_T, is experimentally exciting but essentially conjectural.[25] The state of knowledge is not sufficient to justify deliberating elevating CO_2 other than as a means of avoiding ventilator-associated lung injury; clearly, in the context of evolving understanding of the relevant mechanisms, clinical study with mortality as an outcome would not be justified.[135]

Mechanisms of Benefit (or Harm)

Although evolving studies are providing better understanding of the mechanisms of benefit and harm associated with hypercapnia and acidosis, clinical definitions of lung injury do not take into account the biologic processes that cause the injury. Although some mechanisms are understood, it is not yet possible for the clinician to extrapolate from mechanisms discovered in the laboratory to the care of a patient with lung injury.

Monitoring during Hypercapnia

There are no specific monitors for patients being ventilated with permissive hypercapnia. Regular arterial blood-gas analysis is a requirement, and clinicians will monitor

parameters that lead them to detect or prevent complications such as intracranial hypertension.

THE FUTURE

Future advances in the early diagnosis of acute respiratory failure and the development of specific therapies may reduce the need for ventilator strategies involving permissive hypercapnia. In the interim, ventilator strategies involving hypercapnia appear likely to play a central role in the management of these disease states. This highlights the need to improve our understanding of the biology of hypercapnia, which should lead us to a better understanding of the advantages, disadvantages, and contraindications pertaining to its use in the clinical context. If the requirement for adverse ventilator strategies lessens, the requirement for permissive hypercapnia will lessen in parallel, and concerns related to its use will become less relevant. Nonetheless, a fuller profile of biochemical and physiologic responses to elevated CO_2 will be needed for the clinician of the future to decide whether hypercapnia is dangerous—or potentially beneficial—in the management of a specific patient.

SUMMARY AND CONCLUSIONS

Permissive hypercapnia simply means reducing V_T in order to lessen the likelihood of ventilator-associated lung injury; in so doing, the clinician accepts the inevitable development of higher Pa_{CO_2}. Elevated P_{CO_2} is associated with a long list of physiologic alterations. Some of these effects are harmful, others may be neutral, and some may turn out to be beneficial. In any case, there is ample evidence that high tidal volumes harm patients. In avoiding such high tidal volumes, the clinician must decide for each patient what is the appropriate trade-off between the benefits of avoiding high V_T and the cost (and benefits) of the associated hypercapnia.

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15

FEEDBACK ENHANCEMENTS ON CONVENTIONAL VENTILATOR BREATHS

Neil MacIntyre
Richard D. Branson

CONVENTIONAL POSITIVE-PRESSURE BREATH-DELIVERY STRATEGIES AND MODES

The first generation of positive-pressure mechanical ventilators were simple high-pressure gas regulators on which clinicians could set the circuit pressure and the breathing frequency. In the middle of the twentieth century, more sophisticated devices appeared that allowed direct clinician control of flow and volume along with breath timing and expiratory pressure. As ventilator design improved and microprocessors became available, feedback mechanisms appeared that could provide automatic adjustments in these set variables depending upon a variety of conditions.[1] A simple example was the use of a patient-effort sensor to adjust the number of mechanical breaths provided during assist-control modes or synchronized intermittent mandatory ventilation.[2–4] A variation on this breath rate feedback mechanism was mandatory (or minimum) minute ventilation, which used minute ventilation to adjust the number of positive-pressure breaths delivered.[5] At the same time, the development of flow control valves that could be adjusted based on a clinician-selected airway-pressure target appeared.[6–9] This gave clinicians the choice of using either set flow-volume-targeted modes (volume assist-control ventilation; volume-targeted synchronized intermittent mandatory ventilation [volume SIMV]) or pressure-targeted modes (pressure-targeted assist-control ventilation [PACV]; pressure support; pressure SIMV). Taken together, these flow-targeted, volume-targeted, and pressure-targeted strategies comprise what is commonly referred to today as "conventional" mechanical ventilation.

In the late twentieth and early twenty-first century, increasingly complex and clever feedback mechanisms for these conventional breaths have been introduced. The behavior of these features is made more understandable if one considers that all positive-pressure breaths can be described by three variables: the trigger variable (what initiates a breath—usually an effort sensor or a machine timer); the target variable (what governs gas delivery—usually either a set flow or a set pressure target); and the cycle variable (what terminates the breath—usually a set time, flow, or volume).[6,8] These newer feedback systems are designed to adjust one or more of these breath-delivery variables based on prescribed algorithms to provide more physiologically targeted and patient

interactive ventilatory support. In addition, there has also been the development of feedback mechanisms to adjust the fractional inspired oxygen concentration (FI_{O_2}) and positive end-expiratory pressure (PEEP). These feedback mechanisms are often considered "partial" closed-loop conventional mechanical ventilation. The clinician, however, cannot expect these features to provide safe and effective support automatically. Rather, the clinician must understand their rationale, design principles, lung-protective targets, and evidence-based outcomes to apply them properly. These are the focus of the remainder of this chapter.

FEEDBACK CONTROL OF COMBINATION PRESSURE-TARGETED AND FLOW-TARGETED BREATHS

The advantage of a flow-targeted, volume-cycled breath is that a guaranteed volume is delivered with every breath (even though applied airway pressures may change). The advantages of a pressure-targeted breath (either time- or flow-cycled) are that an airway pressure limit is guaranteed (even though volumes may change), that the rapid initial flow may enhance gas mixing, and that the variable-flow pattern may enhance patient–ventilator synchrony.[7,10,11]

Over the last two decades, a number of engineering innovations have attempted to combine these features by producing feedback algorithms that allow some control of volume with pressure targeting and some control of pressure with flow targeting. Collectively, these are often referred to as *hybrid breaths* or *dual-control breaths*.[12–15] On the current generation of mechanical ventilators, there are two basic approaches to providing these types of breaths: dual control within a breath (DCWB; intrabreath control) and dual control from breath to breath (DCBB; interbreath control). The former uses a measured flow input to switch from pressure targeting to flow targeting in the middle of the breath. The latter uses a measured volume input to manipulate the pressure level of subsequent pressure-targeted breaths.

Dual Control within a Breath

The currently available DCWB breath begins with either patient or machine triggering and is followed by a pressure-targeted flow-delivery algorithm.[16] There is thus a high initial flow to rapidly pressurize the airway and then subsequent flow adjustments according to respiratory system mechanics and patient effort to maintain the target pressure. As the lungs fill, flow decelerates until a flow-cycling mechanism terminates the breath. In these respects, this breath type is similar to the pressure support breath. Unlike pressure support, however, the clinician also must set a minimum tidal volume, flow, and backup rate with the DCWB breath. These backup settings take over control of the breath should the pressure-targeted flow drop below the minimum required to deliver the set tidal volume in the allotted inspiratory time. The breath thus begins like pressure support and can either flow cycle like pressure support (if the volume meets or exceeds the set minimum) or volume cycle like a flow-targeted breath (if necessary to deliver the set volume).[12–14,16]

The reasoning behind DCWB breaths is that the high initial flow provides better gas mixing and also reduces flow dyssynchrony during assisted breaths, whereas the volume guarantee ensures a constant tidal volume (V_T).[10,17–21] DCWB breaths thus can be considered to be "more comfortable" flow-targeted, volume-cycled breaths. Alternatively, they could be considered pressure support with a V_T "safety net."[16]

DCWB breath algorithms exist on several ventilators, but their clinical role remains unclear because the few studies looking at this strategy have generally focused only on device performance.[16,22] Indeed, DCWB mode use is driven primarily by a clinician's belief in the underlying concept. In recent years, DCWB modes have gradually disappeared and have been replaced with the simpler to use DCBB approach described below.

Dual Control Breath to Breath

DCBB techniques use standard pressure-targeted breaths (either pressure support or PACV), but the ventilator has the ability to adjust the pressure target according to a clinician-set V_T and the delivered V_T of previous breaths.[13,14,23–26] When DCBB breaths are exclusively supplied with time cycling, the mode is commonly referred to as pressure-regulated volume control, although there are a number of proprietary names (e.g., Dräger's Autoflow, Covidien's VC+, Hamilton's Adaptive Pressure Ventilation). When DCBB breaths are supplied exclusively with flow cycling, the mode is commonly referred to as volume support. Some ventilators will switch between these two breath types depending on the number of patient efforts (e.g., Maquet's Automode). With all of these modes, instead of setting a target pressure, the clinician selects a V_T. The ventilator then delivers one or more "test breaths" with a small amount of inspiratory pressure. The V_T exiting the ventilator is measured, and total respiratory system compliance is calculated. Thereafter, each subsequent breath uses the previous calculation of system compliance to manipulate the ensuing pressure target to achieve the desired V_T (Fig. 15-1). The maximum pressure change from breath to breath on most systems generally is limited to a few centimeters of water (<3 cm H_2O) to prevent large swings in pressure and volume. The volume signal used for DCBB feedback control is not exhaled V_T but V_T exiting the ventilator. This prevents a runaway effect, which could occur if a leak in the circuit prevented accurate measurement of exhaled V_T.

In volume support, the flow-cycling criterion is either manufacturer-specific (e.g., 25% to 35% of peak flow) or, on many newer machines, clinician-adjustable. A secondary cycling mechanism may be present on some devices if inspiratory time exceeds a certain fraction (e.g., 80%) of a set total cycle time. Also, as with other pressure-targeted

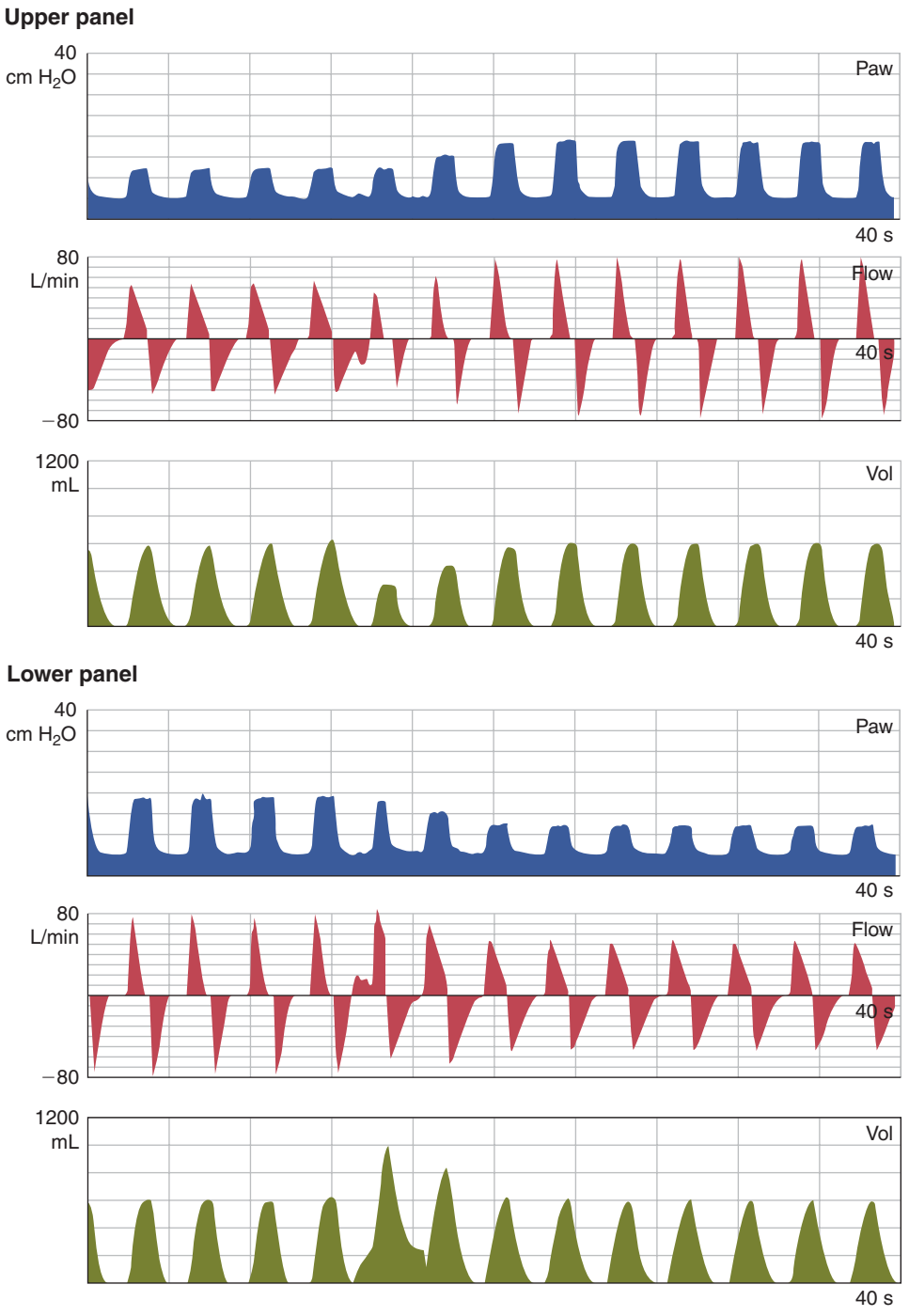

FIGURE 15-1 Behavior of DCBB breaths in a lung model simulation of changing lung compliance. In both the *top* and *bottom panels*, pressure (*Paw*), flow, and volume (*Vol*) are plotted over time. The target tidal volume in both panels is 600 mL. In the *top panel*, lung compliance decreases after the fourth breath. Initially, there is a drop in tidal volume, but then the DCBB algorithm gradually increases the target inspiratory pressure to restore the volume. In the *bottom panel*, lung compliance increases after the fourth breath. Initially, there is an increase in tidal volume, but then the DCBB algorithm gradually reduces the inspiratory pressure target to restore the volume. (Reproduced, with permission, from Branson and Johannigman *Respir Care.* 2005;50:187–201.)

breaths, a rate-of-rise adjustment usually is available on DCBB breaths. When time-cycled DCBB breaths are interspersed with either spontaneous unsupported or pressure-supported breaths, or when flow-cycled DCBB breaths are interspersed with conventional PACV breaths, algorithms similar to SIMV or mandatory minute volume are often used to determine which breath type will be delivered.[27]

Both animal and human studies show that DCBB breaths function as designed using both flow-cycled and time-cycled approaches.[23–29] These studies emphasize that the DCBB

breath is similar to other pressure-targeted breaths with enhanced gas mixing and better patient–ventilator flow synchrony as compared with flow-targeted, volume-cycled breaths. They also confirm that DCBB breaths do provide a volume guarantee without untoward side effects. Not surprisingly, several of these studies showed lower peak pressures with DCBB breaths than with volume assist-control breaths.[23,24] This, however, is a finding consistent with the decelerating flow patterns of all pressure-targeted breaths (e.g., pressure support and PACV).

The role of DCBB modes in providing "lung-protective strategies" for patients with acute lung injury is unclear. Lung-protective strategies are based on data from numerous animal studies and clinical trials that low tidal volumes and low end-inspiratory lung-stretching pressures reduce ventilator-induced lung injury.[30] Setting a low tidal volume (e.g., 6 mL/kg ideal body weight) directly with flow-targeted volume-cycled breaths is the most reliable way to assure that a desired low tidal volume is delivered. Some researchers argue, however, that the set flow breath during low tidal ventilation may be particularly uncomfortable and that the variable flow feature of pressure-targeted breaths may synchronize better with patient efforts under these circumstances.[31,32] Assuring a guaranteed tidal volume with a pressure-targeted DCBB breath would seem an attractive way to combine these features. Kallet et al addressed this issue. Although they found that DCBB breaths did provide a more reliable small tidal volume ventilatory pattern than pure pressure assist control, in a minority of patients up to 14% of tidal volumes were above the desired target value.[33,34] Whether this variability is an acceptable trade-off for improved comfort during lung-protective ventilation needs further study.

DCBB breaths have also been evaluated during the ventilator-withdrawal process. Several evidence-based consensus groups have found that routine use of daily spontaneous breathing trials is critical in assessing ventilator discontinuation potential.[35] Less clear, however, is the role of gradually reducing ventilator support ("weaning"), either before or between spontaneous breathing trials. If weaning is desired, however, the DCBB modes have some conceptual appeal. Theoretically, the DCBB breath could be used to automatically reduce applied inspiratory pressure as the patient's ability to breathe improved. Conversely, inspiratory pressure would increase if patient effort diminished or respiratory system mechanics worsened. Flow-cycled DCBB breaths, either alone or in combination with time-cycled DCBB breaths or various SIMV and/or pressure-support modes, have been used in several weaning studies. In general, they have performed as well as (or sometimes better than) stand-alone SIMV or pressure-support protocols, especially in the rapidly recovering (e.g., postoperative) patient.[29,36–39] A common finding in these weaning studies is that the DCBB breath modes required fewer ventilator manipulations. One must be cautious, however, in interpreting these weaning studies. A number of clinical trials show that the SIMV or SIMV + pressure-support control strategies delay weaning inappropriately as compared with spontaneous breathing trials or stand-alone pressure-support strategies.[40,41] A more appropriate evaluation of DCBB breath-weaning strategies would be a comparison with spontaneous breathing trials delivered according to a protocol.[35,42,43]

Unfortunately, the simplicity of the DCBB modes for weaning may produce problems.[44] For instance, if the clinician-set volume is excessive for patient demand, a recovering patient may not attempt to take over the work of breathing for that volume and thus support reduction and weaning may not progress. In addition, if the pressure level increases in an attempt to maintain an inappropriately high set tidal volume in the patient with airflow obstruction, intrinsic PEEP may result. On the other hand, a patient may receive inadequate support if the clinician-set tidal volume is inadequate for patient demand. Under these conditions, a patient will perform excessive work to maintain a patient-desired tidal volume while the inspiratory pressure is being reduced because volume exceeds the clinician setting. Clinicians need to be aware of the behavior of DCBB breaths under a variety of circumstances to properly use this mode.

Tidal Volume Feedback Modes that Enhance the Dual Control Breath-to-Breath Principle

Airway occlusion pressure ($P_{0.1}$),[45] oxygen saturation (SpO_2),[37–39] and end-tidal CO_2 concentrations[46,47] have been incorporated into DCBB mode-control algorithms to adjust either the target V_T or the breath-delivery pattern. The one system that is commercially available uses end-tidal CO_2 and respiratory rate along with the tidal volume to adjust the applied inspiratory pressure.[47] Known by the proprietary trade name *SmartCare* (Dräger), the computerized feedback system attempts to find an inspiratory pressure support that maintains the respiratory rate and tidal volume in a clinician-set "comfort zone." The end-tidal CO_2 serves as a backup signal to assure adequate ventilation. The system is designed to wean the inspiratory pressure to as low a level as possible within these boundaries and then alert the clinician to perform a spontaneous breathing trial when this pressure reaches 9 cm H_2O.

A number of small observational trials have been done showing that the system did, indeed, keep patients in the clinician-selected "comfort zone" for 95% of the time.[46,47] In a larger randomized clinical trial, this approach appeared to remove ventilator support quicker than "physician-controlled" weaning.[48] Unfortunately, this control group did not have a protocolized spontaneous breathing trial approach, and thus may have had support removal delayed. Indeed, a subsequent trial noted that in the presence of an active protocol for discontinuing mechanical ventilation, automated withdrawal offered no advantage.[49] Even if it is not superior, however, an automated system that is "just as good" as clinicians could have applications in settings with rapidly recovering patients or low availability of clinicians to make frequent assessments.

FEEDBACK CONTROL OF VENTILATOR BREATH DELIVERY BASED ON RESPIRATORY SYSTEM MECHANICS

A novel approach to automated feedback control of ventilator support combines the DCBB principle with an integrated V_T, frequency and inspiratory-to-expiratory (I:E) ratio algorithm based on respiratory system mechanics. Known as *adaptive lung ventilation* or *adaptive-support ventilation* (ASV, Hamilton Medical),[50–55] the breath-control algorithm attempts to partition the frequency, tidal volume, and I:E ratio so as to minimize ventilator–patient inspiratory work and intrinsic PEEP. ASV does this by calculating respiratory system mechanics using several "test breaths." It then uses a "minimal work" calculation to set the frequency–tidal volume pattern that minimizes the combined resistance and compliance components of work. The clinician must input the patient's predicted body weight and the percent of desired minute ventilation. The predicted body weight frames the tidal volume range, avoiding volutrauma and hypoventilation. The predicted needed minute volume is 0.1 L/kg/min. As an example, a 70-kg patient set at 100% would receive a 7 L minute volume. If the percent minute volume was set to 125%, in the presence of increased physiologic dead space the minute ventilation would be 8.75 L. The ASV algorithm then uses a measurement of the expiratory time constants (RCe = resistance × compliance) to ensure an inspiratory time of at least one RCe and an expiratory time of at least three RCes. The actual formula is:

$$f = \frac{\sqrt{1 \quad 2aRC(\dot{V}_A/V_D) - 1}}{aRC} \qquad (1)$$

where *RC* is the respiratory time constant (the product of resistance *R* and compliance *C*), $\dot{V}_A$ and V_D are alveolar ventilation and dead space ventilation, respectively, and *a* is a constant that depends on the flow waveform.

Boundary rules exist to prevent excessive (runaway) settings (Table 15-1). Clinicians must set the desired minute ventilation and the proportion of that minute ventilation that the machine is to supply. Ideal body weight also can be used to calculate the desired minute ventilation based on metabolic demands and predicted dead space. Clinicians also must set the PEEP and FI_{O_2}.

ASV as a pure control mode has been evaluated in a number of ways. Initial lung-model testing[56] demonstrated that the ASV algorithm responded properly to abrupt changes in lung mechanics. Several early clinical studies have compared initial ASV settings with traditional clinician-selected settings and have found that ASV tends to select a lower tidal volume and faster rate (and thus lower inspiratory pressures) than do clinicians.[56–59] Two other early studies suggest that ASV also appropriately adapts to changes in patient position and the change from double- to single-lung ventilation during anesthesia.[55–61] One other study suggested that the I:E algorithm of ASV produced less air trapping in patients with chronic obstructive pulmonary disease.[62] Longer-duration clinical studies with ASV show that the algorithm provides adequate ventilator support in anesthetized patients,[56,59] as well as in patients with respiratory failure.[63]

More recent evaluations of ASV, however, have focused on its ability to provide appropriate lung-protective small tidal volumes. Indeed, when respiratory system compliance is poor, the ASV algorithm supplies a protective low tidal volume ventilator pattern similar to that recommended by the ARDS Network.[54] Problems arise, however, when respiratory system compliance is less deranged (e.g., patients with milder forms of acute lung injury). Under these conditions, the ASV algorithm tends to deliver tidal volumes often in excess of 10 mL/kg ideal body weight.[45,64] The clinical significance of this is unknown but the potential harm from this should be considered by clinicians wishing to use this mode.

ASV also might be considered an automatic weaning mode because the algorithm responds with lower pressures and fewer mandatory breaths as patient effort increases. When spontaneous efforts occur with ASV, the algorithm continues to try to conform to the minimal work tidal volume considerations above and in that sense resembles the feedback features of volume support noted above.[65] The ASV feedback control, however, is more complex than volume support in that the predicted body weight input as well

TABLE 15-1: BOUNDARY CONDITIONS FOR ADAPTIVE LUNG OR SUPPORT VENTILATION

Parameter	Minimum	Maximum
Inspiratory pressure (cm H_2O)	5 above baseline airway pressure (PEEP/CPAP)	10 below P_{max} alarm setting
Tidal volume (mL)	4.4 · IBW	15.4 · IBW or $\dot{V}_E$/5, whichever is lower (may be limited by P_{max} alarm)
Target respiratory rate (bpm)	5 bpm	22 bpm · % min vol/100 (if IBW > 15 kg) 45 bpm · % min vol/100 (if IBW < 15 kg)
Mandatory breath rate (bpm)	5 bpm	60 bpm
Inspiratory time (s)	0.5 s or 1 · RCe, whichever is longer	2 s
Expiratory time (s)	2 · RCe (possibly 3 · RCe)	12 s
I:E ratio range	1:4	1:1

% min vol, clinician-set proportion of predicted minute volume needed by the patient that will be supplied by the ventilator (the percent minute volume is based on predicted body weight, e.g., for an 80-kg patient, 100% of minute volume is a minute ventilation of 8 L/min); *bpm*, allowable breaths/min; *CPAP*, continuous positive airway pressure; *IBW*, ideal body weight; *I:E*, inspiratory-to-expiratory-time ratio; *PEEP*, positive end-expiratory pressure; *Pmax*, clinician-set maximal inspiratory pressure; *RCe*, resistance × compliance; $\dot{V}_E$, exhaled minute volume.

Note: These parameters set the limits on the various parameters used during ASV.

as respiratory system resistance, and compliance (and the resulting time constant) modulate the tidal volume target. A number of studies have evaluated ASV in patients being weaned from mechanical ventilation.[50,63,66–70] In general, these studies show that ASV safely provides adequate ventilator support and has similar (or faster) weaning times as compared with various SIMV and SIMV + pressure support protocols.[66,70] These studies also generally show fewer ventilator manipulations with ASV. As noted earlier for other DCBB approaches, a more appropriate evaluation of ASV weaning strategies would be a comparison with use of spontaneous breathing trials delivered by protocol,[35,42,43] not with SIMV or SIMV + pressure support.

Larger trials in patients with different forms of lung injury clearly are needed to establish the appropriateness of the ASV algorithms in various disease states and the effects of ASV on outcome.

AUTOMATIC ADJUSTMENTS IN PRESSURE AND FLOW BASED ON ARTIFICIAL AIRWAY GEOMETRY

The endotracheal tube (ETT) imposes a significant inspiratory resistance on a spontaneously breathing patient.[71,72] This imposed load can have an impact on flow synchrony during interactive assisted or supported breaths, and can make it difficult to assess potential for ventilator withdrawal during periods of unassisted or unsupported breathing (Fig. 15-2, *left panel*).

Low-level (e.g., 5 to 8 cm H_2O) pressure support has been proposed as a way of eliminating the ETT resistive load.[73–75] Unfortunately, the pressure-support algorithm supplies a constant inspiratory pressure, which, because of the high fixed resistance of the ETT, tends to undercompensate the load at the beginning of the breath (see Fig. 15-2, *middle panel*). Patient muscle unloading thus is uneven and may be suboptimal.

One way to address this is to use a pressure sensor at the distal end of the ETT to target the pressure support applied pressure. This approach would provide a more even pressure application to the contracting inspiratory muscles. Unfortunately, this approach is unreliable because intra-air-way sensors are subject to errors from positioning and mucus occlusion. An alternative is to have the ventilator calculate the ETT resistance properties and use those calculations to manipulate applied pressure in such a way as to compensate for the ETT effects (see Fig. 15-2, *right panel*).[76,77] To accomplish this, the clinician must input the tube geometry (length and diameter) and the percentage of compensation desired (10% to 100%). The ventilator then uses these data to calculate ETT resistance and incorporates this with measurements of instantaneous flow to apply pressure proportional to resistance throughout the total respiratory cycle.

The ETT compensation concept was first introduced in 1993 by Guttmann et al[76] and was applied during both inspiration and expiration. It was believed that the expiratory

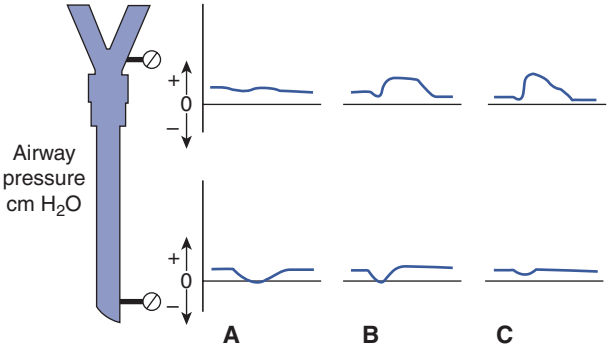

FIGURE 15-2 Effects of the endotracheal tube (ETT) resistance on the application of continuous positive airway pressure (CPAP), pressure support, and CPAP with ETT automatic tube compensation (CPAP-ATC) in a spontaneously breathing patient. Depicted are airway pressure profiles over time in the ventilator circuit (*upper panels*) and the distal trachea (*lower panels*). In the left breath, the CPAP tracing in the ventilator circuit is appropriately constant, whereas the tracheal pressure downswing reflects the patient work required to effect flow through the ETT. In the middle breath, pressure support is applied in the ventilator circuit. This reduces some of the patient work, but because the "square wave" pressure-support breath does not adequately pressurize the trachea rapidly enough, there still can be significant work required by the patient early in the breath. In the right breath, a similar pressure-support breath is applied, but the pressure profile is altered to provide a higher pressure early and the target pressure later (CPAP-ATC). This profile is machine determined, and knowledge of ETT geometry accounts more appropriately for the effects of ETT resistance. It thus creates a truer CPAP pattern in the trachea. Note that this ETT compensation feature also can be combined with pressure support on some ventilators. (Reproduced, with permission, from MacIntyre. *Respir Care.* 2005;50:275–286.)

effect (i.e., circuit pressure actually going below set baseline pressure or "subatmospheric" to "assist" expiratory flow) might further improve patient–ventilator interactions by reducing expiratory work and hyperinflation. In a series of ventilated patients, this approach was shown to improve subjective patient comfort substantially.[78]

Variations on this computational approach to manipulating applied pressure are now available as automatic tube compensation (Dräger, Covidien, and Maquet) and automatic airway compensation (CareFusion). Bench and clinical studies verify that the ETT compensation algorithms on these commercial systems generally perform as designed during both continuous positive airway pressure and pressure support.[79–81] Not all systems, however, have the expiratory feature, and the response characteristics of commercial systems may not be as robust as the Guttman design.[76]

It also must be recognized that the ETT compensation strategy is based on the input geometry of the artificial airway and cannot account for changes in tube characteristics induced by kinks or partial occlusions or the relationship of the tube opening against the tracheal wall. Thus, this strategy should not be considered a perfect surrogate for a tracheal pressure sensor, especially as the duration of intubation increases. Nevertheless, despite these limitations, and despite

the fact that ETT compensation has not been subjected to outcome studies, the simplicity of the concept and safety of the design would seem to warrant its application during pressure support and continuous positive airway pressure under most circumstances.

An interesting extension of the ETT compensation concept is to use a pleural pressure to target the positive-pressure breath.[82] This approach requires an esophageal balloon to measure esophageal pressure, a surrogate for pleural pressure. Conceptually, a pleural pressure target could be used to control the breath directly in such a way as to account for all the components of patient work, not just that caused by the ETT. At the present time, this approach has been explored only with prototype systems in experimental animals.

FEEDBACK SYSTEMS CONTROLLING POSITIVE END-EXPIRATORY PRESSURE AND CONCENTRATION OF FRACTIONAL INSPIRED OXYGEN

Maintenance of normal arterial oxygen saturation (SaO_2) is a key goal of mechanical ventilation. Hypoxemia has well-known consequences, including tissue injury, and if left uncorrected, can result in death. In modern intensive care units, hypoxemia is prevented through a variety of mechanisms including appropriate ventilator settings, sedation, analgesia, and maintenance of homeostasis. The current standard of care for detecting and ameliorating hypoxemia, however, has remained unchanged over the last 30 years. The clinician sets the low arterial oxyhemoglobin saturation (SpO_2) alarm setting and if the SpO_2 falls below this value (commonly 88%), an audible and visual alarm sounds. The alarm must be recognized by the clinician who must enter the room, elucidate the cause (e.g. ventilator disconnect, agitation, worsening pulmonary status), remedy the problem, and possibly increase the FI_{O_2}. This is an antiquated method that is analogous to trying to maintain the heat in your home by turning the furnace on or off based on falling below the "too cold" threshold.

Concentration of Fractional Inspired Oxygen Feedback Systems

The incidence of hypoxemia in ventilated adult intensive care unit patients is unknown. In neonatal intensive care units, hypoxemic events are frequent and life-threatening. Hyperoxemia also carries significant risk in this population. Recent data demonstrate that abdominal muscle contraction during crying and agitation is the most common cause of neonatal hypoxemia. The use of pressure-limited ventilation and uncuffed endotracheal tubes in infants, coupled with diaphragmatic contraction, profoundly limit oxygen delivery. [83] Both lung injury from oxygen toxicity and the retinopathy of prematurity are known complications of excessive oxygen exposure.

Closed-loop control of FI_{O_2} using either indwelling partial pressure of arterial oxygen (Pa_{O_2}) sensors, transcutaneous oxygen monitoring, and pulse oximetry has been attempted numerous times in the last 35 years.[84–91] Most of these investigations met with limited success owing to the sensor response and time required to alter delivered FI_{O_2}. Several of these studies used simple oxygen delivery to a head hood where both increases and decreases in FI_{O_2} occur slowly.

More recently, Claure et al performed a series of important investigations in closed-loop control of FI_{O_2} in neonates.[92–95] In their initial studies, the frequency of hypoxemia was not different between manual FI_{O_2} adjustment and automated FI_{O_2} adjustment. The nursing workload, however, was significantly less with the automated system.[96] In a second trial of sixteen mechanically ventilated infants, they found that, compared with manual adjustment, the percentage of time in the target SpO_2 range (88% to 95%) was greater during the automated control of FI_{O_2} (58% ± 10% vs. 42% ± 9%).[93] The percentage of time with SpO_2 less than 88%, however, increased during the automated period (33% ± 7% vs. 27% ± 9%) because of more frequent episodes of hypoxemia. The 4-hour median FI_{O_2} was lower during the automated period (29% ± 4% vs. 34% ± 5%).

The data suggest that by minimizing hyperoxemia (associated with retinal injury in premature infants), the incidence of hypoxemia may increase. The rapid response of the automated system to the hypoxemia, however, resulted in a similar durations of low SpO_2 between groups; that is, the number of hypoxemic events were more frequent, but the duration of each was shorter.

In their most recent trial of thirty-two premature infants, Claure et al demonstrated similar findings. The proportion of time that SpO_2 was in the target range (SpO_2 of 87% to 93%) was significantly greater during automated control of FI_{O_2} versus manual control (40% ± 14% vs. 32% ± 13%). Time with SpO_2 of less than 87%, however, increased significantly during the automated period (32% ± 12% vs. 23% ± 9%), with more frequent episodes with SpO_2 between 80% and 86%, whereas times with SpO_2 of less than 80% or less than 75% were not different. They also demonstrated significantly fewer manual FI_{O_2} changes (10 ± 9 vs. 112 ± 59 changes per 24 hours), compared with the manual period.[95] Figure 15-3 demonstrates the frequency of low SpO_2 events and required FI_{O_2} corrections in a single neonate on mechanical ventilation during a 4-hour period. This system remains under investigation and is not commercially available.

Johannigman et al investigated closed-loop FI_{O_2} in adult trauma patients with the goals of achieving normoxemia, preventing hypoxemia, and conserving oxygen.[97,98] These goals have significant importance during transport and in military operations. Closed-loop control of FI_{O_2} provides normoxemia regardless of the skill of the caregiver and prevents hypoxemia when patients are unattended.

Oxygen conservation is rarely an issue in the hospital, but is critical in resource-limited environments (e.g., mass casualty, far-forward deployments).

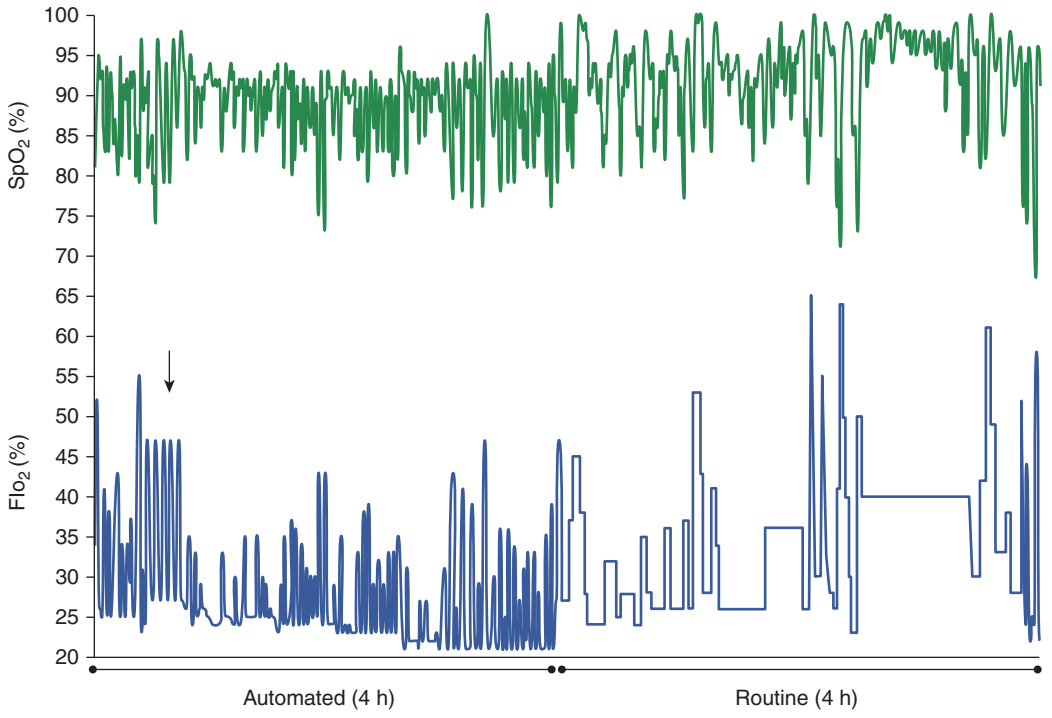

FIGURE 15-3 This recording of SpO_2 and FI_{O_2} illustrates the difficulty in maintaining SpO_2 within the intended range by manual FI_{O_2} adjustments during the routine period. These adjustments were not always consistent, and exposure to high FI_{O_2} was at times prolonged. Automated FI_{O_2} increases were brief in a gradually decreasing basal FI_{O_2}. The *arrow* points to manual FI_{O_2} adjustments during care procedures with the automated system on standby. (Used, with permission, from Claure, D'Ugard, and Bancalari.[93])

In an early pilot and follow-up study of forty-five trauma patients, Johannigman et al compared 4 hours of closed-loop control to 4 hours of manual FI_{O_2} control. They found that the target SpO_2 (92% to 96%) was achieved 82% of the time during closed-loop control versus only 37% of the time during manual control. The most common "out-of-target" condition in the manual control group was hyperoxemia (SpO_2 >97%), seen 61% of the time versus 17% during closed-loop control. The total time spent with SpO_2 less than 88% per patient was small (<1 minute) and was not different between groups. The authors also noted that many trauma patients never manifest hypoxemia, regardless of the study arm. Figure 15-4 is a graph of FI_{O_2} and SpO_2 during the 8-hour trial. This finding was recently supported by a Dutch study demonstrating hyperoxemia in trauma patients in spite of low inspired oxygen (<0.40).[99] These authors demonstrated that even in the face of significant hyperoxemia (Pa_{O_2} >120 mm Hg), if inspired oxygen was equal to or less than 0.40, clinicians rarely reduced FI_{O_2}. This was thought to be secondary to the commonly held belief that FI_{O_2} less than 0.50 is nontoxic to the lungs. This, however, does not account for potential negative consequences at the cellular level as a result of oxidative stress.[100] Oxygen usage was significantly less during closed-loop control (3 L/min) versus manual control (2.1 L/min). This 33% decrease in oxygen usage might be significant where oxygen stores are limited. Additionally, this level of oxygen requirement could be met with an oxygen concentrator.

Both these systems use a proportional-integral-derivative (PID) controller. In this case, a negative feedback PID system. A negative feedback system attempts to minimize the difference between the target value and the actual value. Ideally, the difference between target and measured is zero. In this instance, the FI_{O_2} is changed until the difference between the target SpO_2 and the measured SpO_2 is zero. A PID controller allows the FI_{O_2} to be changed in large steps based on the level of SpO_2 and the difference in set and actual SpO_2. When the target and measured values are close, the changes in FI_{O_2} are smaller. The FI_{O_2} can be adjusted both by changing the stepwise increase or decrease as well as the time between steps. At the time of this writing, no closed-loop FI_{O_2} system for mechanical ventilation is commercially available.

Concentration of Fractional Inspired Oxygen and Positive End-Expiratory Pressure Feedback Systems

Setting PEEP remains one of the most contentious issues in mechanical ventilation. Although automated control of FI_{O_2} is relatively simple, the effects of PEEP on hemodynamics, airway pressures, and lung protection create a much greater challenge. In preliminary findings, Lellouche et al found that in cardiac surgery patients, automated control of PEEP and FI_{O_2} resulted in similar outcomes compared to manual manipulations.[101] Interestingly, this group utilized

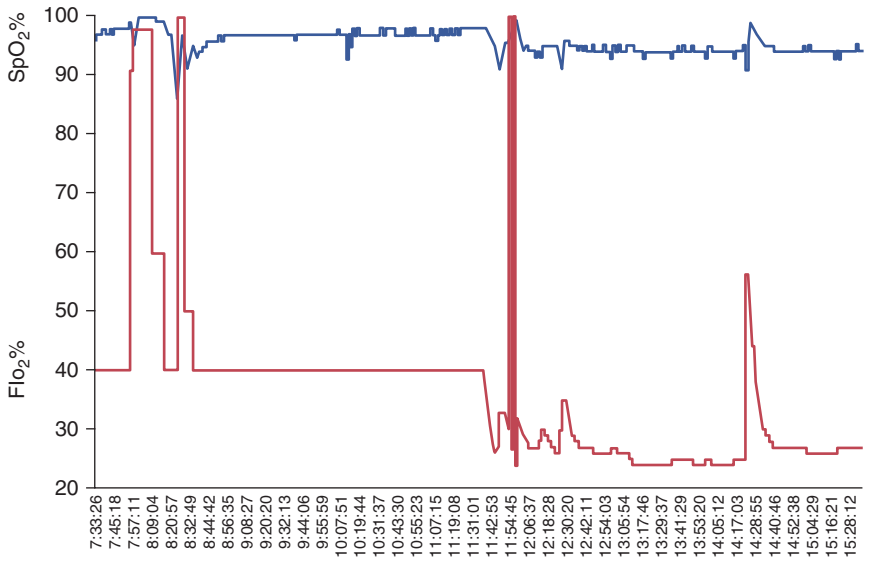

FIGURE 15-4 Example of closed-loop control of SpO_2 in an adult patient with traumatic respiratory failure. The first 4 hours represent the manual control period and the second 4 hours the automatic control period. Increases in FI_{O_2} to 100% are associated with hypoxemia (SpO_2 <88%).

the PEEP–FI_{O_2} table from the original ARDS Network trial to control the algorithm. We believe that a commercially available version of closed-loop control of PEEP would require some inference of hemodynamic performance or confirmation of hemodynamic stability by the caregiver. It may be that a decision-assist system for PEEP would be the first step.

FEEDBACK SYSTEMS DRIVEN BY NOVEL SENSORS OF PATIENT EFFORT

In the last decade, two novel feedback modes for delivering positive pressure in response to patient effort have been introduced.[50] The first is proportional-assist ventilation (PAV), which uses measured patient-generated inspiratory flow and then puts a clinician-set gain on both pressure and flow delivery.[102] PAV needs estimates of respiratory system compliance and resistance, which are determined from intermittent controlled "test" breaths or periodic pauses randomly applied during ventilation. The only clinician setting is then a proportion of the calculated work of breathing that the delivered flow and pressure are meant to overcome. The second is neurally adjusted ventilator assist (NAVA), which uses a diaphragmatic electromyogram signal on an esophageal catheter to determine patient effort during all three phases of breath delivery (i.e., trigger, flow delivery, and cycling).[103] Like PAV, NAVA applies a clinician-set gain to provide pressure and flow adjustments in proportion to the strength of the electromyogram signal. As these modes are not considered "conventional" modes of ventilation, they are not discussed further here. The reader is referred to more detailed accounts of these approaches in Chapters 12 and 13.

CONCLUSION

A positive-pressure breath ideally should provide a V_T that is adequate for gas exchange and appropriate muscle unloading while minimizing any risk for injury or discomfort. The latest generation of ventilators is now using sophisticated feedback systems to "sculpt" positive-pressure breaths according to patient effort and respiratory system mechanics. At the present time, however, these new control strategies are not totally "closed-loop" systems because the automatic input variables are still limited, some clinician settings are still required, and the specific features of the "perfect" breath design still are not entirely clear. Despite these limitations, there is at least some rationale for many of these newer feedback features, even though all of them await outcome studies to justify their widespread use.

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VI

NONINVASIVE METHODS OF VENTILATOR SUPPORT

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16

NEGATIVE-PRESSURE VENTILATION

Antonio Corrado
Massimo Gorini

Conventional mechanical ventilation via endotracheal intubation or tracheostomy in the treatment of acute respiratory failure (ARF) is a lifesaving procedure. Yet it exposes patients to severe complications, including upper airway trauma and nosocomial pneumonia, and may prolong the length of stay in the intensive care unit (ICU) and hospital because additional time may be necessary for weaning.[1–4]

BASIC PRINCIPLES OF NEGATIVE-PRESSURE VENTILATION

Negative-pressure ventilation (NPV) works by exposing the surface of the thorax to subatmospheric pressure during inspiration. This pressure causes thoracic expansion and a decrease in pleural and alveolar pressures, creating a pressure gradient for air to move from the airway opening into the alveoli. When the pressure surrounding the thorax increases and becomes atmospheric or greater, expiration occurs passively owing to the elastic recoil of the respiratory system. The inspiratory changes with NPV, in pleural and alveolar pressures, replicate those during spontaneous breathing. On the contrary, positive-pressure ventilation (PPV) causes an increase in intrathoracic pressures during inspiration (Fig. 16-1).

All NPVs have two major components: an airtight, rigid chamber that encloses the rib cage and abdomen and a pump that generates pressure changes in the chamber.[5,6]

Negative-Pressure Ventilators

TANK VENTILATOR

Tank ventilators enclose the body up to the neck. The advantage is that chest wall expansion is not limited by contact with the sides of the chamber, and only one airtight

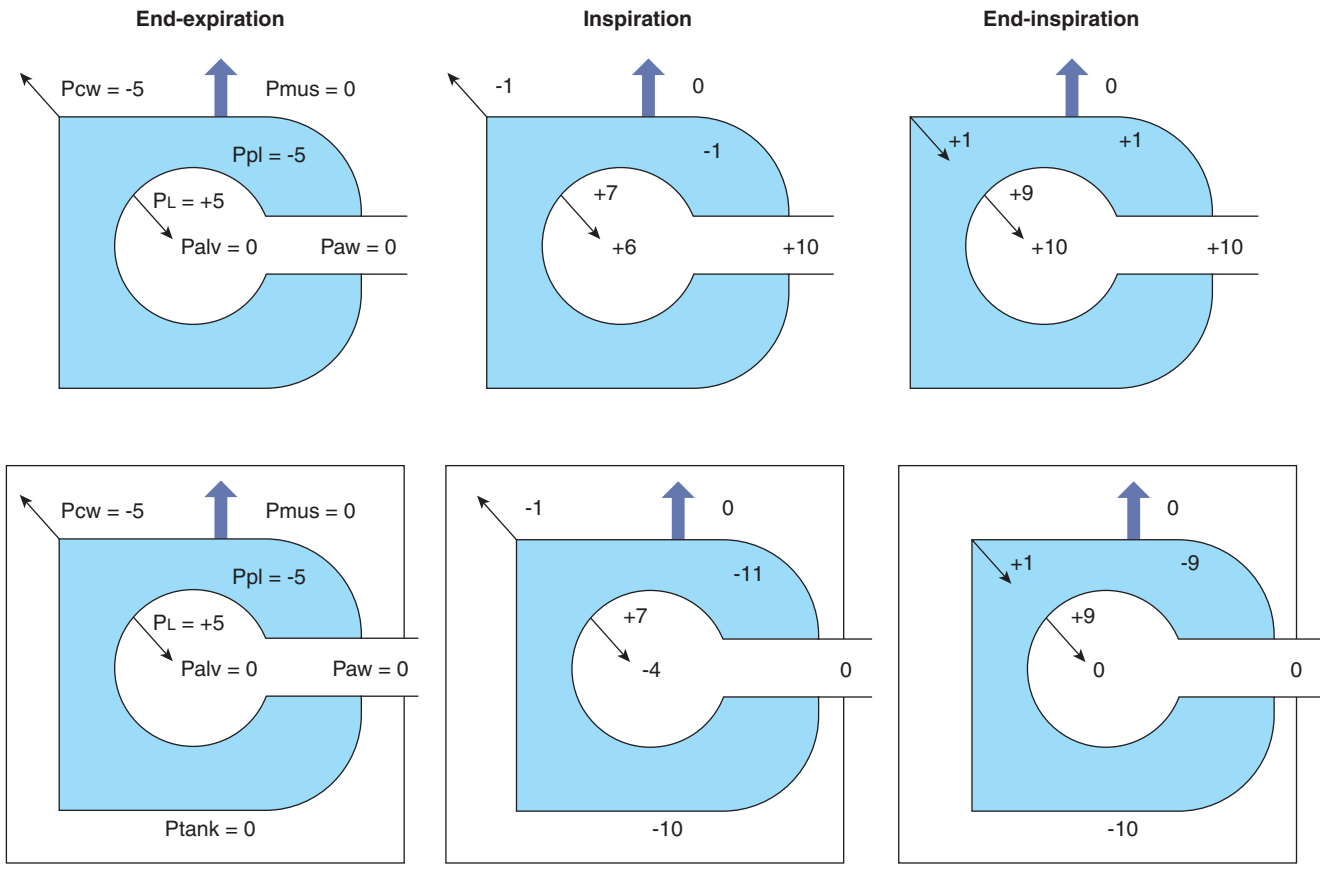

FIGURE 16-1 Airway and intrathoracic pressures during positive-pressure ventilation (*upper panel*) and during negative-pressure ventilation (*bottom panel*). *Palv,* Alveolar pressure; *PCW,* elastic recoil pressure of the chest wall; *PL,* elastic recoil pressure of the lung; *Paw,* airway pressure; *Pmus,* muscle pressure; *Ppl,* pleural pressure; *Ptank,* tank ventilator pressure.

seal is required around the neck. Most modern tank ventilators are constructed of aluminium and plastic and are lighter than previously. The patient's body rests on a thin mattress, and the head protrudes through a porthole at one end of the ventilator. A head and neck rest is provided in most designs to ensure comfort and to prevent upper airway collapse. Most tank ventilators have windows allowing patient observation and portholes for catheters and monitor leads and where procedures can be performed (Fig. 16-2).[7]

JACKET VENTILATOR (PULMO-WRAP, PONCHO-WRAP)

This ventilator is a windproof, water-permeable nylon parka suspended over a rigid grid that includes the rib cage and abdomen. It allows the application of negative pressure over the anterior portion of the chest wall.[8] Airtight seals around the neck, arms, and hips are required to prevent air leakage. The jackets do not restrain expansion of the rib cage and abdomen, but are awkward for many patients to put on and often cold to wear because of air leaks. They are preferable to tank ventilators for home use but less efficient for treating patients with ARF. The tidal volume they develop at any given level of negative pressure is less than that of a tank ventilator, and the peak pressure that patients can tolerate also usually is slightly less.[6]

CUIRASS

This consists of a rigid shell fitting firmly over the anterior portion of the chest. It applies negative pressure over a smaller surface area than either the iron lung or jacket and is the least efficient NPV.[8] Its efficiency improves if the anterior abdominal wall is enclosed in the device and movement of the lateral aspect of the upper rib cage is not restrained. Proper fitting can be difficult, and tailor-made fiberglass shells often are necessary, particularly in patients with kyphoscoliosis.

Negative-Pressure Ventilator Pumps

Negative pressure is generated by bellows or rotary pumps that are separate or incorporated into the structure of the ventilator. Modern rotary pumps perform pressure-preset

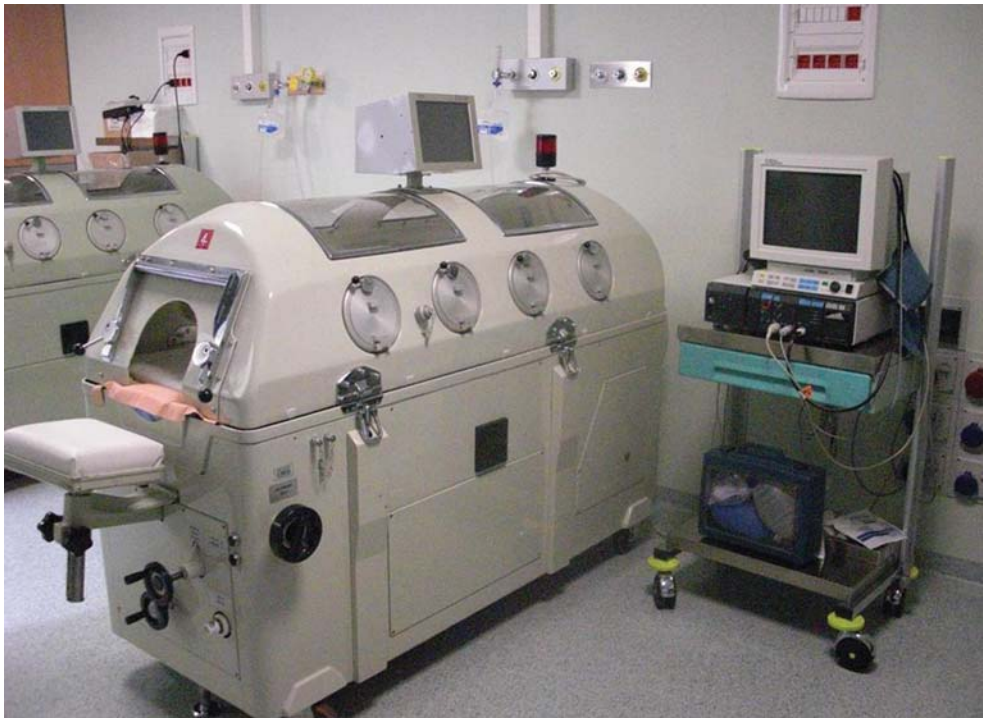

FIGURE 16-2 Microprocessor-based iron lung (Coppa CA 1001, Coppa, Biella, Italy).

ventilation.[9] After a breath is initiated, these pumps apply and maintain a targeted amount of subatmospheric pressure around the chest wall to meet a specified time-cycling criterion (Fig. 16-3). This mode is equivalent to pressure-controlled ventilation available with the latest PPVs. As with positive-pressure preset ventilation, tidal volume during NPV is a complex function of applied pressure and its rate of approach to target pressure, available inspiratory time, and the impedance to breathing (compliance of the respiratory system, airway resistance, and dynamic hyperinflation with intrinsic positive end-expiratory pressure [PEEP]).

Modes for Delivering Negative-Pressure Ventilation

Traditionally, NPV is controlled mechanical ventilation, and the device provides a fixed number of breaths per minute. If mechanical and spontaneous respiratory cycles do not match, the patient "fights" the ventilator, resulting in discomfort. Unlike PPV, during NPV, the airway opening is free; consequently, it is not possible to monitor airway pressure or flow continuously and to use these signals to trigger a mechanical breath. This patient-triggering inability may contribute to poor patient synchrony and induction of upper airway collapse secondary to the lack of coordinated activity between the upper airway and the inspiratory muscles.[10] To overcome this limitation, some NPVs have incorporated patient-triggered modes using pressure change sensed via nasal prongs. There are data indicating that this technology is slow and relatively insensitive to patient inspiratory efforts.[11] Recently, the performance of a prototype microprocessor-based iron lung capable of thermistor triggering was evaluated.[12] The device used to trigger the iron lung was thermally sensitive and similar to that used in sleep studies, and it was activated by temperature changes caused by the onset of inspiratory airflow (Fig. 16-4). In normal subjects and patients with chronic obstructive pulmonary disease (COPD) recovering from ARF, we measured (a) the time delay between airflow onset and start of an assisted breath, (b) pressure-time product for the diaphragm per minute (PTPdi) during triggered breaths, and (c) nontriggering inspiratory efforts (Fig. 16-5). At maximum trigger sensitivity, the time delay was about 0.21 second in both groups. PTPdi was reduced markedly. Nontriggering inspiratory efforts were 1.1% and 2.3% of total breaths, respectively. Although the time delay of the thermistor trigger is longer than most recent flow-triggering and pressure-triggering systems of PPVs,[13] the study suggests that this system permits the use of assisted NPV with an acceptable patient–ventilator interaction.

Presently, NPV can be delivered by five modes: (a) intermittent negative pressure, (b) negative/positive pressure, (c) continuous negative pressure (CNEP), (d) negative pressure/negative end-expiratory pressure (Fig. 16-6), and (e) external high-frequency oscillation.

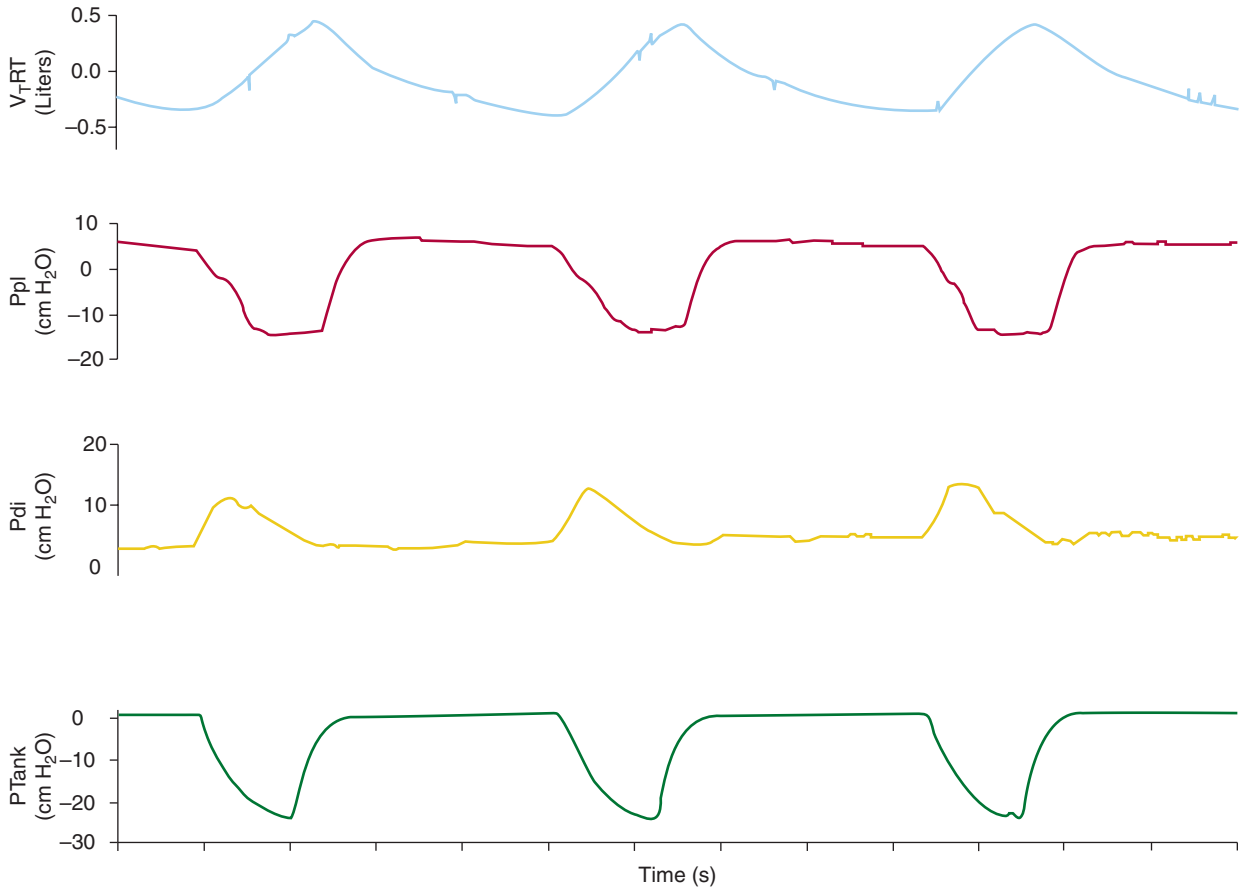

FIGURE 16-3 Recordings of tidal volume by Respitrace (V_T *RT*), pleural pressure (*Ppl*), transdiaphragmatic pressure (*Pdi*), and tank pressure (*Ptank*) in a patient with an acute exacerbation of chronic obstructive pulmonary disease during assist negative-pressure ventilation provided by iron lung.

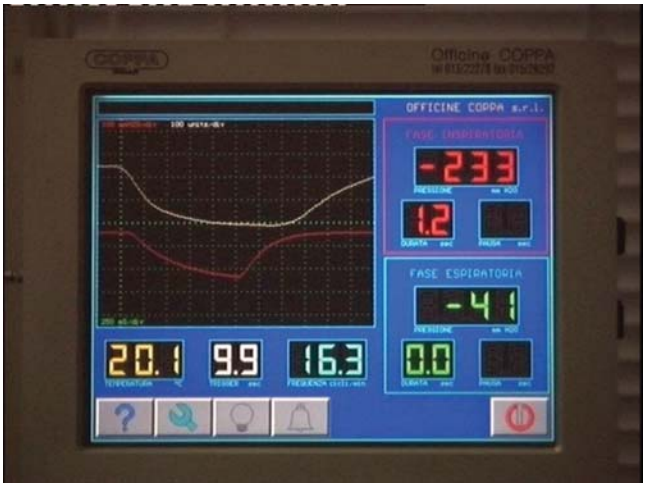

FIGURE 16-4 Control panel of a microprocessor-based iron lung (Coppa CA 1001, Coppa, Biella, Italy) capable of thermistor triggering. The upper trace is the thermistor signal, and the lower trace is the tank pressure.

INTERMITTENT NEGATIVE PRESSURE

The ventilator generates targeted subatmospheric pressure for the selected inspiratory time. Pressure around the chest wall becomes atmospheric during expiration, which occurs passively owing to the elastic recoil of the respiratory system.

NEGATIVE/POSITIVE PRESSURE

The ventilator generates the preset extrathoracic subatmospheric pressure during inspiration and preset extrathoracic positive pressure during expiration. In patients with chest wall disorders, this combination has been found to increase tidal volume more than intermittent negative pressure alone by reducing the end-expiratory volume of the respiratory system.[14] A useful application of this option is to assist cough and promote clearance of sputum in patients with copious secretions i.e., cystic fibrosis and bronchiectasis.[8]

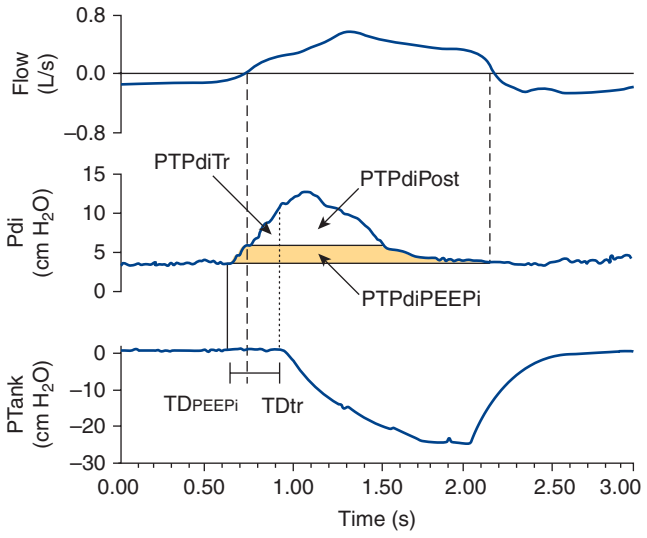

FIGURE 16-5 Recordings of flow, transdiaphragmatic pressure (*Pdi*), and tank pressure (*Ptank*) in a patient with chronic obstructive pulmonary disease receiving assist NPV. The *continuous vertical line* indicates the onset of inspiratory effort, the *dashed vertical line* indicates the start of inspiratory flow, and the *dotted vertical line* indicates the start of an assisted breath. The partitioning of the pressure-time product of the diaphragm is shown: effort required to overcome intrinsic positive end-expiratory pressure (*PTPdiPEEPi*), effort required to trigger the assisted breath (*PTPdiTr*), and effort exerted in the post-trigger phase (*PTPdiPost*). TDPEEPi and TDtr indicate the time delay between the onset of inspiratory effort and the start of inspiratory flow and the time delay between the onset of inspiratory flow and the start of assisted breath, respectively. (Used, with permission, from Gorini, et al. Effect of assist negative pressure ventilation by microprocessor based iron lung on breathing effort. *Thorax.* 2002;57:258–262.)

FIGURE 16-6 Control panel of a microprocessor-based iron lung (Coppa CA 1001, Coppa, Biella, Italy) during intermittent negative pressure (*upper-left panel*), negative and/or positive pressure (*upper-right panel*), continuous negative extrathoracic pressure (*lower-left panel*), and negative pressure or negative extrathoracic end-expiratory pressure (*lower-right panel*) ventilation.

CONTINUOUS NEGATIVE EXTRATHORACIC PRESSURE

The ventilator provides a constant subatmospheric pressure throughout the respiratory cycle, and the patient breathes spontaneously.

NEGATIVE PRESSURE AND NEGATIVE EXTRATHORACIC END-EXPIRATORY PRESSURE

The ventilator generates the preset subatmospheric pressure during inspiration and maintains a preset level of negative pressure throughout the expiration.

EXTERNAL HIGH-FREQUENCY OSCILLATION

High-frequency ventilation using a jet system can be applied via a tracheal tube or a tracheotomy. Alternatively, a cuirass can be used to apply high-frequency oscillation externally.[15] The Hayek oscillator includes a cuirass, power unit, and control unit. The power unit has (a) a diaphragmatic pump, which can operate over a wide range of frequencies to generate an oscillating pressure wave, and (b) a vacuum pump, which enables the oscillation to be superimposed on a negative-pressure baseline. Peak inspiratory (up to −70 cm H_2O) and peak expiratory (up to 70 cm H_2O) pressures, frequency (8 to 999 cycles per minute), and inspiratory-to-expiratory timing (I:E) ratio (1:6 to 6:1) can be set on the control unit.

Two studies suggest that external high-frequency oscillation can provide effective ventilation in healthy subjects[15] and improve end-tidal carbon dioxide (CO_2) and oxygen (O_2) saturation (SaO_2) in patients with severe stable COPD.[16] In five patients with ARF, short-term application of external high-frequency oscillation improved oxygenation by 16% and reduced Pa_{CO_2} by 6%, compared with conventional PPV.[15] In a randomized, controlled study, a 4-hour period of external high-frequency oscillation improved cardiac index and tissue perfusion in adult patients after coronary artery bypass grafting compared with conventional PPV.[17]

PHYSIOLOGIC EFFECTS

Gas Exchange

Pioneering studies showed NPV, particularly that provided by tank ventilators, to be a highly effective form of mechanical ventilation, capable of maintaining normal arterial blood-gas tensions in patients with little or no spontaneous respiratory activity.[18–20] Recently, it has been shown[21] that CNEP, NPV, and NPV plus negative extrathoracic end-expiratory pressure provided by a microprocessor-based iron lung were able to improve ventilatory pattern, arterial blood gases, and pH significantly (Fig. 16-7).

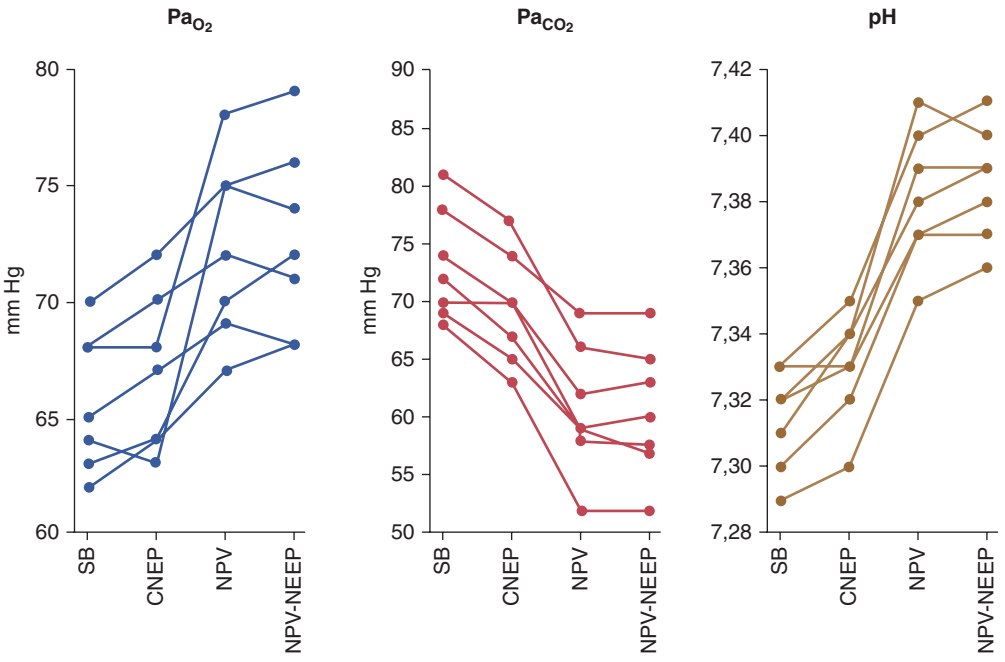

FIGURE 16-7 Values for Pa_{O_2}, Pa_{CO_2}, and pH in seven patients with acute exacerbation of chronic obstructive pulmonary disease during spontaneous breathing (*SB*), continuous negative extrathoracic pressure (*CNEP*), negative pressure ventilation (*NPV*), and negative extrathoracic end-expiratory pressure added to NPV (*NPV-NEEP*). (Reprinted with permission of the American Thoracic Society. Copyright © 2012 American Thoracic Society. Used, with permission, from Gorini, et al. *Am J Respir Crit Care Med.* 2001;163:1614–1618. Official Journal of the American Thoracic Society.)

Respiratory Muscles

Two studies[22,23] reported that in patients with acute exacerbation of COPD, NPV was effective in improving respiratory muscle strength and in decreasing Pa_{CO_2}. In patients with chronic respiratory failure secondary to COPD and restrictive diseases, NPV reduced electrical and mechanical activity of the inspiratory muscles.[24–28] Rodenstein et al[29] showed that controlled NPV provided by an old iron lung requires a short period of adaptation to obtain inspiratory muscle rest. Other studies show that when inspiratory and expiratory times are adjusted carefully to approximate the subject's spontaneous timing components, NPV results in a substantial suppression of electromyographic activity of inspiratory muscles.[25,26] Assist-control NPV provided by a cuirass is effective in relief of dyspnea induced experimentally in normal subjects by a combination of inspiratory resistive loading and hypercapnia, probably reducing inspiratory muscle workload.[30]

The effects of NPV provided by a microprocessor-based iron lung capable of providing CNEP and assist-control NPV on respiratory mechanics and inspiratory muscle effort in patients with COPD with ARF were evaluated by measuring the pressure-time product of the diaphragm and the electromyographic activity of parasternal muscles.[21] Compared with spontaneous breathing, CNEP (−5 cm H_2O) resulted in a significant decrease in dynamic intrinsic PEEP and pressure-time product of the diaphragm, whereas assist-control NPV caused a significant improvement in the pattern of breathing associated with a marked reduction in both pressure-time product of the diaphragm and electromyographic activity of the parasternal muscles. The application of −5 cm H_2O of negative extrathoracic end-expiratory pressure during NPV further decreased the pressure-time product of the diaphragm slightly and improved patient–ventilator interaction by reducing dynamic intrinsic PEEP and nontriggering inspiratory effort (Fig. 16-8). Reduction in diaphragmatic effort obtained during assist-control NPV[21] is similar to that measured in patients with an acute exacerbation of COPD with pressure-support ventilation.[31,32]

Upper Airway

The application of NPV during sleep in normal subjects,[33] and in patients with chronic respiratory failure secondary to COPD[10] and neuromuscular disorders,[34,35] may result in the development of recurrent episodes of apnea and hypopnea, as well as altered sleep quality.[10,34] However, a recent controlled study in patients with neuromuscular disorders showed that NPV resulted in a general improvement in sleep quality and oxygen saturation.[36] It has been reported that in normal subjects during voluntary respiratory muscle relaxation, NPV caused a decrease in the caliber of the upper airway at the glottic or supraglottic level.[37] In normal, awake subjects, the glottis width did not decrease with the increase in negative pressure applied to the chest wall.[38] Consequently, the increasing level of NPV resulted

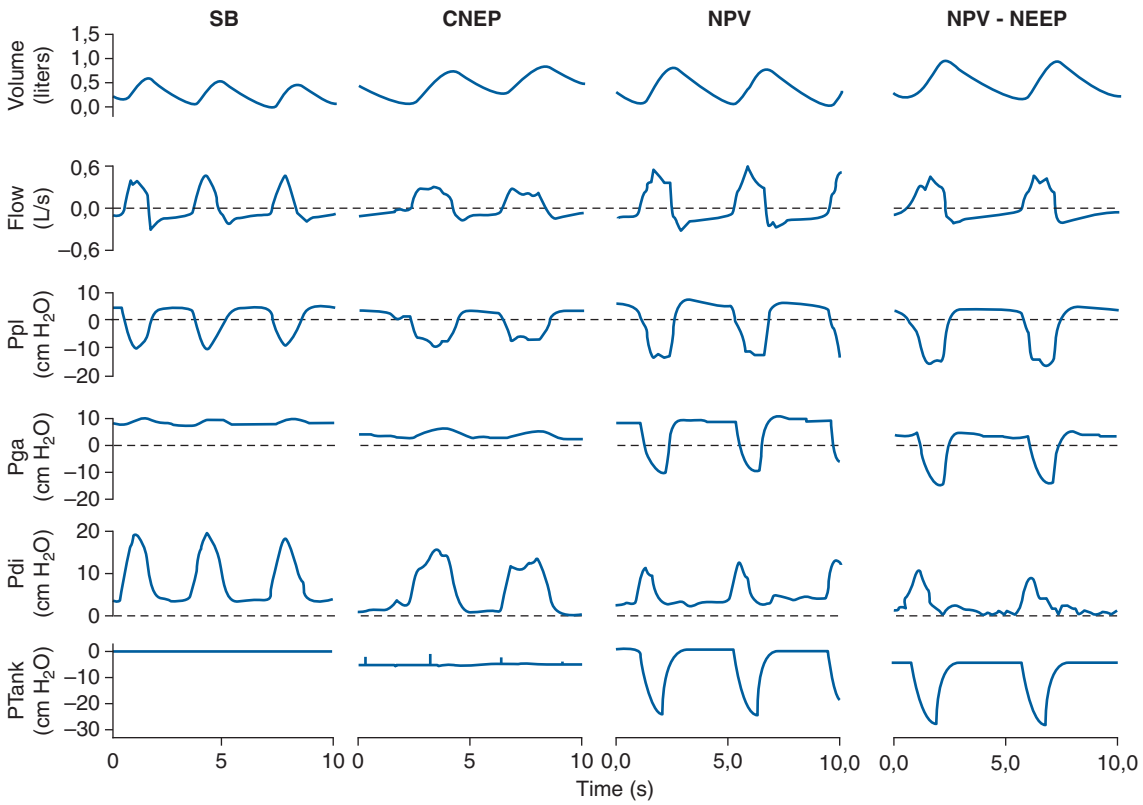

FIGURE 16-8 Recordings of volume, flow, pleural pressure (*Ppl*), gastric pressure (*Pga*), transdiaphragmatic pressure (*Pdi*), and tank pressure (*Ptank*) in a patient with an acute exacerbation of COPD during spontaneous breathing (*SB*), continuous negative extrathoracic pressure (*CNEP*), negative-pressure ventilation (*NPV*), and negative extrathoracic end-expiratory pressure added to NPV (*NPV-NEEP*). The *dashed lines* indicate the level of zero in flow, Ppl, Pga, and Pdi recordings. (Reprinted with permission of the American Thoracic Society. Copyright © 2012 American Thoracic Society. Used, with permission, from Gorini, et al. *Am J Respir Crit Care Med.* 163:1614–1618. Official Journal of the American Thoracic Society.)

in progressive increases in tidal volume and minute ventilation. On the contrary, control positive-pressure ventilation provided by mask caused inspiratory adduction of the vocal cords, which reduced the tidal volume effectively reaching the lungs.[39,40]

The mechanisms of upper airway obstruction observed with NPV at supraglottic level have not been elucidated fully. During spontaneous breathing, activation of the pharyngeal and laryngeal muscles precedes activation of the inspiratory muscles, resulting in stiffening of the upper airway walls. When NPV is applied during sleep or in completely relaxed subjects, this coordinated respiratory muscle activity may be abolished. Consequently, the subatmospheric pressure developed in the upper airway during inspiration may result in their collapse.[5,10,34,37] Upper airway obstruction has been reported in two of ten patients with acute-on-chronic respiratory failure during treatment with NPV[41] and was the reason for NPV failure in 16% of patients in a large prospective cohort study.[42]

Lower Esophageal Sphincter

NPV may induce a lower esophageal sphincter dysfunction in healthy subjects[43] and in patients with COPD.[44] This dysfunction may cause regurgitation of stomach contents and expose patients to the risk of aspiration. It can be prevented completely with metoclopramide.[44]

Cardiovascular

The hemodynamic effects of mechanical ventilation are complex and are the result of changes in intrathoracic pressure and lung volume, which independently can affect the determinants of cardiovascular performance.[45–47] The increase in intrathoracic pressure caused by PPV decreases both venous return to the right ventricle and left-ventricular afterload. The net effect of this reduction depends on the cardiac function. When left-ventricular function is impaired, cardiac output increases in response to the rise in intrathoracic pressure because the decrease in left-ventricular afterload secondary to the reduction in transmural pressure has a greater effect than the decrease in venous return.[48] When left-ventricular function is normal, the increase in intrathoracic pressure reduces cardiac output because the decrease in venous return has more effect than the decrease in left-ventricular afterload.[49] In clinical situations such as hypovolemia, septic shock, and gas trapping associated with airflow obstruction, the reduction in cardiac output is more relevant.[50]

Although the hemodynamic effects of NPV have not been studied extensively,[51] the effects are assumed to be the opposite of those of PPV, that is, more physiologic and more likely to maintain a normal cardiac output. The exposure of the entire body (except for the airway opening) to NPV by tank ventilators, however, results in the same hemodynamic effects as occurs with PPV.[52] These effects occur because intrathoracic pressure actually is raised relative to body surface pressure, reducing the gradient for venous return. This consequence is not seen when NPV is confined to the thorax and upper abdomen using a cuirass or poncho-wrap.[53,54] Unlike tank ventilators, these machines selectively decrease intrathoracic pressure so that right-atrial pressure becomes more negative relative to the rest of body, potentially enhancing the gradient for venous return. In an animal model of acute lung injury, NPV plus negative extrathoracic end-expiratory pressure, provided by poncho-wrap, resulted in a similar improvement in gas exchange and in higher cardiac output compared with PPV plus PEEP.[53] In anaesthetized dogs, PPV plus PEEP and NPV plus negative extrathoracic end-expiratory pressure applied by iron lung had a similar effect on cardiac output, whereas the latter was higher with NPV plus negative extrathoracic end-expiratory pressure applied by poncho-wrap compared with the other two modes.[54]

NPV provided by cuirass does not induce adverse hemodynamic effects in stable patients with COPD,[55] whereas a significant reduction in cardiac output has been reported with mask ventilation with PEEP in patients with COPD, both when stable[56] and during acute exacerbations.[57] Short-term studies have compared the effects of CNEP provided by cuirass[58] or poncho-wrap[59,60] with those of PEEP in intubated patients with acute lung injury receiving volume-controlled ventilation. CNEP was adjusted to obtain the same change in transpulmonary pressure[60] or functional residual capacity[58] as with PEEP. The combination of volume-controlled ventilation with CNEP, compared with volume-controlled ventilation with PEEP, resulted in significant increases in oxygen delivery and cardiac index, whereas arterial oxygen content and Pa_{O_2}/FI_{O_2} ratio did not differ between the two modes of ventilation.[58–60] Further studies are required to define the feasibility of long-term clinical treatment with CNEP during controlled ventilation via endotracheal intubation and its effects on clinical outcomes. Children with congenital heart diseases, submitted to right-sided heart surgery with Fontan-type procedures, have unique cardiopulmonary physiology. In the absence of a right ventricle, pulmonary blood flow, the major determinant of cardiac output, is exquisitely sensitive to changes in intrathoracic pressure. In these patients, NPV, provided by cuirass, markedly increased pulmonary blood flow and cardiac output compared with volume-controlled PPV.[61,62]

Recently, the effects of CNEP applied to the chest through a cuirass during PPV in synchronized intermittent mandatory ventilation mode were evaluated in twenty patients with normal left-ventricular ejection fraction 2 hours after coronary artery bypass graft. With CNEP and synchronized intermittent mandatory ventilation, the stroke-volume index and cardiac index were significantly increased compared to ventilation with synchronized intermittent mandatory ventilation and PEEP. CNEP also reduced venous pressure and wedge pressure. Although the improvement in cardiac index and stroke volume was modest, the application of CNEP during PPV may have a greater benefit in patients with reduced ventricular function.[63]

RATIONALE, ADVANTAGES, AND LIMITATIONS

Rationale

NPV can be used to widen the field of application of noninvasive ventilator techniques. It is well known that compared with standard medical treatment, mask ventilation reduces the need for endotracheal intubation[64–66] and reduces hospital mortality[64–67] in selected patients with an acute exacerbation of COPD. A randomized study comparing mask with conventional mechanical ventilation in patients with exacerbations of COPD who failed medical treatment has shown that mask ventilation avoided endotracheal intubation in 48% of patients.[68] Mask ventilation, however, is not without its problems, and failure rates of 7% to 50% are reported.[69] Severe respiratory acidosis[70–72] and illness at presentation,[70,73] excessive airway secretions,[73] and inability to minimize the amount of air leakage[73] are major factors associated with failure of this technique.

In clinical studies, NPV has been used successfully in patients with severe respiratory acidosis or impaired level of consciousness.[74–76] During NPV, the airway opening is free, unlike in PPV, and consequently, performing bronchial aspiration or fiberoptic bronchoscopy to remove excessive airway secretions is easy. Finally, NPV can be used in patients who cannot tolerate a mask because of facial deformity, or as a rescue therapy to avoid endotracheal intubation in those in whom mask ventilation fails. Routine implementation of noninvasive PPV in critically ill patients with acute exacerbations of COPD or severe cardiogenic pulmonary edema was associated with improved survival and reduction of nosocomial infection.[77] For these reasons, mask ventilation is recommended as the standard method of ventilator support for exacerbations of COPD; invasive mechanical ventilation is regarded as second-line rescue therapy when mask ventilation fails.[78]

To verify the hypothesis that using both noninvasive mask and iron-lung ventilation should further reduce the need for endotracheal intubation in patients with acute on chronic respiratory failure, a prospective cohort study was carried out in 258 consecutive patients[42]: 77% of the patients were treated exclusively with noninvasive ventilation (40% with NPV, 23% with mask, and 14% with the sequential use of both) and 14% with invasive ventilation. In patients in whom NPV or mask ventilation failed, sequential use of the alternative technique allowed a significant reduction

in the failure of noninvasive mechanical ventilation (from 23.4% to 8.8%, p = .002, and from 25.3% to 5%, p = .0001, respectively). Overall hospital mortality (21%) was lower than that estimated by Acute Physiology and Chronic Health Evaluation (APACHE) II score (28%). This study shows that use of NPV and mask ventilation made it possible to avoid endotracheal intubation in the vast majority of unselected patients with acute-on-chronic respiratory disorders needing ventilator support.[42] Another recent study reported that using both modalities of noninvasive ventilation in patients with acute-on-chronic respiratory failure, the total rate of success in avoiding endotracheal intubation was 81.6%.[79]

Advantages

As with other modalities of noninvasive ventilation, the major advantage of NPV is the avoidance of endotracheal intubation and its related complications[1–4] while preserving physiologic functions such as speech, cough, swallowing, and feeding. Moreover, because the airway opening is free, airway suction and therapeutic and diagnostic maneuvers by fiberoptic bronchoscopy are performed more easily during NPV[41] than during mask ventilation.

Limitations

The following limitations should be considered when treating patients with NPV. First, the lack of upper airway protection, as with all modalities of noninvasive ventilation, may result in aspiration, especially in unconscious patients. Second, upper airway obstruction may occur or be enhanced in unconscious patients, patients with neurologic disorders that cause bulbar dysfunction, and patients with obstructive sleep apnea syndrome.[10,33–35] This effect compromises the effectiveness of ventilation with NPVs and requires shifting to PPV. In unconscious patients with normal bulbar function, the positioning of an oropharyngeal airway can minimize the risk of airway collapse. Third, tank and wrap ventilators restrict patients to the supine position, which may induce muscular back and shoulder pain. Fourth, severe obesity and kyphoscoliosis often compromise the possibility to put the patients in an iron lung or other NPV.

The incidence of complications and side effects of NPV delivered by iron lung was evaluated recently in 153 patients with acute-on-chronic respiratory failure[42] (Table 16-1). While NPV outcomes, such as complications and mortality rate, are within the ranges reported for noninvasive PPV,[80] it must be stressed that there are some difficulties in introducing this modality in the vast majority of ICUs, where mask ventilation is preferred as a noninvasive means of ventilation.[81,82] The main reasons are that the iron lung is cumbersome and needs a large amount of space, and most caregivers presently have little or no experience with NPV, rather than problems associated with NPV per se.

TABLE 16-1: SIDE EFFECTS AND COMPLICATIONS DURING NEGATIVE-PRESSURE VENTILATION IN 153 PATIENTS TREATED WITH IRON LUNG FOR ACUTE-ON-CHRONIC RESPIRATORY FAILURE

	Number of Patients (%)
Patients with complications	38 (25%)
Upper airway obstruction	24 (16%)
Large air leaks	0 (0%)
Back pain	8 (5%)
Claustrophobia	17 (11.4%)
Gastric insufflation	2 (1.3%)
Major complications	
Patients with complications	3 (2%)
Pneumonia	1 (0.6%)
Pneumothorax	0 (0%)
Gastrointestinal bleeding	3 (2%)

Source: Used, with permission, from Gorini et al.[42]

INDICATIONS AND CONTRAINDICATIONS

Acute Respiratory Failure

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Large studies with different experimental designs have reported the effectiveness of NPV in the treatment of patients with acute-on-chronic respiratory failure caused mainly by COPD (Table 16-2).[42,75,79,83–89] The effectiveness of NPV provided by iron lung in patients with hypercapnic encephalopathy was evaluated retrospectively in 150 consecutive patients (79% with COPD).[74] On admission, severe hypoxemia (Pa_{O_2} = 56 ± 22 mm Hg) and hypercapnia (Pa_{CO_2} = 112 ± 21 mm Hg) with respiratory acidosis (pH 7.13 ± 0.13) were present, Glasgow coma score ranged from 3 to 8, and the mean APACHE II score was 31.6 ± 5.3. The failure rate of NPV (death or need for endotracheal intubation) was forty-five of 150 (30%); the observed mortality rate was 24% versus 67.5% predicted mortality based on APACHE II. Nine patients (6%) required intubation because of a lack of control of the airway. In recent years, the effectiveness of NPV for the treatment of acute-on-chronic respiratory failure in patients with COPD has been confirmed in two case-control studies[75,87] and in two randomized, prospective control studies[88,89] (Table 16-2).

NEUROMUSCULAR DISORDERS

Few uncontrolled studies have investigated the effect of NPV in the treatment of neuromuscular patients with ARF. NPV, provided by iron lung[90–92] or pneumowrap,[93] was successful in avoiding endotracheal intubation and

TABLE 16-2: CLINICAL STUDIES ON THE EFFECTS OF NPV IN PATIENTS WITH ACUTE-ON-CHRONIC RESPIRATORY FAILURE

Authors	Experimental Design	Number of Patients	COPD (%)	Setting	Ventilator	Success* (%)
Gunella et al[83]	RS	560	84	Respiratory ICU	Iron lung	90
Corrado et al[84]	RS	2564	78	Respiratory ICU	Iron lung	90
Corrado et al[85]	RS	105	100	Respiratory ICU	Iron lung	89
Corrado et al[74]	RS	150	79	Respiratory ICU	Iron lung	70
Todisco et al[79]	PCS	152	72	Respiratory ICU	Iron lung	84
Gorini et al[42]	PCS	258	70	Respiratory ICU	Iron lung	77
Corrado et al[75]	CCS (NPV vs invasive MV)	66	100	Respiratory ICU	Iron lung	77 vs. 73
Corrado et al[87]	CCS (NPV vs. mask ventilation)	106	100	Respiratory ICU	Iron lung	79 vs. 75
Corrado et al[88]	RCS (NPV vs. invasive MV)	44	100	Respiratory ICU	Iron lung	82 vs. 73
Corrado et al[89]	RCS (NPV vs. mask ventilation)	141	100	Respiratory ICU	Iron lung	87 vs. 68

CCS, case-control study; *PCS*, prospective cohort study; *RCS*, prospective, randomized, controlled study; *RS*, retrospective study.
*Avoiding endotracheal intubation or death.

in facilitating weaning from invasive ventilation in small groups of patients. In a retrospective study, we reported the effects of NPV provided by iron lung in the treatment of fifteen neuromuscular patients with ARF.[94] On admission, all patients exhibited severe hypoxemia ($Pa_{O_2} = 37.6 \pm 12.4$ mm Hg) and hypercapnia ($Pa_{CO_2} = 88.2 \pm 20.4$ mm Hg) with uncompensated respiratory acidosis (pH 7.25 ± 0.08). The treatment was successful in twelve of fifteen patients (80%). Although these reports suggest that NPV can be effective in the treatment of ARF in patients with neuromuscular diseases, prospective, controlled studies are needed to clarify the impact of noninvasive ventilation on clinical outcome in these patients.

PEDIATRIC DISEASES

During the 1970s and 1980s, several uncontrolled[95–98] and controlled[99,100] studies showed that NPV was effective in the management of the neonatal respiratory distress syndrome. More recently, Samuels et al[101] performed a prospective, randomized, controlled trial over a period of 4 years in 244 neonates comparing CNEP (−4 to −6 cm H_2O) with standard therapy that included continuous positive airway pressure of 4 cm H_2O. They found that need for intubation was slightly less with CNEP than with standard therapy (86% vs. 91%).

Infants with ARF who fail to respond to conventional ventilation are considered elective candidates for extracorporeal membrane oxygenation. In 1989, an uncontrolled study reported that the use of CNEP administered by a tank ventilator in conjunction with invasive ventilation was successful in five neonates suffering from respiratory failure and persistent pulmonary hypertension, thus avoiding the use of extracorporeal membrane oxygenation.[102] The benefit of combining invasive ventilation and CNEP in these patients has been confirmed by the same group in a crossover prospective, randomized study.[103] Patients treated with CNEP showed a greater increase in Pa_{O_2} than did those treated with PEEP without any increase in morbidity.

Chronic Respiratory Failure

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

There is no evidence that long-term NPV treatment can improve respiratory muscle function, exercise endurance, quality of life, and survival in patients with severe COPD.[28,104–108] It is important to stress that until now, no other ventilator technique has been shown to be effective in the long-term treatment of stable patients with COPD.

RESTRICTIVE DISORDERS

Many studies, although uncontrolled, have shown that NPV can be used successfully for long-term home ventilation in patients with restrictive ventilatory impairment secondary to neuromuscular and chest wall diseases.[109–114] NPV devices, however, are more cumbersome and difficult to use than recent home PPVs. In patients who need discontinuation of mask ventilation secondary to intolerable nasal irritation or upper airway congestion,[115] and in those

with other clinical condition, such as facial deformity or lack of teeth, NPV should be used as an alternative to mask ventilation.

Other Applications

NEGATIVE PRESSURE VENTILATION DURING RIGID BRONCHOSCOPY

Some studies report that in patients submitted to interventional rigid bronchoscopy under general anesthesia, NPV,[116–118] compared with spontaneous assisted ventilation, was able to prevent apnea and significant intraoperative derangement of acid–base balance, and was associated with a reduction in administration of opioids and shortened recovery time.

COMPARISON WITH OTHER MODES

Negative-Pressure Ventilation versus Invasive Mechanical Ventilation

Two studies have compared the effects of NPV and conventional invasive mechanical ventilation (IMV) in patients with COPD and severe ARF.[75,88] A retrospective case-control study, carried out in sixty-six patients,[75] showed that NPV was associated with a similar mortality rate to that of IMV (23.1% and 26.9%, respectively) and a reduction in duration of ventilation in survivors. These findings were recently confirmed in a prospective, randomized, controlled study.[88] Forty-four patients with an exacerbation of COPD and severe respiratory acidosis (mean pH 7.20 ± 0.04) were assigned either to iron-lung ventilation (twenty-two patients) or IMV (twenty-two patients). Primary end points were improvement in gas exchange and complications related to mechanical ventilation. Compared with baseline, NPV and IMV induced a similar and significant improvement in Pa_{O_2}/FI_{O_2}, Pa_{CO_2}, and pH after 1 hour and at discontinuation of treatments. Among patients treated with NPV, four (18.2%) needed endotracheal intubation. Major complications tended to be more frequent in patients treated with IMV than in those treated with NPV (27.3% vs. 4.5%), whereas mortality rate was similar (27.3% vs. 18.2%). Ventilator-free days and length of hospital stay were significantly lower in the iron-lung group than in the IMV group.

Negative-Pressure Ventilation versus Noninvasive Positive-Pressure Ventilation

A direct comparison between the two noninvasive ventilator techniques in the treatment of patients with COPD in ARF was reported in a retrospective case-control study involving fifty-three pairs of patients, well matched for age, sex, causes of ARF, APACHE II score, and pH, who were treated with iron-lung and mask ventilation.[87] Treatment failure (death and/or need for endotracheal intubation) was 20.7% in the NPV group and 24.5% in the mask ventilation group. Duration of mechanical ventilation (29.6 ± 28.6 vs. 62.3 ± 35.7 hours) and length of hospital stay (10.4 ± 4.3 vs. 15 ± 5.2 days) were significantly lower in patients treated with NPV than in those treated with mask ventilation.

This finding was recently confirmed by a multicenter prospective randomized crossover study[89] carried out in 141 patients (seventy assigned to NPV and seventy-one to mask ventilation). To establish the failure of the technique employed as first-line therapy, major and minor criteria for endotracheal intubation were used. When a major criterion was fulfilled, endotracheal intubation was promptly performed. When at least two minor criteria were met, patients were shifted from one technique to the other. When used as first-line therapy, the success of NPV (87%) was significantly greater (P = 0.01) than mask ventilation (68%) because of the number of patients who met minor criteria for endotracheal intubation (Fig. 16-9). After the shift between the techniques, however, the need of endotracheal intubation and hospital mortality was similar in the two groups. The total rate of success using both techniques increased from 77.3% to 87.9% (P = 0.028) (Fig. 16-9). These data show that when the two techniques are combined, endotracheal intubation can be avoided in a high percentage of cases.

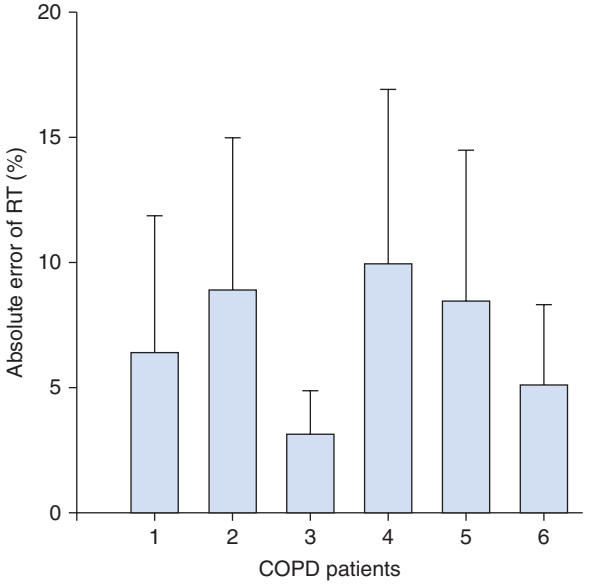

FIGURE 16-9 Error of inductance plethysmography (Respitrace, *RT*) in estimating tidal volume during NPV in patients with an acute exacerbation of COPD. The error of the Respitrace was assessed as $(VT,_{Respitrace} - VT,_{pneumotachograph})/VT,_{pneumotachograph} \times 100$. Individual values are shown.

TABLE 16-3: CHARACTERISTICS OF SOME NEGATIVE-PRESSURE VENTILATOR PUMPS

Model	Inspiratory Pressure (cm H_2O)	Expiratory Pressure (cm H_2O)	CNEP (cm H_2O)	T_I (s)	T_E (s)	Ventilation Modes	Inspiratory Trigger	Pump	Alarms
Iron Lung Coppa CA 1001	0 to −80	−30 to +80	0 to −30	0.4–9.9	0.4–9.9	C, A/C, CNEP	Thermistor	Inside the model	P max, MF
Porta Lung Emerson 33-CR	0 to −90	—	Yes	Up to 5	*	C, A/C, A, CNEP	Pressure	Outside	No
Porta Lung Life Care NEV-100, Respironics	−5 to −100	−30 to +30	−5 to −30	0.5 −5	†	C, A/C, C+S, A/C+S	Pressure	Outside	Pmin, MF
New Negavent DA-3 plus mod Pegaso V, Dima Italia	−5 to −99	−25 to +99	−5 to −99	‡	‡	C, A/C, CNEP	Pressure	Outside	Pmax, Pmin
Hayek RTX, Medivent International	Up to −50	Up to +50	Yes	§		C, RS, CNEP		Outside	

A, assist; *A/C*, assist/control; CNEP, continuous negative extrathoracic pressure; *C*, control; *I:E*, inspiratory-to-expiratory ratio; *MF*, machine failure; *Pmax*, maximum pressure; *Pmin*, minimum pressure; *RS*, respiratory synchronized; *S*, sigh; T_E, expiratory time; T_I, inspiratory time.

*Rate 0 to 49 cycles/min, I:E ratio: 1:3 to inverse ratio.

†Rate 4 to 60 cycles/min, I:E ratio: 1:0.5 to 1:29.

‡Rate 1 to 50 cycles/min, I:E ratio 1:9.9 to 5:1.

§Rate 6 to 1200 cycles/min, I:E ratio: 1:6 to 6:1.

VARIATIONS IN DELIVERY AMONG VENTILATOR BRANDS

Table 16-3 reports the characteristics of modern negative-pressure pumps. A study by Smith et al[9] on five NPV pumps, using a lung model, showed that tidal volume during NPV is related both to target pressure and the pressure waveform generated by the pump. For the same target, pumps generating a square wave and produce a tidal volume up to 30% greater than pumps that generate a half sine wave.[9] Most modern NPV pumps respond rapidly to changing leaks to maintain the preset pressure[9] and allow independent setting of the pressure to be delivered during inspiration and expiration, as well as inspiratory and expiratory duration.

ADJUSTMENTS AT THE BEDSIDE

Guidelines concerning the bedside management of patients ventilated with NPV are scarce.[6,8] The effectiveness of NPV depends on strict supervision by well-trained nurses and physiotherapists with considerable expertise in this technique. Proper fit of the airtight seal around the neck and correct position of the head and neck rest are very important in optimizing comfort and preventing kinking and upper airway obstruction.[6]

Values ranging from −30 to −40 cm H_2O have been recommended for the setting of negative pressure during inspiration.[6] In our experience, the setting of pressures and timing depends on the clinical condition and chest wall impedance of patients. In patients with severe respiratory acidosis and hypercapnic encephalopathy, we used control NPV with a frequency of 12 to 15 cycles per minute and an I:E ratio of 1:3 to 1:4, whereas assist-control NPV is used preferentially in patients with tachypnea and respiratory distress to facilitate patient–ventilator synchrony. Inspiratory negative pressure is set initially at values ranging from −30 to −40 cm H_2O and then adjusted in each patient to obtain a tidal volume of about 6 mL/kg.[87]

Positive expiratory pressures of 10 to 15 cm H_2O are set to assist cough in patients with excessive secretions[8] or to increase tidal volume in restrictive disorders;[14] negative extrathoracic expiratory pressure is set to counterbalance intrinsic PEEP in patients with COPD (usually ranging from −4 to −6 cm H_2O)[12] or to improve oxygenation in patients with severe hypoxemia (ranging from −5 to −10 cm H_2O). Arterial blood gases are checked approximately 30 minutes after mechanical ventilation starts and after any setting changes. During NPV, oxygen is supplemented by nasal cannula, venturi mask, or mask with reservoir. The flow is adjusted to keep O_2 saturation usually between 92% and 94%. Bronchodilators also can be administered by metered-dose inhaler or by aerosol.

TROUBLESHOOTING

Many problems must be considered when treating acute patients with NPVs.

TABLE 16-4: TYPICAL SETTING OF IRON LUNG USED IN CONTROL MODE FOR THE TREATMENT OF PATIENTS WITH ACUTE-ON-CHRONIC RESPIRATORY FAILURE

- Negative inspiratory pressure: Usually from −30 to −40 cm H_2O at first, and then adjusted so as to obtain a tidal volume of approximately 6 mL/kg.
- Expiratory positive pressure: From +10 to +15 cm H_2O in patients with excessive secretions to assist cough or to improve patient–ventilator synchrony.
- The timing must be adjusted some breaths below patient's spontaneous rate.
- Typical setting for a ventilatory rate of 15 cycles/min: $T_I = 1.2$ s; $T_E = 2.8$ s; ($T_I/T_{TOT} = 30\%$).
- Typical setting for a ventilatory rate of 27 cycles/min: $T_I = 0.8$ s; $T_E = 1.4$ s; ($T_I/T_{TOT} = 36\%$); when patient is "captured," respiratory rate is reduced progressively.

Setting in Control Mode

The old iron-lung models have only this mode of ventilation, which may cause patients to "fight the ventilator," resulting in discomfort and ineffective ventilation. In order to "capture" the patient to the superimposed frequency of the machine, we can operate mainly on the timing. Table 16-4 reports some examples of iron-lung settings in the control mode to overcome this concern.

Monitoring of Tidal Volume

During NPV, the patient airway opening is free, which is a disadvantage for continuous monitoring of tidal volume. Currently, tidal volume is monitored intermittently using a Wright spirometer connected to a face mask. Continuous monitoring can be achieved with the use of inductance plethysmography (Respitrace), which permits an indirect evaluation of tidal volume. Recently, we compared tidal volume measured by a pneumotachograph and by Respitrace in patients with COPD in acute exacerbation treated by iron lung. The error of the Respitrace, assessed as ($VT,_{Respitrace} - VT,_{pneumotachograph}$)/$VT,_{pneumotacograph} \times 100$, ranged from 3% to 10% (Fig. 16-10). These observations suggest that inductance plethysmography may be a useful tool, allowing continuous estimate of tidal volume during NPV.

Nursing Care

The major problems related to the assistance of patients with NPV by iron lung are transfer from the bed to inside the chamber of the tank ventilator and access to patients for nursing procedures during ventilation. Well-trained nurses, however, can manage both transfer, by using aids (e.g., a roll mattress and a mechanical elevator), and nursing procedures (e.g., insertion of a urinary catheter and venous lines, placement of electrocardiograph electrodes and SaO_2 probe for monitoring the level of oxygenation) easily using the portholes in the tank ventilator. We have measured the time spent by nurses in the second day after admission in patients with COPD in ARF treated with the iron lung.[76] The following procedures were considered: transfer of patients from the bed to inside the tank ventilator, measurement of tidal volume and minute ventilation by a Wright spirometer, tracheobronchial suction, arterial blood-gas sampling, drug administration, and other procedures. The total time spent by nurses for these procedures was 250 minutes. Even though there are no studies comparing nursing workload in patients submitted to NPV and IMV, Nava et al[119] have reported that nursing workload in patients treated with IMV was 527.5 ± 51.1 minutes in the first 48 hours after admission.

IMPORTANT UNKNOWNS

It is completely unknown if NPV may play a role in the treatment of patients with acute lung injury. Physiologic studies[58–60] have shown the advantageous hemodynamic effects of NPV applied to the chest wall in patients with acute lung injury, although studies on clinical outcomes are completely lacking. The absence of this information is

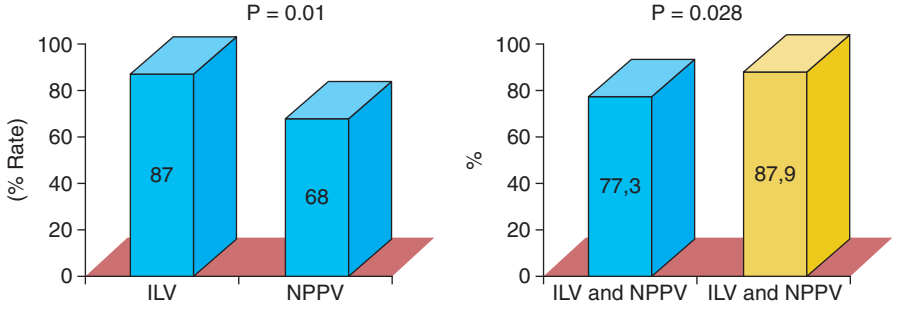

FIGURE 16-10 The rate of success of iron-lung ventilation (ILV) and noninvasive positive pressure ventilation (NPPV) as first-line therapy in 141 patients presenting with an acute exacerbation of COPD. *Left panel:* The success of ILV (87%) was significantly greater than that of NPPV (68%) (P = 0.01). *Right panel:* Mean rate of success of ILV and NPPV used as first line of treatment and total rate of success of both techniques used sequentially.

particularly relevant because some physiologic studies suggest that NPV may result in reduced lung biotrauma compared with PPV.[115,121,122] Physiologic studies[52,54] show that NPV by iron lung has the same hemodynamic effects as PPV. Recently the effects of NPV, applied with a custom-made whole-body chamber, were compared to those of PPV in a model of acute lung injury in anesthetized, surfactant-depleted rabbits. NPV resulted in a superior oxygenation unrelated to lung perfusion and was associated with more effective inflation of lung volume during both inspiration and expiration.[123] The same group using dynamic computed tomography in six anesthetized rabbits with acute respiratory distress syndrome induced by repeated saline lavage, reported that NPV was associated with increased percentage of ventilated lung at mid-inspiration and midexpiration compared to PPV.[124]

Future studies should determine whether iron-lung ventilation may be applied successfully to patients with cardiogenic pulmonary edema.

THE FUTURE

Inspiratory Trigger System

Sinderby et al[125] used diaphragmatic electrical activity, recorded by electrodes attached to a nasogastric tube, to trigger ventilatory support. This signal is directly related to phrenic nerve activity and probably to the output of the respiratory center; unlike airway pressure or flow, it is not affected by mechanical dysfunction (dynamic hyperinflation and intrinsic PEEP). By overcoming the problem associated with the current technology for triggering, this "neural trigger" has the potential to improve patient–ventilator interaction during both positive-pressure and negative-pressure mechanical ventilation.

Design of Tank Ventilator

Most iron lungs, although improved in design, remain cumbersome and need a large amount of space. A lighter and completely transparent chamber incorporated into the ICU bed would enable the posture of patients to be changed from supine to semirecumbent. This step should permit a major implementation of NPV in the ICU.

Potential Clinical Application

The clinical relevance of intra-abdominal pressure, which may cause organ dysfunction, is being recognized increasingly in the ICU settings.[126,127] It has been suggested that NPV applied around the abdomen by a cuirass might be a potential tool to treat intra-abdominal hypertension.[128] This hypothesis has been investigated in a physiologic study of thirty patients admitted to an ICU.[129] Continuous NPV decreased intra-abdominal pressure from 8.7 ± 4.3 to 6 ± 4.2 mm Hg (p <.001). There was a further decrease in intra-abdominal pressure when more negative pressure was applied. Future studies with clinical outcome are necessary to assess the effectiveness of this technique for the treatment of increased abdominal pressure.

SUMMARY AND CONCLUSIONS

Evidence now exists that (a) NPV unloads respiratory muscles and improves gas exchange in patients with COPD and ARF; (b) volume-controlled ventilation with CNEP, compared with volume-controlled ventilation with PEEP, increases oxygen delivery and cardiac index in patients with acute lung injury and children submitted to right-sided heart surgery; (c) iron-lung ventilation, in expert hands, is as effective as mask ventilation and invasive ventilation in the treatment of acute-on-chronic respiratory failure; and (d) NPV can been used successfully for home mechanical ventilation in patients with chronic respiratory failure who are unable to tolerate mask ventilation. Furthermore, the use of both NPV and mask ventilation may avoid endotracheal intubation and its complications in most of these patients, widening the field of application of noninvasive ventilator techniques.

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NONINVASIVE RESPIRATORY AIDS: ROCKING BED, PNEUMOBELT, AND GLOSSOPHARYNGEAL BREATHING

Nicholas S. Hill

ROCKING BED AND PNEUMOBELT

The rocking bed and pneumobelt are noninvasive ventilators that were developed and saw their greatest use during the latter years of the polio epidemics but are used rarely today. They both rely on the effect of gravity to assist diaphragmatic motion and are particularly well suited to patients with severe diaphragmatic weakness or paralysis. Neither one should be used in the management of acute respiratory failure, and both have limited present-day applicability. Despite the similarities, there are also important differences, such as portability and suitability for nocturnal versus daytime use. This chapter reviews the historical development, mechanisms of action, and present-day uses of the rocking bed and pneumobelt. Glossopharyngeal breathing, another noninvasive approach to ventilator assistance, is discussed briefly at the end of the chapter.

Historical Development

The conceptual groundwork for development of the rocking bed was laid during the early 1930s by Eve,[1] who described the use of manual rocking to assist ventilation in two patients with acute respiratory paralysis. The technique consisted of placing the patient supine on a stretcher that was pivoted on a fulcrum placed at waist level. The patient then was rocked up and down approximately 45 degrees in either direction. Eve noted that the "weight of the viscera pushed the flaccid diaphragm alternatively up and down," achieving artificial respiration.[1] The technique was adopted subsequently by the British Navy as the recommended means of resuscitation for drowning victims.[2] Later studies demonstrated that this tilting method compared quite favorably with other resuscitation methods of the day, and it remained an acceptable means of resuscitation until mouth-to-mouth resuscitation gained acceptance during the 1960s.[3,4]

Automatic rocking beds were first introduced as ventilatory aids during the late 1940s. Wright[5] was the first to describe the management of respiratory insufficiency using an oscillating bed that had been designed originally to assist circulation. This experience led to the development of the McKesson Respiraid rocking bed, which was accepted by the Council on Physical Medicine and Rehabilitation in 1950.[6] Intended mainly as an aid to weaning patients with poliomyelitis from dependence on the tank respirator,[7] it facilitated nursing care and enhanced patient freedom but was quite noisy, bulky, and heavy (455 kg).[6,7] The Emerson rocking bed (J. H. Emerson Co., Cambridge, MA), also introduced during the late 1940s, was quieter and lighter than the McKesson bed and became the dominant model during the 1950s. Hundreds of rocking beds were manufactured between 1950 and 1960 (Emerson JH, personal communication), but after introduction of the Salk and Sabin vaccines and control of the polio epidemics, demand fell drastically. Many survivors of the polio epidemics continued to use rocking beds for ventilator support, sometimes for decades,[8] but most have since died or switched to other ventilators, and present-day use is rare.

The intermittent abdominal pressure respirator or insufflator (pneumobelt) was introduced at the end of the polio epidemics in an attempt to address the limitations of existing ventilators.[9] The pneumobelt was designed to allow complete freedom of the upper extremities and mouth during use in the sitting position and was intended mainly as a daytime ventilatory aid during meals or wheelchair use. Several modifications of the pneumobelt have been reported since the original description, but these never gained wide acceptance. These modifications include a piston-like device that compresses the abdomen while the patient sits in a wheelchair[10] and a combination of the pneumobelt and intermittent positive-pressure breathing.[11] Like the rocking bed, the pneumobelt has seen only limited use since control of the polio epidemics.

Mechanism of Action

Eve compared the rocking-induced motion of the abdominal viscera within the thorax with that of a piston within a cylinder.[1] As the head moves down, the viscera and diaphragm slide cephalad, assisting exhalation (Fig. 17-1). In the foot-down position, the abdominal contents and diaphragm slide caudad, assisting inhalation (Fig. 17-2).

A number of early studies on the efficacy of rocking compared it as a method of resuscitation with others then used commonly.[3,4] These studies used fresh corpses or live subjects with pharmacologically induced paralysis or voluntarily suspended respirations to show that rocking produced tidal volumes ranging from a few hundred milliliters to a liter, and success in the resuscitation of near-drowning victims was reported.[2] Later, Plum and Whedon[12] found that the automatic rocking bed was not as effective as the tank respirator but produced adequate alveolar ventilation in eleven convalescent patients with respiratory paralysis secondary to poliomyelitis. The bed, however, was unable to sustain adequate ventilation in five patients during the acute stages of respiratory paralysis. Plum and Whedon recommended that use of the rocking bed be reserved for stable patients who are capable of at least some spontaneous breathing, a recommendation that holds true today.

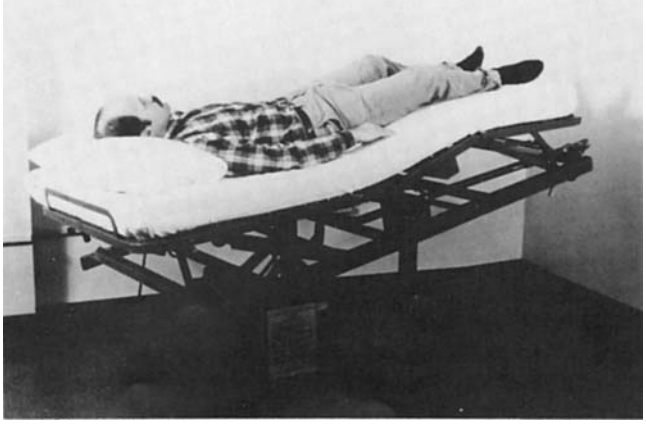

FIGURE 17-1 Rocking bed in 10-degree head-down position. Sliding of the viscera and diaphragm cephalad assists exhalation.

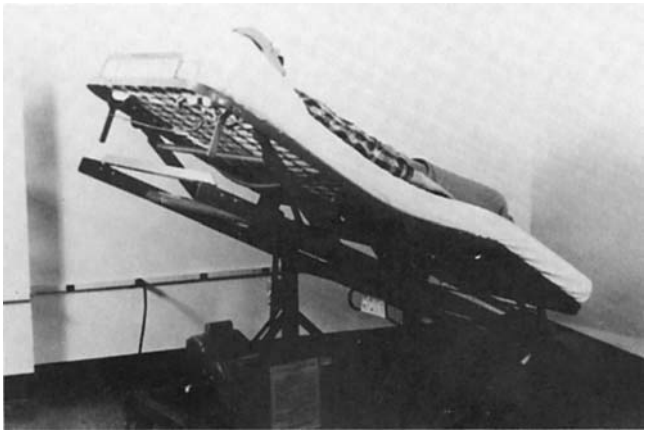

FIGURE 17-2 Rocking bed in 27-degree foot-down position. Sliding of the abdominal viscera and diaphragm caudad assists inhalation. (Used, with permission, from Hill.[17])

Colville et al[13] subsequently examined the physiologic effects of rocking on respiratory mechanics and identified factors responsible for the wide individual variations in tidal volumes generated during rocking. They found that the greatest displacement of the diaphragm occurred during rocking from horizontal to the 40-degree foot-down position (Fig. 17-3). Beyond this angle, relatively little further displacement of the diaphragm occurred. Likewise,

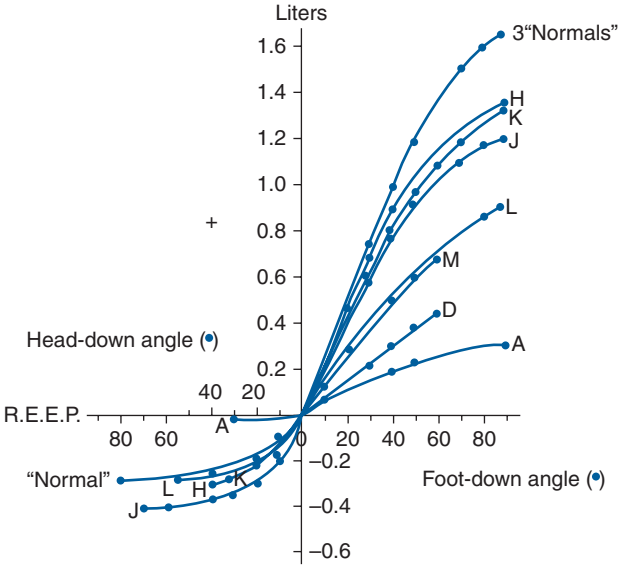

FIGURE 17-3 Relationship between angle of rocking bed and static lung volume in three normal individuals and in patients with poliomyelitis, as indicated by letters. Note that the greatest volume shift occurs between 0 degrees and the 40-degree foot-down angle. Note also the marked variability between individuals. *REEP*, resting end-expiratory position. (Used, with permission, from Colville P, et al. Effects of body tilting on respiratory mechanics. *J Appl Physiol.* 1956;9:19–24.)

relatively little displacement of the diaphragm occurred during rocking from the horizontal to the head-down position. This indicated that in the horizontal position, the resting diaphragm was fairly close to its uppermost position, so the greatest passive motion could be achieved by applying gravitational force in the caudad direction.

Along these lines, Joos et al[14] found that tidal volumes were greater in some patients when rocking was achieved entirely in the head-up position (5 to 42 degrees above the horizontal plane) rather than between the head-down and head-up positions (10 degrees below to 27 degrees above the horizontal plane). In addition, others found that relatively little increase in minute volume could be achieved by increasing the rate of rocking beyond 15 to 16 rocks per minute.[3] At higher rocking frequencies, the tidal volume tended to diminish, negating the effects of the increased rocking rate.

With regard to the large individual variation (see Fig. 17-3), Colville et al[13] found that as the compliance of the abdominal wall increased, the greater was the tidal volume during rocking. Thus, rocking was relatively ineffective in patients with severe kyphoscoliosis, who have low abdominal and diaphragmatic compliance and short abdominal lengths. Taken together, these findings indicate that the efficacy of the rocking bed is highly dependent on patient body characteristics and that function is likely to be optimal when rocking is between the near-horizontal and the 40-degree foot-down positions at rocking rates between 12 and 16 rocks per minute. Wider manipulations of rocking rate and arc, however, may be useful in optimizing alveolar ventilation in some patients.

The pneumobelt[9] operates by a mechanism similar to that of the rocking bed in that it assists diaphragmatic motion by causing piston-like motions of the abdominal viscera within the thoracic "cylinder." The major difference is that the pneumobelt assists exhalation by applying positive pressure to the abdominal surface rather than using gravitational force. It consists of an inflatable rubber bladder held firmly over the abdomen by an adjustable corset (Fig. 17-4). Inflation of the bladder squeezes the viscera, forcing the diaphragm cephalad and actively assisting exhalation. On deflation of the bladder, gravity pulls the viscera and diaphragm back to their original positions, assisting inhalation (Fig. 17-5). Because of this dependence on gravitational force, the pneumobelt must be used in a sitting position, optimally at angles of 45 degrees or greater. Below 30 degrees, the ability to assist ventilation is diminished markedly. Thus, nocturnal use of the pneumobelt is limited to patients who can sleep in a sitting position.[15]

Despite this limitation, the pneumobelt can be a very useful device in appropriately selected patients. The ability of the pneumobelt to augment tidal volume is linearly related to the inflation pressure of the bladder between pressures of approximately 15 and 50 cm H_2O. Pressures exceeding 50 cm H_2O are rarely tolerated because of abdominal discomfort. As with the rocking bed, the ability of the device to augment tidal volume varies considerably among individuals. Important factors that contribute to the variability among individuals include abdominal and chest wall compliances. High abdominal compliance favors efficient functioning of the device, but high chest wall compliance may allow expansion of the chest wall during bladder inflation, reducing efficiency.[9] Thus, like the rocking bed, body habitus is also an important determinant of ventilator efficiency for the pneumobelt. Although thin patients can be ventilated effectively,[16] both devices work less efficiently in extremely thin or obese patients and in those with severe kyphoscoliosis. The sitting position in patients with severe kyphoscoliosis often brings the lower rib cage in contact with the thighs, rendering proper positioning of the pneumobelt impossible.

FIGURE 17-4 Pneumobelt is shown attached via a connecting hose to a Bantam positive-pressure ventilator (Puritan-Bennett Corp, Lenexa, KS). (Used, with permission, from Rondinelli et al. In: Delisa JA, ed. *Rehabilitation Medicine: Principles and Practice*. Philadelphia, PA: Lippincott; 1988.)

Application

Rocking beds are no longer available commercially. Pneumobelts (small, medium, or large) can be obtained via home medical equipment vendors via Philips Respironics, Inc. (Murrysville, PA). Positive-pressure volume-limited

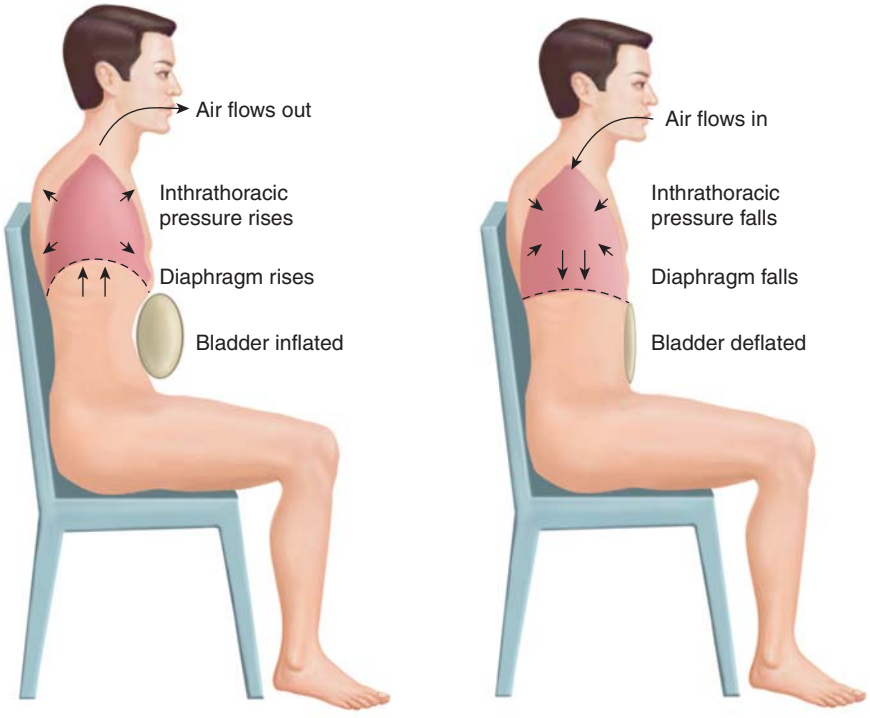

FIGURE 17-5 The pneumobelt functions by exerting positive pressure on the abdominal viscera, forcing the diaphragm up and assisting exhalation (*left*). When the bladder deflates, gravity returns the diaphragm to its original position, assisting inhalation (*right*). (Reproduced with the permission from the American College of Chest Physicians. Hill NS. Clinical applications of body ventilators. *Chest.* 1986;90:897–905.)

ventilators with sufficient pressure-generating and volume-generating capabilities can be used. Most portable "bilevel" positive-pressure devices, however, are insufficient.

Consisting of a bed frame that is suspended on an axis 100 cm above the ground, rocking beds are bulky (193 cm long by 84 cm wide) and heavy (approximately 136 kg). Although the axis of rotation can be adjusted, they usually are set to rotate 10 degrees in the head-down direction and 27 degrees foot-down. As noted previously, maintaining the rocking arc in the head-up range may improve efficacy in some patients.[14] Adjustable cranks allow raising of the head and knees to minimize slippage. Excessive flexion of the hips, however, may impair functioning.[14] A foot rest also may be attached to prevent downward sliding, but with proper positioning of the head and knees, this is usually unnecessary.

The most attractive feature of the rocking bed is its ease of application. With use of a foot stool, most patients can position themselves on it with minimal assistance. Paralyzed patients require help from one or two attendants depending on body weight. The patient lies supine with the head and knees raised slightly to maximize comfort. A baseline minute volume is measured using a portable spirometer. Rocking then is commenced at rates between 12 and 16 rocks per minute, again adjusted to optimize patient comfort. The patient is coached to exhale during head-down rocking and to inhale while the head moves up. When synchronization has been achieved, further adjustments in rocking rate may be made to optimize minute volume. An arterial blood-gas determination may be helpful after an hour or two during the initial trial to assess adequacy of alveolar ventilation.

Patients then are encouraged to initiate rocking at bedtime and to extend the hours of use gradually until they are able to sleep through the night. Most patients find the rocking bed quite comfortable and encounter little difficulty in learning to sleep while rocking. Motion sickness is unusual, presumably because the bed rocks in one plane only, but it may disturb some patients. The bed limits daytime mobility, so most patients use it only nocturnally. If daytime ventilatory assistance is necessary, another technique, such as noninvasive positive pressure ventilation or the pneumobelt, is recommended for daytime supplementation.

Application of the pneumobelt is slightly more difficult than that of the rocking bed, usually requiring at least one attendant unless the patient has full upper extremity strength. The corset is positioned while the patient is sitting comfortably. The rubber bladder is positioned over the abdomen with the curved lower border of the corset over the pubis and the horizontal upper border over the xiphoid. Some coverage of the lower rib cage may serve to minimize paradoxical motion of the ribs during assisted exhalation, although some authors have found more efficient functioning if the corset is placed below the xiphoid.[16] If the corset extends too far below or above the lower rib margin, another of the three available sizes should be tried. The corset then is tightened using the three straps that surround the abdomen until the rubber bladder is held firmly but not uncomfortably

against the abdomen. After baseline spontaneous respiratory rate and tidal volume are measured, the rubber bladder is attached to a positive-pressure ventilator using a connecting hose. Volume-limited positive-pressure ventilators that generate adequate pressures and volumes will operate the pneumobelt successfully, but portable "bilevel-type" pressure-limited devices that are popular to provide noninvasive positive-pressure ventilation are not adequate because their pressure-generating capabilities are too limited.

The ventilator is set at a rate that approximates spontaneous respiratory frequency and an inspiratory-to-expiratory (I:E) ratio of approximately 1:1.5. Some authors have found that function is optimal at rates of 12 to 14 breaths/min,[16] but this may depend on the underlying respiratory disorder. Some patients prefer rates as high as the low 20s per minute (see "Case 2: Use of the Pneumobelt" below). Ventilator assistance is initiated by intermittently inflating the rubber bladder with peak inflation pressures of 20 to 25 cm H_2O. Inflation pressure then is raised gradually until the patient's assisted tidal volume increases to the desired range, usually 30% to 50% over spontaneous breathing or the patient reaches the limit of tolerance. Peak pressures of 30 to 50 cm H_2O are usually sufficient, but pressures up to 60 cm H_2O may be necessary in some patients.[16] Pressures exceeding 60 cm H_2O rarely are tolerated because of discomfort. Considerable coaching usually is necessary during initial adaptation to encourage synchronization of patient breathing with ventilator cycling. Patients who will be successful usually learn to synchronize their breathing with the ventilator after a few sessions.

In addition to measurement of minute volume, efficacy is assessed using arterial blood-gas determinations that are done as soon as the patient is comfortable and synchronizing well. The desired amount of ventilator assistance will vary depending on the patient, but a decrease in arterial carbon dioxide tension (Pa_{CO_2}) of approximately 5 to 10 mm Hg below spontaneous breathing levels is acceptable during the initial sessions. Subsequent use of the device also depends on the patient. Most often, because the pneumobelt must be used in the sitting position, it is used as a daytime ventilator aid to supplement another device used nocturnally. As illustrated by Case 2 (see below) and another case report,[15] however, occasional patients may adapt to nocturnal use. The monthly rental for the belt itself is less than $100, but ventilator costs and associated respiratory therapy services raise monthly charges to the $500 to $1000 range.

Long-term follow-up of patients using either the rocking bed or pneumobelt should include assessment for symptoms or signs of chronic hypoventilation such as morning headache, hypersomnolence, and ankle swelling. Daytime spontaneous arterial blood-gas determinations are particularly useful for assessing the adequacy of ventilatory assistance,[17,18] and attempts should be made to increase assisted minute volume if Pa_{CO_2} remains substantially above 50 mm Hg. Nocturnal oximetry or polysomnography are useful not only to assess adequacy of nocturnal oxygenation but also to detect obstructive apneas that may be induced by negative-pressure ventilators[19] and also may occur during use of the rocking bed or pneumobelt.

Complications of rocking bed or pneumobelt use are relatively few. Some patients using the pneumobelt for many consecutive hours develop skin abrasions, and others have trouble coordinating their breathing with either of the ventilators so that efficacy may be inadequate. If appropriate patients are selected, the risk of worsened respiratory failure or arrest during use is low because such patients should be capable of some spontaneous breathing. As deterioration occurs with progressive neuromuscular syndromes or acute respiratory infections, however, patients may have to switch to other, more effective ventilators.

Indications

Considering that the rocking bed and pneumobelt share similar mechanisms of action, it is not surprising that they also share indications for use (Table 17-1). Because both assist ventilation essentially by augmenting diaphragmatic motion, they are particularly useful in patients with bilateral diaphragmatic weakness or paralysis. Abd et al[20] demonstrated the utility of this application in patients with bilateral diaphragmatic paralysis following open-heart surgery. In this study, ten patients were weaned from conventional positive-pressure ventilation to the rocking bed and continued to use it nocturnally until phrenic nerve function recovered after 4 to 27 months.

The rocking bed and pneumobelt also may be used in the management of chronic respiratory failure caused by a

TABLE 17-1: INDICATIONS AND CONTRAINDICATIONS FOR THE ROCKING BED AND PNEUMOBELT

Indications
Chronic respiratory failure[a] caused by:
Bilateral diaphragmatic paralysis
Muscular dystrophies
Duchenne
Limb-Girdle
Myotonic
Postpolio syndrome
Amyotrophic lateral sclerosis
Multiple sclerosis
Traumatic quadriplegia[b]
Contraindications
Acute respiratory failure or rapidly progressive neuromuscular disease
Excessive secretions
Upper airway dysfunction
Excessive obesity or thinness
Severe kyphoscoliosis

[a]With intact upper airway and appropriate body habitus.

[b]Pneumobelt only.

variety of slowly progressive neuromuscular syndromes that weaken the diaphragm and leave upper airway function intact. Chalmers et al[21] described their experience with fifty-three neuromuscular patients, thirty with postpolio syndrome, twelve with various muscular dystrophies, four with adult-onset acid maltase deficiency, and four with motoneuron disease (amyotrophic lateral sclerosis). Forty-three of the patients used the rocking bed for an average of 16 years with good control of symptoms and stabilization of gas exchange in most patients. Seventeen patients discontinued use: nine because of discomfort and eight because progression of respiratory insufficiency necessitated more efficacious therapy. The pneumobelt has been used in patients with high spinal cord lesions, mainly as a daytime supplement, often in combination with positive pressure ventilation administered noninvasively or via a tracheostomy.[16] In this setting, the pneumobelt frees the face of encumbrances and improves speech and mobility. It also may be used for total ventilator support.[22] Surprisingly, those with the least ability to sustain spontaneous breathing adapt best to pneumobelt use.[22]

Because both ventilators have limitations that are influenced heavily by the patient's body habitus, however, a number of caveats should be borne in mind (see Table 17-1). Neither device is suitable for use in acute respiratory failure mainly because a period of adaptation is necessary for optimal efficiency and also because excessive secretions interfere with function.[12] In addition, care should be exercised to select patients who have an appropriate body habitus, adequate upper airway function, and a condition that is sufficiently stable or slowly progressive so that the anticipated duration of use will justify the effort and time required for adaptation.

Because the rocking bed is suited for nocturnal use and the pneumobelt for daytime use, the two may be used in complementary fashion. A patient might use the rocking bed during sleep and the pneumobelt for daytime desk work or wheelchair use.

Many choices are available currently for noninvasive ventilation of patients with chronic respiratory failure secondary to idiopathic diaphragmatic paralysis or slowly progressive neuromuscular conditions. Noninvasive positive-pressure ventilation administered via a nasal mask is unquestionably the mode of first choice because of its convenience, ease of application, portability, and avoidance of the intermittent upper airway obstructions and oxygen desaturations associated with the use of negative-pressure ventilators.[19,23] Nevertheless, other noninvasive ventilators still should be considered in patients with chronic respiratory failure who are unable to use noninvasive positive-pressure ventilation, as illustrated in a recent report of a woman with scapuloperoneal muscular dystrophy who used a rocking bed successfully when loss of upper extremity strength rendered her incapable of applying her nasal ventilator.[24]

Efficacy comparisons between the rocking bed and pneumobelt and other noninvasive ventilators are limited because few relevant studies are available. In acutely anesthetized intubated subjects, Bryce-Smith and Davis[25] showed that the rocking bed produced barely adequate tidal volumes when rocking through an arc of 40 degrees and was much less effective than negative-pressure ventilators, including the tank ventilator and chest cuirass. Goldstein et al[26] demonstrated that cuirass-type negative-pressure ventilators augment tidal volumes and suppress diaphragmatic electromyographic activity more effectively than did the rocking bed in patients with neuromuscular disease. Both types of ventilators, however, were deemed effective, and considering that this was an acute daytime study, the rocking bed may have been more effective at reducing diaphragmatic electrical activity had patients been monitored overnight after a suitable adaptation period. Even so, the conclusion that the rocking bed is less effective than negative-pressure ventilators seems justified. In one case, the rocking bed was combined with noninvasive positive-pressure ventilation via a nasal mask to enhance efficacy and achieve "necessary ventilatory support."[27]

In summary, both the pneumobelt and rocking bed currently have limited indications (see Table 17-1). They are unsuitable for use in acute respiratory failure, must be used in patients with a relatively "normal" body habitus, and have marginal efficacy even under optimal circumstances. Noninvasive positive-pressure ventilation has convenience and efficacy advantages over these devices. Nonetheless, there are occasional patients who are unable to tolerate a nasal mask or negative-pressure ventilator who may prefer the relatively greater comfort of the rocking bed or the daytime freedom that the pneumobelt affords. The following cases illustrate such applications.

CASE 1: USE OF THE ROCKING BED

J.F., a 47-year-old man with myotonic dystrophy, first presented with symptoms of chronic hypoventilation, including morning headache and daytime hypersomnolence. He was found to have global muscular weakness, although he was still able to walk with a cane. Pulmonary function studies demonstrated a severe restrictive defect with a forced vital capacity (FVC) of 1.5 L (31% of predicted) and a forced expiratory volume in 1 second (FEV_1) of 1.3 L. Room-air arterial blood-gas determinations revealed a pH of 7.36, a Pa_{CO_2} of 53 mm Hg, and a Pa_{O_2} of 69 mm Hg. Nocturnal polysomnography showed mild obstructive sleep apnea and sustained mild oxygen desaturations consistent with hypoventilation. A trial of noninvasive positive-pressure ventilation via a nasal mask was initiated. Despite much coaching and trials with different masks, the patient declined further use after 2 months because of intolerable mask discomfort. Megestrol, 40 mg PO TID, then was begun, followed within a month by normalization of blood gases and resolution of symptoms.

Two years later, the patient again developed symptoms of morning headache and daytime hypersomnolence. A daytime arterial blood-gas determination showed a pH of 7.36, a Pa_{CO_2} of 65 mm Hg, and a Pa_{O_2} of 42 mm Hg. Nocturnal polysomnography was repeated (see Fig. 17-6), showing periodic breathing and sustained severe oxygen desaturations. Oxygen supplementation was begun, but the Pa_{CO_2}

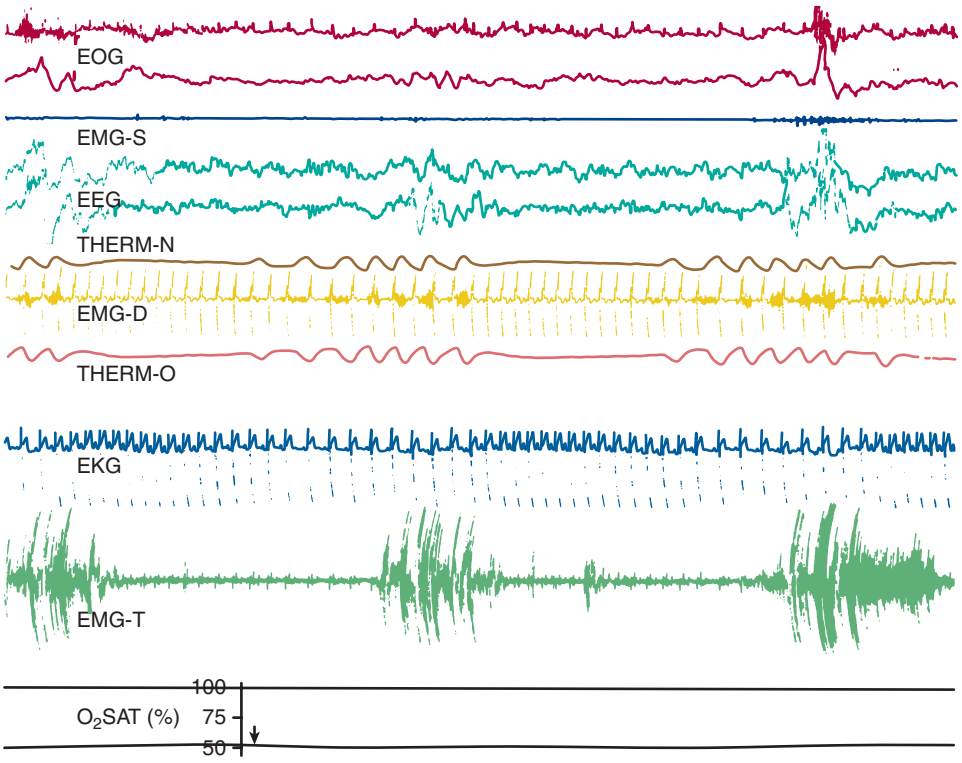

FIGURE 17-6 Nocturnal polysomnogram in patient 1, obtained in August 1991 during spontaneous room-air breathing, shows periodic breathing with sustained severe oxygen desaturation. *EEG*, electroencephalogram; *EKG*, electrocardiogram; *EMG*, electromyelogram; *EMG-D,* diaphragmatic EMG; *EMG-S*, submental electromyogram; *EMG-T*, temporal EMG; *EOG*, electrooculogram; *l*, left; *O_2SAT*, oxygen saturation; *r*, right; *THERM-N*, nasal thermistor; *THERM-O*, oral thermistor.

rose to 76 mm Hg. Nasal ventilation was tried once more and was rejected rapidly by the patient. Initiation of negative-pressure ventilation using a pneumowrap brought about a rapid improvement in symptoms and daytime gas exchange, with a room-air arterial blood-gas determination showing a pH of 7.42, a Pa_{CO_2} of 55 mm Hg, and a Pa_{O_2} of 65 mm Hg. The patient's wife, however, refused to consider use of the pneumowrap at home because placing the patient in it each night seemed too difficult.

Nocturnal ventilation using the rocking bed then was begun at a rocking rate of 16 rocks per minute. Tidal volume during the initial rocking trial ranged from 300 to 350 mL. The patient's wife found the rocking bed more acceptable because of simpler application. After a several-day adaptation period, the patient was able to sleep for 4 to 5 hours using the device, and he was discharged home. Nocturnal polysomnography obtained after several months of use showed good synchronization of chest wall motion with the rocking bed, but some obstructive hypopneas and apneas continued to occur (Fig. 17-7). The oxygen desaturations associated with the obstructive events were ameliorated by 2 liters/min of nasal oxygen used nocturnally (Fig. 17-8). The patient slept 7 to 8 hours nightly using the rocking bed with supplemental oxygen, and a daytime unassisted room-air arterial blood-gas determination after 15 months showed a pH of 7.42, a Pa_{CO_2} of 52 mm Hg, and a Pa_{O_2} of 78 mm Hg. After 3 years of clinical stability with nocturnal rocking bed use, the patient was hospitalized with pneumonia and progressive respiratory failure; he declined intubation and died.

This case illustrates that trials of a variety of noninvasive ventilators may be necessary before an acceptable one is identified. It also shows that many considerations, including pragmatic limitations in the home, help to determine the final selection. Here the rocking bed was selected not because of greater efficacy or patient preference but because of greater ease of application as perceived by the patient's wife.

CASE 2: USE OF THE PNEUMOBELT

M.C., a 24-year-old man with Duchenne muscular dystrophy, presented with a weakening voice, morning headaches, and hypersomnolence. Pulmonary function studies showed severe restriction with reductions of both FVC and FEV_1 to 0.5 L (14% of predicted). Arterial blood-gas determinations on room air showed a pH of 7.36, a Pa_{CO_2} of 68 mm Hg, and a Pa_{O_2} of 55 mm Hg. The patient was admitted to the hospital for a trial of noninvasive ventilation.

Noninvasive positive-pressure ventilation was tried initially, but the patient could not tolerate a face mask or lip seal. (Comfortable nasal masks were not available commercially at that time.) Negative-pressure ventilators were tried,

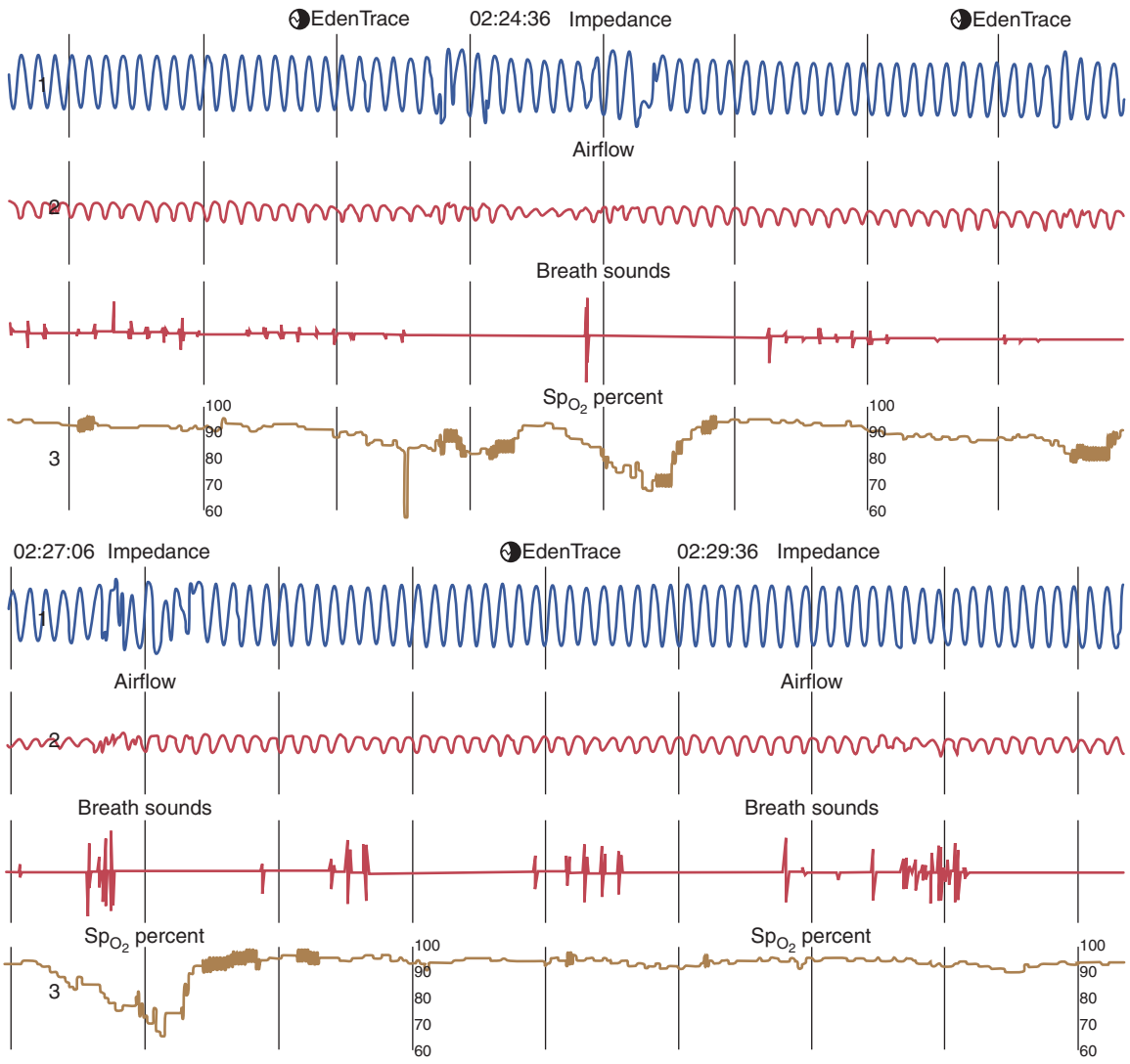

FIGURE 17-7 Continuous nocturnal recording of case 1 during rocking bed use without oxygen supplementation. Tracing shows consistent regular chest wall motions at a rate of 16 breaths/min, indicating good synchronization with the rocking bed. However, periodic obstructive hypopneas are signified by decreases in airflow followed by oxygen desaturations and arousals, as evidenced by disruption of chest wall synchrony. *Channel 1* is chest wall impedance, *channel 2* is combined nasal and oral thermistor, and *channel 3* is finger pulse oximetry. *Vertical lines* indicate 30-second intervals. Monitoring was performed using Edentec monitor (Edentec, Inc., Eden Prairie, MN).

but the patient found the iron lung too bulky and the pneumowrap too restricting and uncomfortable. Standard chest shells fit poorly because of his mild scoliosis. Only the pneumobelt, which was quite effective in augmenting his minute volume, was acceptable to the patient. His spontaneous respiratory rate was 28 breaths/min, tidal volume was 90 mL, and minute volume was 2.5 L/min. The pneumobelt was set at a rate of 22 breaths/min and a positive pressure of 35 cm H_2O, producing a tidal volume of 200 mL and a minute volume of 4.4 L/min. Arterial blood-gas determination after 2 hours during the initial trial showed a pH of 7.41, a Pa_{CO_2} of 59 mm Hg, and a Pa_{O_2} of 78 mm Hg.

The patient was discharged with instructions to use the pneumobelt at night and as needed during the daytime. Arrangements were made to attach a ventilator platform to his wheelchair to facilitate daytime use. The patient rapidly adapted to nocturnal use and encountered little difficulty in sleeping while sitting upright. In addition to nocturnal use, he used the ventilator for 2 to 3 hours during the daytime. A daytime room-air arterial blood-gas determination during spontaneous breathing after full adaptation 7 months after initiation showed a pH of 7.37, a Pa_{CO_2} of 49 mm Hg, and a Pa_{O_2} of 84 mm Hg. A nocturnal polysomnogram showed excellent synchrony of chest wall movement with the ventilator and no evidence of obstructive apneas (Fig. 17-9). Oxygen saturations remained between 95% and 98% throughout the night while the patient was breathing room air.

The patient continued to use the pneumobelt both nocturnally and during the daytime for the next 2 years and

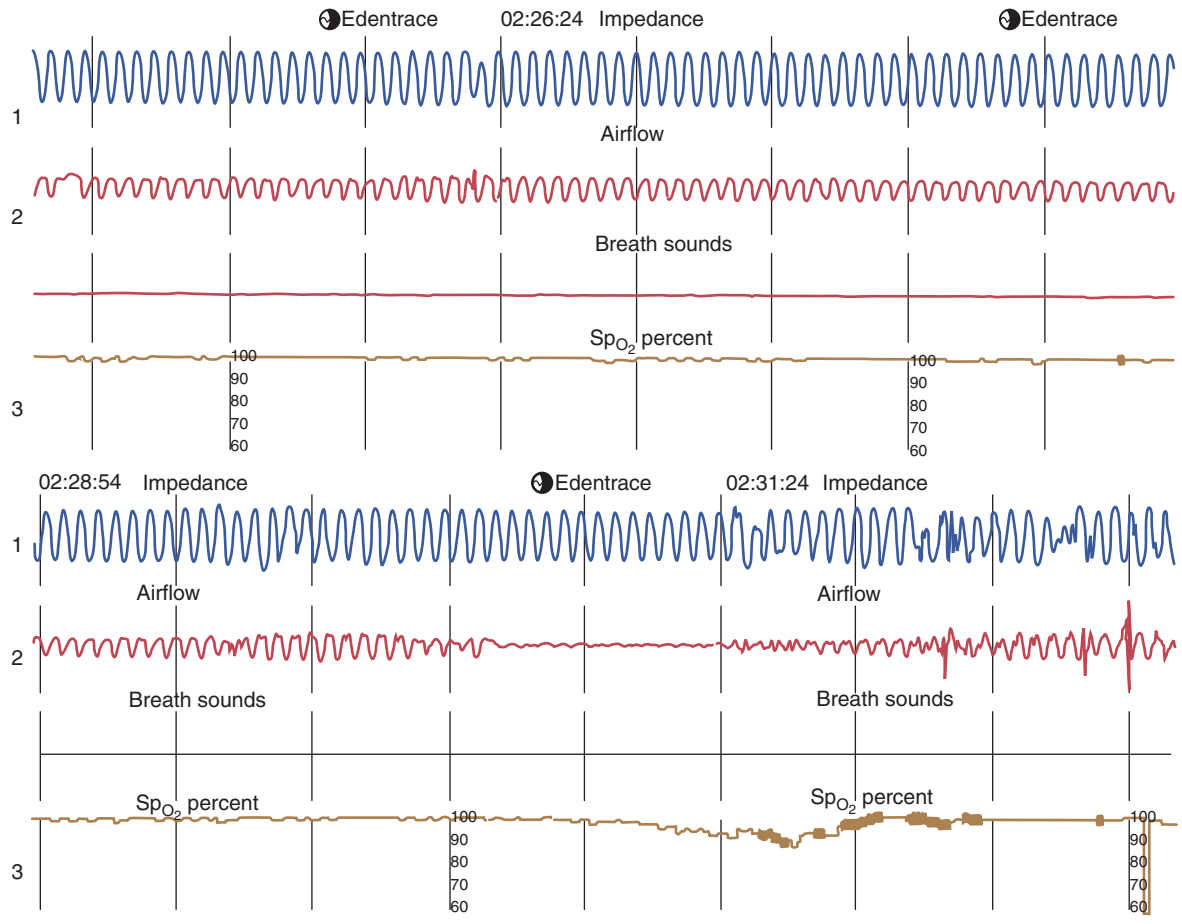

FIGURE 17-8 Nocturnal recording of case 1 using rocking bed and 2 L/min O_2 via nasal cannula. Tracing again shows excellent synchrony of chest wall motion with rocking. A 50-second obstructive apnea is apparent in the lower tracing, but is associated with only a mild oxygen desaturation to 90%. *Channel 1* is chest wall impedance, *channel 2* is combined nasal and oral thermistor, and *channel 3* is finger pulse oximetry.

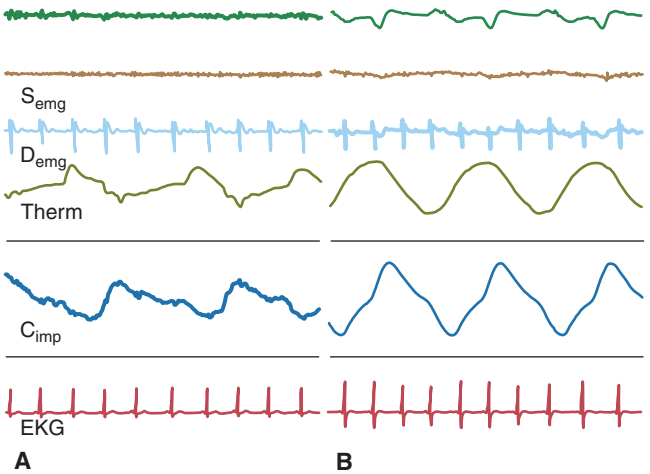

FIGURE 17-9 Nocturnal recording of case 2. **A.** Spontaneous breathing at a rate of 20 breaths/min. As expected, airflow increases, whereas chest wall dimensions decrease. **B.** During use of pneumobelt at a rate of 22 breaths/min, chest wall and ventilator are synchronized. However, chest wall motion is paradoxical, expanding during expiration. Diaphragmatic electromyogram (D_{emg}) failed to detect electrical muscular discharge during either spontaneous breathing or ventilator use. C_{imp}, chest wall impedance; *ECG*, electrocardiogram; *EMG*, electromyelogram; *Semg*, submental EMG; *THERM*, nasal thermistor.

found it particularly useful for reducing dyspnea associated with eating. During this time, his pulmonary function deteriorated gradually, necessitating increasing daytime use of the pneumobelt. Eventually, he had very little free time from the ventilator, amounting to 1 to 2 hours/day. Shortly, in September 1985, the patient developed pneumonia and required endotracheal intubation because of airway secretions that were unmanageable with either the pneumobelt or an iron lung, despite manual cough assistance (mechanical assistance was not tried). He was unable to resume pneumobelt use, and a tracheostomy was performed. He lived at home for an additional 3 years following tracheostomy placement but died unexpectedly when his ventilator inadvertently became detached from his tracheostomy tube.

This case shows that the pneumobelt may be used as the main mode of ventilator support in exceptional patients who prefer it to other forms of noninvasive ventilation. This patient was able to adapt quickly to nocturnal use while sleeping in the sitting position. The pneumobelt was an appropriate choice for him not only because he preferred it but also because he had a favorable body habitus and slowly progressive respiratory failure that allowed a

several-week adaptation period. The pneumobelt proved to be temporizing in this patient, although it provided adequate ventilator assistance even when he was almost entirely dependent on ventilator support. It was inadequate, however, when he developed a pulmonary infection, illustrating the limitations of the device in the face of acute respiratory failure.

GLOSSOPHARYNGEAL BREATHING

Glossopharyngeal, or "frog," breathing was first described by Dail et al[28] after they observed a polio patient who had begun using it spontaneously. The technique consists of repetitive gulping motions in which the tongue thrusts small boluses of air into the lungs (Fig. 17-10). The 40-mL to 80-mL boluses take roughly 0.5 second and are repeated eight to twelve times in succession to achieve a tidal volume of 500 to 600 mL, followed by passive exhalation. Roughly ten of these tidal volume maneuvers are performed each minute so that a minute volume of 4 to 8 L/min can be attained. In this way, persons with severely weakened respiratory muscles can use the technique to sustain ventilation and free themselves from the need for continuous ventilator assistance. Patients who become adept at the technique typically use it for periods ranging from a few minutes to several hours, but some ventilator-dependent patients can use it for up to 14 consecutive hours without other aids to ventilation (Sternburg L, personal communication).

Glossopharyngeal breathing also may be used to aid spontaneous breathing in patients with marginal pulmonary reserve by supplementing each tidal breath with 1 to 2 boluses of air or to assist coughing. Coughing is assisted by repeating boluses until tidal volumes of 2 to 2.5 L/min are achieved, allowing greater expiratory flows.[28,29] Complications are infrequent, with occasional patients complaining of aerophagia or chest tightness when fully inflating their lungs to assist cough.

Glossopharyngeal breathing requires intact function of upper airway structures, including the glottis, and therefore is of little value in patients with severe global weakness or bulbar dysfunction. Efficiency is also impaired by reduced chest wall or lung compliance or increased airway resistance, limiting use in patients with chest wall deformities or chronic obstructive pulmonary disease. In addition, because the upper airway contractions are voluntary, it cannot be used during sleep. Use of the technique complements any of the noninvasive aids to ventilation to extend "free time" from the ventilator.[30]

Glossopharyngeal breathing was used widely during the 1950s when it was taught to many patients with respiratory paralysis secondary to poliomyelitis. It is used less often today, however, partly because skilled teachers are few and also because most conditions leading to chronic respiratory insufficiency are associated with global muscle weakness or alterations in respiratory system compliance or airway resistance. Nonetheless, occasional glossopharyngeal breathers are found among survivors of the polio epidemics,[29] and some patients with muscular dystrophy or cervical spinal cord lesions learn to use the technique, sometimes spontaneously. Illustrative is a recent case study of a 6-year-old boy with a high cervical lesion secondary to tumor resection who

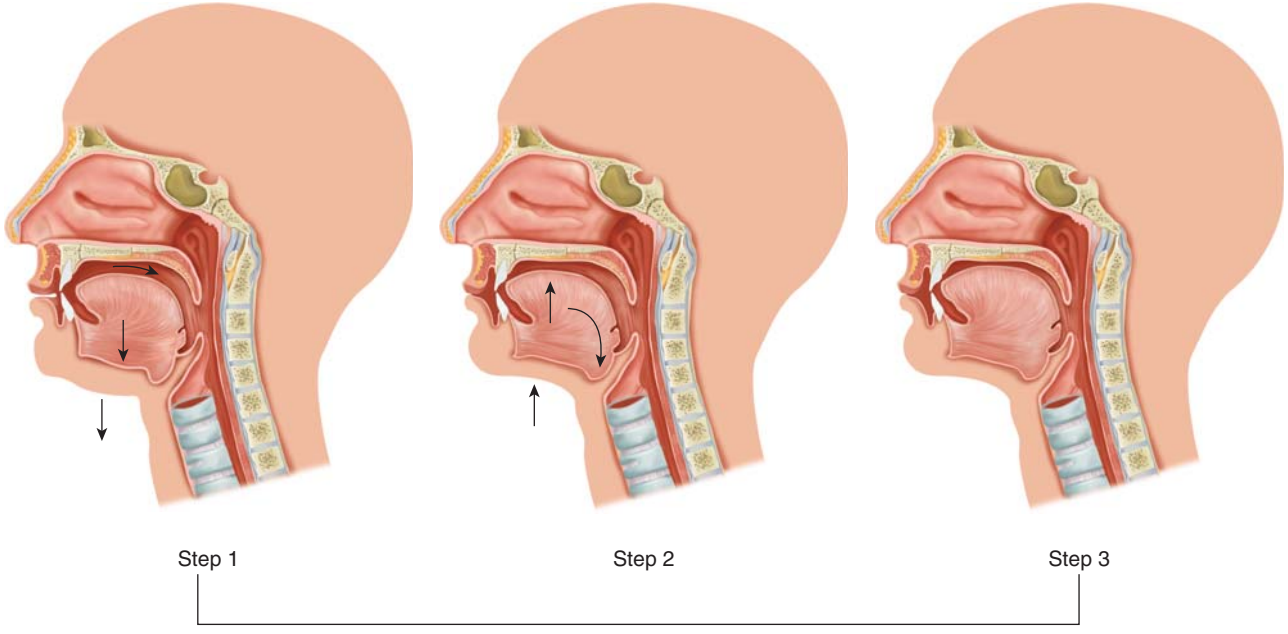

FIGURE 17-10 Illustration of steps taken by patient using glossopharyngeal breathing. In *step 1*, the mouth fills with air as the tongue is retracted. In *step 2*, the lips are closed and the tongue is raised to the roof of the mouth forcing air through the open glottis. In *step 3*, the larynx is closed, trapping air in the lungs, and the cycle is then repeated. (Used, with permission, from Maltais F. Glossopharyngeal breathing. *Am J Respir Crit Care Med.* 2011;184:381).

learned glossopharyngeal breathing on his own and was able to use it for ventilator-free breathing for up to 12 hours a day during a 16-year period. Despite having a tracheostomy, he was able to achieve a vital capacity of 3.3 L to augment cough.[30]

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18

NONINVASIVE POSITIVE-PRESSURE VENTILATION

Nicholas S. Hill

Noninvasive ventilation (NIV) refers to the provision of mechanical ventilation without the need for an invasive artificial airway. Many different approaches to assisting ventilation noninvasively have been used in the past, including negative-pressure ventilators, pneumobelts, and rocking beds (see Chapters 16 and 17).[1] By virtue of its effectiveness and convenience compared with other noninvasive approaches, however, noninvasive positive-pressure ventilation (NIPPV) using a mask (or *interface*) that conducts gas from a positive-pressure ventilator into the nose or mouth has become the predominant means of administering NIV throughout the world. NIPPV has long been used to treat chronic respiratory failure caused by chest wall deformities, slowly progressive neuromuscular disorders, or central hypoventilation.[2] In more recent years, NIPPV has been increasingly used to treat patients with various forms of acute respiratory failure.[3] For the purposes of this discussion, NIPPV refers to active ventilator assistance achieved by the noninvasive provision of a mechanical positive-pressure breath during inhalation, and *continuous positive airway pressure* (CPAP) refers to the provision of a nonfluctuating positive-pressure. This chapter discusses the rationale for use, evidence for efficacy of noninvasive positive-pressure techniques in both acute and chronic settings, selection of appropriate patients, techniques for administration, and pitfalls and complications.

WHY USE NONINVASIVE VENTILATION AND HOW DOES IT WORK?

Rationale

NIV has become an integral component of ventilator support in both acute and chronic settings because it avoids the complications of invasive ventilation. Invasive mechanical ventilation is highly effective and reliable in supporting alveolar ventilation, but endotracheal intubation carries well-known risks of complications that have been described elsewhere in detail (see Chapter 39).[4,5] These complications have been lumped into three main categories: complications related to insertion of the tube and mechanical ventilation, those caused by loss of airway defense mechanisms, and those that occur after removal of the endotracheal tube.[4]

In the first category, aspiration of gastric contents; trauma to the teeth, hypopharynx, esophagus, larynx, and trachea; arrhythmias; hypotension; and barotrauma may occur during placement of a translaryngeal tube.[6,7] Tracheostomy tube placement incurs risks of hemorrhage, stomal infection, intubation of a false lumen, mediastinitis, and acute injury to the trachea and surrounding structures, including tracheal rupture,[8] and esophageal and vascular injury.[6] In the second category, endotracheal tubes serve as a source of continual irritation, interfere with airway ciliary function, and require frequent suctioning that contributes to airway injury, patient discomfort, and mucus hypersecretion. They also provide a direct channel to the lower airways for microorganisms and other foreign materials, leading to biofilm formation, chronic bacterial colonization, and ongoing inflammation. As a consequence, health care–acquired pneumonias are seen in up to 20% of mechanically ventilated intensive care unit (ICU) patients (see Chapter 46),[9] and sinusitis is seen in 5% to 25% of nasally intubated patients, related to blockade of the sinus ostia and accumulation of infected secretions in the paranasal sinuses (see Chapter 47).[10] In the third category, hoarseness, sore throat, cough, sputum production, hemoptysis, upper airway obstruction secondary to vocal cord dysfunction or laryngeal swelling, and tracheal stenosis all may follow extubation.[11]

In addition, from the point of view of the patient, translaryngeal intubation is uncomfortable and compromises the ability to eat and communicate, contributing to feelings of powerlessness, isolation, and anxiety.[12] This increases the need for sedation, delaying weaning, prolonging the duration of invasive mechanical ventilation, and potentiating the risks of further complications. If tracheostomy placement becomes necessary, sophisticated equipment including suctioning paraphernalia and a high level of technical expertise among caregivers are required. Tracheostomies promote upper airway colonization with gram-negative bacteria, increasing the risk of pneumonias.[7] Furthermore, long-term tracheostomies are complicated by tracheomalacia, granulation tissue formation, and tracheal stenoses that sometimes obstruct the airway, chronic pain, and tracheoesophageal or even tracheoarterial fistulas.[11] These considerations and potential complications may limit the options for chronic care placement, add substantially to the costs of care,[13] and even preclude home discharge in patients with limited caregiver and financial resources.

NIV can avoid many of these complications if candidates are selected properly using guidelines that are discussed in detail later. NIV leaves the upper airway intact, preserves airway defense mechanisms, and allows patients to eat, drink, verbalize, and expectorate secretions. NIPPV reduces the infectious complications of mechanical ventilation, including nosocomial pneumonia and sinusitis.[14,15] It also enhances patient comfort, convenience, and mobility at no greater[16] or even less[13] cost than endotracheal intubation. NIV can be administered outside the ICU setting as long as adequate nursing and respiratory therapy support can be provided, allowing for more rational use of acute care beds, and it greatly simplifies care for patients with chronic respiratory failure in the home.

Mechanisms of Noninvasive Positive-Pressure Ventilation Action

ACUTE RESPIRATORY FAILURE

NIPPV improves the respiratory status of failing patients via a number of mechanisms. Most important, NIPPV reduces the work of breathing by the same mechanism as invasive positive-pressure ventilation: By applying supra-atmospheric

pressure intermittently to the airways, it increases transpulmonary pressure, inflates the lungs, augments tidal volume, and unloads the inspiratory muscles. Exhalation is achieved by passive lung recoil. Studies in patients with severe stable chronic obstructive pulmonary disease (COPD) or restrictive thoracic disorders show that NIPPV reduces or, if inflation pressure is sufficient, even eliminates diaphragmatic work.[17,18] In patients with severe COPD exacerbations, the addition of positive end-expiratory pressure (PEEP) to inspiratory pressure support further reduces the work of breathing by counteracting the effects of auto-PEEP. This combination (pressure support plus PEEP) lowers diaphragmatic pressure swings even more than with either pressure support or PEEP alone.[19] These actions lead to a prompt reduction in respiratory rate, sternocleidomastoid muscle activity, dyspnea, and carbon dioxide (CO_2) retention.

Other beneficial actions include an increase in functional residual capacity that opens collapsed alveoli, reducing shunt and enhancing ventilation–perfusion ratios in certain forms of respiratory failure, such as acute cardiogenic pulmonary edema. These effects improve oxygenation and may further reduce the work of breathing because the respiratory system is shifted to a more compliant position on its pressure-volume curve. In addition, CPAP alone (and with NIPPV) may improve left-ventricular function by virtue of an afterload-reducing effect of increased intrathoracic pressure.[20] This effect occurs mainly in patients with dilated, hypocontractile left ventricles whose heart function is more dependent on afterload than on preload. The increased intrathoracic pressure reduces both preload and afterload, but the latter effect predominates, lowering transmyocardial pressure and enhancing cardiac output.[21]

A major effect of NIPPV that appears to be responsible for benefits reported in many studies, including reduced complication rates, mortality, and hospital lengths of stay, is a reduction in health care–acquired infections. Two prospective surveys[14,15] observed roughly a fourfold reduction in the risk of health care–acquired pneumonia compared with physiologically matched endotracheally intubated patients, even after controlling for severity of illness. Patients treated with NIPPV also tend to receive fewer other invasive interventions, such as urinary bladder catheters or central intravenous lines,[15] and this also likely contributes to a lower rate of health care–acquired infections and episodes of sepsis.

Despite the advantages of NIPPV related to the avoidance of airway invasion, the lack of a direct connection to the lower airway also poses a number of challenges. The patient must be able to protect his or her airway and clear secretions adequately, or failure is inevitable. The patient's upper airway must permit airflow into the lungs, so NIPPV cannot be used in patients with high-grade, fixed, upper-airway obstructions. In addition, air leaks around the interface seal or via other routes are nearly ubiquitous with NIPPV and may interfere with the efficacy of ventilation. Furthermore, the patient must be able to cooperate and synchronize breathing with the ventilator, or no reduction in the work of breathing can be achieved, but the patient cannot be heavily sedated or paralyzed to achieve synchrony. Thus, patients who are to receive NIPPV must be selected carefully and managed with an eye to these limitations in ways that differ from the approach used for invasive mechanical ventilation.

CHRONIC RESPIRATORY FAILURE

Long-term NIPPV is used mainly nocturnally during sleep, when intermittent air leaking through the mouth or under the mask seal is universal, but sufficient air usually enters the lungs to assist ventilation.[22] The adaptations that permit air entry into the lungs while NIPPV is administered during sleep are poorly understood, but resistance to airflow in the upper airway is undoubtedly an important factor. In one study, large amounts of air leaking through the mouth during nasal CPAP increased nasal resistance,[23] an effect that was countered by provision of heated, humidified air, consistent with the idea that nasal mucosal cooling was responsible. Increases in nasal resistance secondary to this mechanism, upper airway infection, or allergy is likely to reduce delivered tidal volumes during nasal NIPPV. Passive positioning of the soft palate is also important in maintaining patency of the upper airway,[24] as underlined by the observation that patients treated with nasal CPAP experience increased air leaking through the mouth after uvulopharyngoplasty.[25]

Glottic aperture is also important in determining the flow of gas into the lower airways during NIPPV. Compared with the awake state, the glottic aperture narrows and delivered tidal volume falls when NIPPV is administered during stage 1 or 2 sleep.[26,27] In deeper sleep (stage 3 or 4), the glottic aperture widens, permitting more ventilation; if minute volume is increased excessively, however, the glottic aperture narrows once again, partly related to the reduction in the partial pressure of arterial carbon dioxide (Pa_{CO_2}). These findings indicate that both sleep stage and the amount of ventilator assistance influence glottic aperture, which is a potentially important determinant of the efficacy of NIV. They also apply mainly to controlled modes of ventilation;[28] glottic aperture is not as important when NIPPV is administered via a pressure-limited "bilevel" ventilator in the spontaneous mode.[29]

Three theories have been proposed to explain the mechanism by which stabilization of daytime gas exchange is achieved in patients with chronic respiratory failure who are receiving ventilator assistance for as little as 4 to 6 hours nightly. One postulates that NIV rests chronically fatigued respiratory muscles, thereby improving daytime respiratory muscle function.[30,31] Supporting this theory are studies demonstrating that respiratory muscles do indeed rest during NIV;[32–34] also, indices of respiratory muscle strength and endurance may improve in patients with chronic respiratory failure after varying periods of noninvasive ventilatory assistance.[32–35] Conversely, chronic respiratory muscle fatigue has never been defined adequately or demonstrated convincingly; other studies have failed to demonstrate improvement

in respiratory muscle function after initiation of NIV,[36] and some studies have demonstrated that patients with neuromuscular disease have stable Pa_{CO_2} values for years despite a progressive decline in pulmonary function.[37]

A second theory proposes that NIV improves respiratory system compliance by reversing microatelectasis of the lung, thereby diminishing daytime work of breathing.[38] This theory derives from studies showing improvements in forced vital capacity (FVC) without changes in indices of respiratory muscle strength after periods of positive-pressure ventilation. Once again, however, data are conflicting, with a number of studies showing no changes in vital capacity after periods of NIV.[35,36] In addition, computed tomographic scanning of the chest indicates that microatelectasis is not an important contributor to chest wall restriction in patients with respiratory muscle weakness.

A third theory proposes that NIV lowers the respiratory center "set point" for CO_2 by reversing chronic hypoventilation.[30,39] During deeper stages of sleep, particularly rapid eye movement sleep, upper airway muscle tone and the activity of nondiaphragmatic inspiratory muscles diminish.[40] This response may be exaggerated in patients with ventilatory impairment, leading to progressive nocturnal hypoventilation. Repeated episodes of nocturnal hypoventilation are thought to lead to a gradual accumulation of bicarbonate, desensitization of the respiratory center to CO_2, and worsening of daytime hypoventilation.[39] Nocturnal ventilator assistance reverses nocturnal hypoventilation and allows excretion of bicarbonate and a gradual downward resetting of the respiratory center set point for CO_2, thereby reducing daytime hypercarbia. In addition, NIPPV may improve the quantity and quality of sleep by preventing hypoventilation-related arousals that lead to sleep fragmentation,[41] reducing fatigue, and improving daytime function. Evidence for this theory derives from studies showing that when ventilator assistance is discontinued for a night in patients with chronic respiratory failure who have been using nightly NIV, the degree of nocturnal hypoventilation is less than before initiation, suggesting a resetting of respiratory center sensitivity for CO_2.[42] Also, nocturnal ventilation, oxygen (O_2) saturation, sleep quality, and daytime symptoms deteriorate without reductions in respiratory muscle strength or vital capacity when nocturnal NIPPV is discontinued temporarily in patients with restrictive thoracic disease and improve promptly when NIPPV is resumed.[35,41] Moreover, in sixteen patients with chronic respiratory failure secondary to restrictive thoracic disorders followed prospectively for 3 years after starting NIPPV, Pa_{CO_2} improved in association with an increase in the slope of the ventilatory response curve, whereas the maximal inspiratory pressure remained unchanged.[43] These studies suggest that amelioration of nocturnal hypoventilation with resetting of respiratory center CO_2 sensitivity and improved sleep quality may be the most important mechanisms contributing to the efficacy of long-term NIPPV. The three theories, however, are not mutually exclusive, and all could contribute more or less, depending on the patient.

Clearly, much remains to be learned regarding specific mechanisms of action of NIV. Understanding of these mechanisms is complicated by the application of NIV in both acute and chronic settings using many different techniques for patients with varying etiologies of respiratory failure. The ability to unload respiratory muscles appears to be key, particularly in the acute setting. Mechanisms controlling upper airway responses and respiratory center adaptations are less well understood but appear to be critical to success in the long-term setting.

EPIDEMIOLOGY OF NONINVASIVE POSITIVE-PRESSURE VENTILATION

Acute care applications of NIPPV are increasing in Europe and North America.[44,45] An observational study of NIV utilization for COPD and cardiogenic pulmonary edema patients in acute respiratory failure in a single twenty-six-bed French ICU revealed an increase from 20% of ventilator initiations in 1994 to nearly 90% in 2001.[45] In association with this increase, the occurrence of health care–acquired pneumonias and ICU mortality fell from 20% and 21% to 8% and 7%, respectively. In an Italian study examining outcomes of NIPPV in two different time periods during the 1990s, success rates remained steady despite an increase in acuity of illness scores, suggesting that sicker patients in the later time period were being managed as successfully as less ill patients in the earlier period. Both groups of authors speculated that increased experience and skill of the caregivers was responsible for the increased use and improved outcomes.[44,45]

Sequential surveys of European (mainly French) ICUs demonstrated an increase in the use of NIV as a percentage of total initiations of ventilations from 16% in 1997 to 23% in 2002, with utilization in patients with COPD and cardiogenic pulmonary edema increasing from 50% to 66% and from 38% to 47%, respectively.[46] Esteban et al conducted a worldwide survey in more than twenty countries that compared the trends of mechanical ventilation use and demographics between 1998 and 2004, enrolling more than 1600 patients and showing an increase in NIPPV use from 4.4% to 11.1%[47] The differences in rates between the French ICU survey and the worldwide survey may reflect lower utilization rates in some countries as well as the differing methodologies between the two surveys. The French survey examined use in terms of incidents whereas the worldwide survey focused on prevalence of use. Considering that NIPPV is used for shorter periods of time on average than invasive ventilation, prevalence will accordingly be lower.

Some hospital units lend themselves well to NIPPV applications and have very high utilizations rates. In Italy, Confalonieri et al[48] reported high utilization rates of NIV in specialized respiratory intensive care units, which are similar to "intermediate" or "step-down" units in the United States, where a large proportion of patients have COPD either as an etiology of acute respiratory failure or as a comorbidity. In that setting, 425 of 586 (72.5%) patients requiring

mechanical ventilation were treated initially with NIV (374 using NIPPV and fifty-one using an "iron lung").[48]

In a 2003 national audit of COPD exacerbations in the United Kingdom, however, NIV was unavailable in nineteen of 233 hospitals and 39% of ICUs, 36% of "high-dependency units," and 34% of hospital wards.[49] Similar results were seen in a North American survey of use of NIV in seventy-one hospitals in Massachusetts and Rhode Island.[50] Overall use of NIPPV was estimated to be 20% of total ventilator initiations, but 30% of hospitals had estimated rates of less than 15%. Reasons for low utilization were mostly attributed to lack of physician knowledge of NIPPV, inadequate equipment, and lack of staff training. Most disturbingly, estimated use of NIV for COPD exacerbations and cardiogenic pulmonary edema was only 29% and 39% of ventilator initiations, respectively.[50] A follow-up study in Massachusetts using data collected prospectively from 2005 to 2007 revealed an overall 38.7% NIV utilization rate, with 80% and 69% of COPD and cardiogenic pulmonary edema patients, respectively, receiving NIV as the initial mode.[51] More recently, clear evidence for the dramatic increase in NIPPV use derived from a Nationwide Inpatient Survey constituting more than 7 million hospital admissions from 1998 to 2008. NIPPV use increased from 1% to 4.5% of total admissions while there was a concomitant fall in invasive mechanical ventilation from 6% to 3.5%. Mortality rates improved in most groups, but the authors raised concerns about a small subgroup of patients who were transitioned from initial NIPPV to invasive ventilation and had a 29% mortality, higher than in patients who were treated with invasive ventilation from the start.[52]

A national survey of U.S. Veterans Affairs hospitals showed that despite wide availability of NIV, its perceived use was low.[53] Almost two-thirds of respiratory therapists responding to the survey thought that NIV was used less than half of the time when its use was indicated. The survey also revealed that wide variations in the perception of NIV use was dependant partly on the size of the ICUs, with larger ones reporting more frequent use.[53] Along these lines, a Canadian study reported that between 1998 and 2003, only 66% of patients meeting criteria for NIPPV actually received it.[54]

Suboptimal utilization has been reported in non-Western countries as well. A Korean survey reported that NIV was used in just two of twenty-four university hospitals and comprised only 4% of ventilator initiations. A majority of the physician staff (62%) and 42% of the nurses expressed a desire for additional educational programs on NIV.[55] In an Indian survey of 648 physicians, perceived NIV use was mostly limited to the ICU (68.4%), and COPD was the most common indication for its use.[56] Findings of this survey were similar to those of the Korean, European, and North American surveys in that rates of NIV use varied widely between centers, with a substantial portion reporting low rates. Thus, although overall use of NIV is clearly increasing, these findings underline the need for NIV educational programs at individual hospitals that permit caregivers to develop the requisite expertise in administering NIV.

NONINVASIVE POSITIVE-PRESSURE VENTILATION IN THE ACUTE CARE SETTING

Evidence for Efficacy

Numerous acute applications of NIPPV have been described, but only a few are supported by strong evidence (Table 18-1). The following sections discuss important applications according to the type of respiratory failure.

Obstructive Diseases

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Patients with exacerbations of COPD usually are good candidates for NIPPV because they respond to partial ventilator support, hypoxemia is usually mild to moderate, and the condition is most often reversible within a few days. Thus numerous earlier uncontrolled studies have reported that NIPPV avoids intubation in patients with COPD, with success rates ranging from 58% to 93%. Some studies have reported the use of CPAP alone to treat acute exacerbations of COPD,[57,58] based on the rationale that by counterbalancing auto-PEEP, it will reduce the work of breathing.[59] In these studies, relatively low levels of nasal CPAP (5 to 9.3 cm H_2O) were associated with improvements in Pa_{CO_2} and arterial oxygen tension (PA_{O_2}), and few patients required intubation. The lack of controls, however, renders these studies inconclusive.

Kramer et al[60] randomized thirty-one patients with various etiologies for respiratory failure, twenty-one of whom had COPD, to receive NIPPV or conventional therapy. Among COPD patients who received NIPPV in their study, respiratory rate and Pa_{CO_2} fell more rapidly during the first hour of therapy than among controls, and intubation rates were reduced to 9% compared with 67% in controls. In a multicenter European trial[17] of eighty-five patients with COPD randomized to receive face-mask pressure-support ventilation (PSV) or conventional therapy, respiratory rate but not Pa_{CO_2} fell significantly in the NIPPV group during the first hour; intubation (26% vs. 74%), complication (16% vs. 48%), and mortality (9% vs. 29%) rates and hospital lengths of stay (35 vs. 23 days) all were significantly lower in the NIPPV than in the control group.

Another randomized, controlled trial compared the efficacy of standard medical therapy with NIPPV in thirty patients with acute hypercapnic respiratory failure caused by exacerbations, pneumonia, or congestive heart failure.[61] Those randomized to NIPPV had greater improvements in pH and respiratory rate within 6 hours, higher success rate (93%), and shorter hospital lengths of stay (11.7 vs. 14.6 days, $p < 0.05$) than controls. The largest study to date on NIPPV for exacerbations of COPD randomized 236 patients to receive NIPPV or standard therapy at fourteen British centers.[62] NIPPV was administered in general respiratory wards by nurses who had a few hours of in-service training with

TABLE 18-1: TYPES OF ACUTE RESPIRATORY FAILURE TREATED WITH NONINVASIVE VENTILATION GRADED

	References
A. Strong Evidence—Recommended	
Exacerbation of COPD	17, 59 to 64, 66 to 70
Acute cardiogenic pulmonary edema	104 to 126
Immunocompromised (hematologic malignancy, bone marrow or solid-organ transplantation, AIDS)	140 to 144
Facilitation of weaning/extubation patients with COPD	168 to 180
B. Intermediate Evidence—Guideline	
Asthma	66 to 83
Community-acquired pneumonia in patients with COPD	134
Extubation failure in patients with COPD	175, 177 to 180
Hypoxemic respiratory failure	96 to 100
Do-not-intubate patients (COPD and CHF)	150 to 157
Postoperative respiratory failure (lung resection, bariatric, CABG)	158 to 167
C. Weaker Evidence—Optional	
Acute respiratory distress syndrome (ARDS) with single-organ involvement	144 to 147
Community-acquired pneumonia (non-COPD)	135 to 140
Cystic fibrosis	84 to 86
Facilitation of weaning/extubation failure (non-COPD)	174, 176
Neuromuscular disease/chest wall deformity	79, 83, 84
Obstructive sleep apnea/obesity hypoventilation	88, 89
Trauma	148, 149
Upper airway obstruction	
D. Not Recommended	
Acute deterioration in end-stage interstitial pulmonary fibrosis	94, 95
Severe ARDS with multiple organ dysfunction	
Postoperative upper airway or esophageal surgery	
Upper airway obstruction with high risk for occlusion	

Abbreviations: AIDS, acquired immune deficiency syndrome; *CABG*, coronary artery bypass graft; *CHF*, congestive heart failure; *COPD*, chronic obstructive pulmonary disease.

Level of evidence: **A**, multiple randomized, controlled trials and meta-analyses; **B**, single controlled trial and cohort series or multiple randomized studies with conflicting findings; **C**, anecdotal reports and case series; **D**, not recommended based on contrary evidence or expert opinion.

the technique. Patients treated with NIPPV had lower intubation (15% vs. 27%) and mortality (10% vs. 20%) rates than controls, but the benefit was seen only in patients with pH values of 7.3 or greater. The authors concluded that although NIPPV proved to be effective in their study, these sicker patients probably should have been treated in an ICU.

In addition to the favorable findings regarding the use of NIPPV for acute exacerbations of COPD, some studies have found that 1-year survival rates are better and the need for rehospitalization and consumption of ICU beds over the next year are less for patients treated with NIPPV as opposed to conventional therapy.[63,64] Although these latter studies were not randomized, so the results could have reflected a selection bias favoring less ill patients in the NIPPV group, it is also possible that NIPPV avoids late complications of invasive ventilation, such as sustained muscle weakness or swallowing dysfunction.[10]

Among the many controlled and uncontrolled studies examining the efficacy of NIPPV in exacerbations of COPD, only two have obtained unfavorable results. In one,[65] twenty-five of forty-nine consecutive COPD patients with acute exacerbations were treated with nasal NIPPV, and twenty-four were intolerant and served as the "control" group. Blood gases in both groups improved at similar rates, and no differences in outcome were apparent between the two groups. In the second, Barbe et al[66] randomized twenty-four patients with acute exacerbations of COPD to receive nasal NIPPV or standard therapy. Four of fourteen patients randomized to NIPPV were intolerant; among the remaining patients, blood-gas improvements and hospital lengths of stay were similar, and no differences in intubation or mortality rates were apparent, leading the authors to conclude that NIPPV is ineffective in COPD. Both studies, however, enrolled consecutive patients who, on average, had less-severe blood-gas abnormalities than patients enrolled in favorable studies; none of the patients in the study of Barbe et al[66] required intubation, as did almost three-quarters of the controls in the studies of Kramer et al[60] and Brochard et al.[17] These observations support the contention that the patients in the two unfavorable studies were less ill than those in the favorable studies, and argue that NIPPV should be reserved for sicker patients with COPD who are at risk of requiring intubation.

Multiple randomized, controlled trials lend themselves to meta-analysis. An earlier meta-analysis by Keenan et al[67] concluded that NIPPV significantly reduces mortality and reduces the cost of hospitalization by an average of $3244 (Canadian) compared with conventional therapy. Peter et al[68] examined both COPD and non-COPD causes of acute respiratory failure in their meta-analysis, and concluded that NIPPV significantly reduces the need for intubation as well as mortality. Meta-analyses by Keenan et al[69] and Lightowler et al[70] (Cochrane analysis) observed absolute and relative risk reductions of 28% and 0.42 for intubation, 10% and 0.41 for mortality, and 4.57 and 3.21 hospital days, respectively (all $p < 0.05$) (Fig. 18-1). The analysis of Keenan et al also concluded that there is little evidence to support NIPPV use in milder COPD, although they analyzed only two studies of mild patients. The analysis of Lightowler et al also found that Pa_{CO_2}, heart rate, and dyspnea scores improved more rapidly than in conventionally treated patients. A more recent meta-analysis by Quon et al[71] derived similar findings, observing reductions of 65% in intubations, 55% in mortality, and 1.9 days in hospital length of stay among COPD patients

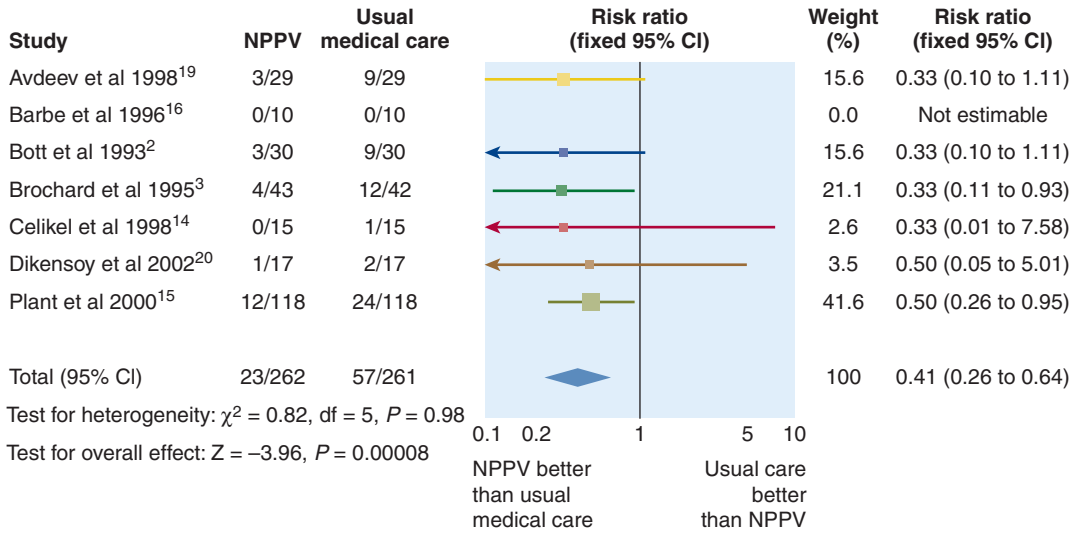

FIGURE 18-1 Forest plot of eight randomized, controlled studies on NPPV in patients with acute respiratory failure secondary to COPD. The reduction in mortality rate was consistent among studies. (Used, with permission, from Lightowler. Noninvasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis. *Br Med J.* 185–189, 2003.)

admitted with exacerbations and treated with NIPPV. These studies lend strong support to the use of NIPPV for patients with COPD in the acute care setting, leading consensus groups to recommend that the modality "be considered" in selected patients,[72] and the Canadian Thoracic Society Guideline committee to recommend that NIV be considered the ventilatory modality of first choice for patients with acute respiratory failure secondary to exacerbations of COPD.[73] The need for careful patient selection cannot be overemphasized (see "Selection Guidelines" below). NIPPV is best used to avoid intubation, not to replace it. Although NIPPV should be viewed as the ventilator therapy of first choice for appropriate COPD patients, those with contraindications to NIPPV should be intubated and ventilated without delay.

In view of the idea that NIPPV is best used to avoid intubation, Squadrone et al[74] asked whether it can serve as an alternative to intubation in patients with COPD and advanced acute hypercapnic respiratory failure (pH ≤ 7.25, Pa_{CO_2} ≥ 70 mm Hg, respiratory rate ≥ 35 breaths/min). Sixty-four such patients had similar mortality rates and hospital lengths of stay but fewer serious complications (mainly infectious) and a trend toward a higher weaning rate at 30 days compared with a historically matched control group of invasively ventilated patients. The authors concluded that NIPPV can be used as an alternative to invasive mechanical ventilation in severely ill patients with COPD, but considering that the failure rate approached two-thirds in the NIPPV group and that the more recent report by Chandra et al[52] raised concerns about this approach, NIPPV should be applied with great caution in such patients. As pointed out previously, the use of historical controls is a serious design limitation that may favor the treatment group.

Few data provide guidance on selecting patients who might benefit from continued use of NIPPV after hospital discharge. In an uncontrolled retrospective study, Tuggey et al[75] found that patients treated with NIV during their acute admissions and sent home with it had many fewer hospital days per year (25 vs. 78 days; $p = 0.004$) and incurred much lower costs per year ($7407 vs. $23,065) after starting domiciliary NIV than before. Despite the small number of patients and uncontrolled design, these results support the idea that domiciliary NIV should be considered in "revolving-door patients" who require repeated hospital admissions and highlight the need for more definitive studies addressing this question.

ASTHMA

Although acute asthma would be anticipated to respond favorably to NIPPV because it shares pathophysiologic features with COPD, much less evidence supports this application. One early report described seventeen patients with asthma who had an average initial pH of 7.25, a Pa_{CO_2} of 65 mm Hg, and were treated with face-mask PSV.[76] Only two required intubation (for increasing Pa_{CO_2}), average duration of ventilation was 16 hours, and no complications occurred.

More recently, Fernandez et al[77] reported on fifty-eight patients with status asthmaticus, thirty-three of whom were retrospectively deemed candidates for NIPPV because of persisting CO_2 retention (Pa_{CO_2} > 50 mm Hg) and because they met other clinical criteria.[77] Of these, eleven were intubated according to clinician preference, and twenty-two were managed noninvasively. The noninvasively and invasively treated groups had similar initial Pa_{CO_2} values, which improved less rapidly in the noninvasive group. Only 14% of the NIPPV-treated patients eventually required intubation, and they had shorter ICU and hospital lengths of stay than the intubated group. Thus far, four randomized, controlled trials have been reported. Holley et al[78] were able to enroll only one-tenth of the roughly 350 patients their power analysis had projected.

Not surprisingly, their major outcome variable—intubation rate—was not reduced significantly in their NIPPV group (one of nineteen versus two of sixteen in controls), and they observed no deaths. Their major finding was that physicians who a priori believed that NIPPV was effective were less likely to enroll patients in the trial because of concern that the patients might require intubation if randomized to the control group. Soroksky et al[79] randomized thirty-three patients with severe acute asthma (average initial forced expiratory volume in 1 second [FEV_1] roughly 33%) to receive NIPPV or sham therapy via a face mask. The NIPPV group had a significantly greater increase in FEV_1 within the first hour (53.5% vs. 28.5%) and fewer hospitalizations (three of seventeen versus ten of sixteen) compared with the sham group. Both groups received aerosolized bronchodilators via a nebulizer, not the ventilator. The authors speculated that the greater improvement in airflow in the NIPPV group might be related to a bronchodilator effect of positive-pressure.

The third randomized trial[80] supports the notion that NIPPV may have an initial bronchodilator effect in acute asthma. In this study, forty-four patients with status asthmaticus (mean FEV_1 33% predicted) received "low" NIPPV (inspiratory and expiratory pressure 6 and 4 cm H_2O, respectively), "high" NIPPV (inspiratory and expiratory pressure 8 and 6 cm H_2O, respectively), or oxygen supplementation in controls. For the first hour, they received hydrocortisone but no bronchodilators. After the initial hour, the "high" NIPPV group had an improvement in FEV_1 over baseline of 20%, compared to no improvement in controls ($P < 0.05$).

In the fourth trial,[81] undoubtedly underpowered, fifty-three patients with severe asthma were randomized to NIPPV (inspiratory pressure 12 cm H_2O, expiratory pressure 5 cm H_2O) plus standard therapy or standard therapy alone. The NIPPV group spent less time in the ICU and used less bronchodilation, but no other significant differences were observed, including rate of improvement in FEV_1 or gas exchange, or rate of intubation.

These studies suggest that NIPPV may be effective at improving airflow, correcting gas-exchange abnormalities, avoiding intubation, and reducing the need for hospitalization in patients with acute severe asthma. Published studies, however, are either uncontrolled or underpowered or the findings have not been replicated. A Cochrane analysis concluded that evidence for use of NIPPV for acute asthma was "very promising" but "controversial" and that more controlled studies are needed.[82] Furthermore, medical therapy alone may be quite effective.[83] Lacking more evidence, no firm conclusions can be drawn regarding the relative effectiveness of NIPPV versus conventional therapy in exacerbations of asthma. The British Thoracic Society Standards of Care Committee opined that NIPPV should not be used routinely for acute asthma.[84] Nonetheless, an empiric trial of NIPPV might be considered in patients not responding promptly to standard medical therapy if selected according to commonly used criteria (see "Selection Guidelines" below). Also, more research into the role of positive-pressure in enhancing acute bronchodilation seems warranted.

CYSTIC FIBROSIS

NIPPV has been used to treat acutely deteriorating patients with end-stage cystic fibrosis. In one study, six patients with FEV_1 ranging from 350 to 800 mL and severe acute-on-chronic CO_2 retention (initial Pa_{CO_2} ranging from 63 to 112 mm Hg) were treated with NIPPV for periods of 3 to 36 days; four survived until a heart-lung transplantation could be performed.[84] The same investigators reported more recently on 113 patients with cystic fibrosis treated with NIPPV for acute deteriorations.[85] Ninety of these patients (median FEV_1/FVC ratio of 0.5) were listed for lung transplantation, twenty-eight survived to transplantation, ten remained on the list at the time of reporting, and the remainder expired. NIPPV improved hypoxia but not hypercapnia. These case series suggest that NIPPV may serve as a rescue therapy to provide a "bridge to transplantation" for patients with acutely deteriorating cystic fibrosis, but control of airway secretions is still a big challenge and mortality is high if the wait for an organ is prolonged beyond a few months.[86]

UPPER AIRWAY OBSTRUCTION

The inappropriate use of NIPPV in patients with tight, fixed upper airway obstruction should be avoided so as not to delay the institution of definitive therapy. In my experience, however, NIPPV can be used to treat patients with reversible upper airway obstruction, such as that caused by glottic edema following extubation, sometimes in combination with aerosolized medication and/or helium–oxygen gas mixture. Although no controlled trials demonstrate the efficacy of this approach in adults, a controlled trial in ten infants with respiratory failure showed that NIPPV[87] and CPAP were equally efficacious in lowering respiratory rate, but NIPPV contributed to patient–ventilator asynchrony. If used, NIPPV should be administered cautiously and monitored closely because these patients are at risk for precipitous deteriorations.

DECOMPENSATED OBSTRUCTIVE SLEEP APNEA OR OBESITY HYPOVENTILATION SYNDROME

Patients with acute-on-chronic respiratory failure caused by sleep apnea syndrome, often in combination with obesity hypoventilation, have been treated successfully with NIPPV and transitioned to CPAP once stabilized,[88] but no controlled trials have evaluated this application. Sturani et al[89] described the successful use of nasal NIPPV administered with the biphasic intermittent positive airway pressure (BiPAP) device (18 cm H_2O inspiratory and 6 cm H_2O expiratory pressures) in five morbidly obese patients (mean body mass index of 50 kg/m^2) with severe sleep apnea. Anecdotally, high inflation pressures, sometimes necessitating use of volume-limited ventilators that have greater pressure-generating capabilities than portable pressure-limited ventilators, may be needed because of high respiratory system impedance.

Restrictive Diseases

Although NIPPV to treat patients with chronic respiratory failure secondary to restrictive thoracic diseases is well accepted (see "Chronic Respiratory Failure" above), it is used for only a small portion of patients admitted to acute care hospitals with respiratory failure. Accordingly, few studies on the management of acute respiratory failure in these patients have been reported. Small uncontrolled series have reported success using NIPPV to alleviate gas-exchange abnormalities and to avoid intubation in patients with acute respiratory failure secondary to neuromuscular disease[90] and kyphoscoliosis.[91] Despite the lack of evidence, the British Thoracic Society Standards of Care Committee considers that NIPPV "is indicated" in patients with acute or acute-on-chronic respiratory failure secondary to restrictive thoracic diseases.[92]

A regimen for managing acute deteriorations in patients with chronic respiratory failure secondary to neuromuscular disease, reported by Bach et al,[93] requires that patients receive NIV at home 24 hours a day during the exacerbation. When O_2 saturation falls below 90% as determined by continuous pulse oximetry, airway secretions are removed aggressively using manually assisted coughing and mechanical aids such as the cough insufflator–exsufflator until O_2 saturation returns to the 90% range. In this small series of patients, the need for hospitalization was reduced dramatically after institution of the regimen.[79]

Limited information is available on NIPPV therapy for patients with acutely deteriorating restrictive lung diseases such as idiopathic pulmonary fibrosis. Such patients usually fare poorly with mechanical ventilation.[94] On the other hand, in a recent retrospective cohort of eleven patients with idiopathic pulmonary fibrosis and acute respiratory failure treated with NIPPV,[95] five survived the hospitalization and lived for more than 3 months. Thus, some such patients could be considered for NIPPV if they have a possible reversible superimposed condition and are otherwise good NIPPV candidates.

Hypoxemic Respiratory Failure

Hypoxemic respiratory failure is defined as a P_{CO_2}/FI_{O_2} ratio of less than 200 and a respiratory rate greater than 35 breaths/min; contributing diagnoses include acute pneumonia, acute pulmonary edema, acute respiratory distress syndrome (ARDS), and trauma.[96] It is an extremely broad category of acute respiratory failure. Hence, perhaps not surprisingly, studies of NIPPV to treat it have yielded conflicting results. Meduri et al[97] were the first to report the successful application of NIPPV in such patients. In a randomized trial,[98] the same authors found no benefit of NIPPV over conventional therapy among all entered patients. Initial hypercapnia predicted a favorable outcome: Patients with an initial Pa_{CO_2} of greater than 45 mm Hg had significantly lower intubation and ICU mortality rates and shorter ICU lengths of stay than normocapnic patients. The authors concluded that hypoxemic respiratory failure without CO_2 retention responds poorly to NIPPV.

Conversely, Antonelli et al[96] randomized sixty-four patients with hypoxemic respiratory failure to NIPPV or immediate intubation. Improvements in oxygenation were similar in the two groups, and only 31% of the NIPPV-treated patients required intubation. NIPPV-treated patients had significantly fewer septic complications such as pneumonia or sinusitis (3% vs. 31%), and there were trends toward decreased mortality and ICU length of stay (27% vs. 45% and 9 vs. 15 days, respectively) compared with intubated controls. Another randomized, controlled trial of sixty-one patients with various forms of acute respiratory failure found a significantly reduced intubation rate when patients with acute hypoxemic respiratory failure were treated with NIPPV as opposed to conventional therapy (7.5 vs. 22.6 intubations per 100 ICU days); mortality rates, however, were not significantly different.[99]

More recently, Ferrer et al[100] randomized patients with severe hypoxemia (defined as a P_{CO_2} of less than 60 mm Hg or an arterial oxygen saturation [SaO_2] of less than 90% on 50% FI_{O_2} for at least 6 to 8 hours) to receive NIPPV or conventional therapy. Intubation rate was decreased from 52% to 25%, the incidence of septic shock was reduced, and both ICU (39% vs. 18%) and 90-day mortality were lower in the NIPPV group than in controls. In contrast to some previous studies, substantial benefit was observed in patients with severe pneumonia, whereas patients with cardiogenic pulmonary edema had no reduction in intubation rate.

The favorable results of these latter studies might be interpreted to show broad support for the use of NIPPV in patients with hypoxemic respiratory failure. In fact, a recent survey of European pulmonologists and anesthesiologists showed that 48% (more pulmonologists than anesthesiologists) considered acute hypoxemic respiratory failure as a preferred indication for NIPPV.[101] A systematic review, however, noted that although intubations in patients with acute hypoxemic respiratory failure seem to be reduced by NIPPV, the heterogeneity between studies precluded any firm conclusions and recommended against the routine use of NIPPV in these patients.[102] Also, when overall results are favorable in a heterogeneous group of patients, it cannot be assumed that each subgroup benefits equally. It is possible that harm to a particular subgroup could be obscured by benefit in other subgroups. The following subsections examine evidence regarding the use of NIPPV in specific subgroups of patients with acute hypoxemic respiratory failure that may be more appropriate to apply to individual patients.

ACUTE CARDIOGENIC PULMONARY EDEMA

CPAP, although not a form of mechanical ventilatory assistance per se, was described as a treatment for acute pulmonary edema dating back to the 1930s.[103] Over the past 15 years, a number of studies have demonstrated that CPAP (10 to 12.5 cm H_2O) is effective in treating acute pulmonary

edema. Rasanen et al[194] randomized forty patients with cardiogenic pulmonary edema to either face-mask CPAP or standard medical therapy, and demonstrated that CPAP more rapidly improves oxygenation and respiratory rate. In a study of fifty-five patients with pulmonary edema, Lin and Chang[105] found that those randomized to face-mask CPAP (adjusted to maintain a PA_{O_2} of 80 mm Hg or greater) had a lower intubation rate (17.5% vs. 42.5%, $p < 0.05$) than conventionally treated controls. Bersten et al[106] and Lin et al[92] subsequently performed randomized studies on thirty-nine and 100 patients, respectively, demonstrating more rapid improvements in respiratory rates and oxygenation and a reduced need for intubation in patients treated with CPAP. The study of Bersten et al[106] also showed a significant reduction in the length of ICU stay among CPAP-treated patients, and the study of Lin et al[107] showed a trend for a lower hospital mortality rate. The average absolute reduction in intubation rate among these studies was 28% (from 47% in controls to 19% for CPAP). These studies provide strong evidence to support the use of CPAP to treat acute cardiogenic edema.

As discussed earlier, the combination of increased inspiratory pressure and positive expiratory pressure (i.e., pressure support plus PEEP or NIPPV) might be expected to reduce work of breathing more effectively than CPAP alone, bringing about more rapid relief of dyspnea and improvement in gas exchange. Thus, more recent studies have focused on the use of NIPPV to treat acute cardiogenic pulmonary edema. One prospective, uncontrolled study found that face-mask PSV improved pulse oximetry, pH, and Pa_{CO_2} within 30 minutes in twenty-nine patients with acute pulmonary edema, only one of whom required intubation.[108] A second prospective, uncontrolled study[109] reported similar effects on gas exchange, but five of twenty-six patients required intubation, and successfully treated patients had higher Pa_{CO_2} (54 vs. 32 mm Hg) and lower creatine phosphokinase levels (176 vs. 1282 IU) (both $p < 0.05$) than failure. Furthermore, four patients died in the first study and five in the second, three and four, respectively, with myocardial infarctions. The authors concluded that NIPPV is a "highly effective technique." The accompanying editorialist, however, cautioned about applying NIPPV to patients with acute myocardial infarctions.[110]

Several randomized, controlled trials have been performed subsequently comparing NIPPV with conventional O_2 therapy to treat patients with acute cardiogenic pulmonary edema. Masip et al[111] found that inspiratory and expiratory pressures of 15 and 5 cm H_2O, respectively, lowered the intubation rate from 33% in eighteen controls to 5% among twenty-two patients randomized to NIPPV ($p = 0.037$). NIPPV also improved oxygenation more rapidly, but hospital lengths of stay and mortality rates were similar in the two groups. Sharon et al[112] randomized forty patients to receive NIPPV plus low- or high-dose nitroglycerin. The NIPPV group had higher rates of intubation (80% vs. 20%), myocardial infarction (55% vs. 10%), and death (10% vs. none) compared with the nitroglycerin controls (all $p < 0.05$), leading the authors to conclude that NIPPV was less effective and potentially harmful compared with high-dose nitroglycerin. This inference, however, is suspect because the treatments were not comparable, and the inordinately high intubation rate in the NIPPV group (80%) is difficult to explain. In a larger study, Nava et al[113] randomized 130 patients with acute pulmonary edema to receive NIPPV (average: 14.5 cm H_2O of pressure support and 6.1 cm H_2O of PEEP) or O_2 therapy; hypercapnic and normocapnic patients were prospectively distributed equally between groups. As in the earlier studies, NIPPV improved oxygenation, respiratory rate, and dyspnea more rapidly than conventional therapy, but mortality and hospital lengths of stay did not differ between the groups. Overall, the rates of intubation were not significantly different (25% in controls vs. 20% for NIPPV); in the hypercapnic subgroup, however, the intubation rate was lower in the NIPPV group than in controls (6% vs. 29%, $p = 0.015$). These studies suggest that NIPPV is effective therapy for acute pulmonary edema, but whether this is true only for hypercapnic patients awaits further evaluation.

The question of whether NIPPV (the combination of pressure support and PEEP) is superior to CPAP alone is important because CPAP can be delivered more simply and less expensively. An earlier randomized trial comparing the two to treat acute pulmonary edema showed significantly more rapid reductions in respiratory rate, dyspnea scores, and hypercapnia in the NIPPV group compared with the CPAP-treated group.[114] The study was stopped prematurely after enrollment of twenty-seven patients, however, because of a greater myocardial infarction rate in the NIPPV group (71% vs. 31% in controls). This difference may have been attributable to unequal randomization because more patients in the NIPPV group presented with chest pain. The results nonetheless raise concerns about the safety of ventilator techniques used to treat acute pulmonary edema.

More recent randomized, controlled trials comparing NIPPV with CPAP have not detected differences in the myocardial infarction rate. Crane et al[115] randomized sixty patients with cardiogenic pulmonary edema to three different therapies: conventional, CPAP (10 cm H_2O), or bilevel ventilation (15 cm H_2O inspiratory and 5 cm H_2O expiratory pressures). Treatment success was 15% in the control group, 35% in the CPAP group, and 45% in the bilevel group ($p = 116$). Although myocardial infarction rate did not differ among the groups, hospital mortality was 30% in the control group, 0% in the CPAP group, and 25% in the bilevel group ($p = 0.029$). The difference in mortality was not statistically significant until after the first week of hospitalization, after patients had stopped using the devices.

Several additional studies have randomized patients with acute cardiogenic pulmonary edema to CPAP or noninvasive PSV plus PEEP and have found no differences in myocardial infarction rates.[116,119] Physiologic variables improved equally in both groups, intubation and mortality rates were similar, and troponin I levels and the speed of clinical resolution were nearly identical. In addition to finding no increase in the myocardial infarction rate in NIV-treated patients, these

latter studies also found no clear advantage of NIPPV over CPAP alone. These findings must be interpreted with caution, however, because patients with myocardial infarction or acute ischemia were excluded.

In the largest study reported to date, Gray et al[120] randomized 1069 patients with cardiogenic edema to receive CPAP (5 cm H_2O) alone, NIPPV (inspiratory and expiratory pressures 8 and 4 cm H_2O, respectively) or oxygen plus routine therapy in controls. No differences were noted between the CPAP and NIPPV groups, so they were combined in the analysis. Although dyspnea and pH improved more rapidly in the positive-pressure groups than in controls, no differences were apparent in intubation or mortality rates. The authors concluded that noninvasive positive-pressure treatment of cardiogenic pulmonary edema was useful to alleviate symptoms, but not to improve other outcomes. The very low intubation rate in this study (roughly 3% in all groups), however, was much lower than in most previous studies despite the use of low positive-pressures, suggesting that the patients had relatively mild respiratory compromise. Thus, the study may not be comparable to the earlier studies showing significant avoidance of intubations or even mortality.

A number of meta-analyses[121–126] have concluded that CPAP alone is effective in reducing dyspnea, improving vital signs and gas exchange, and reducing intubation and mortality rates, without any significant effect on myocardial infarction rates. Similar benefits have been attributed to NIPPV, except that improved mortality has been found in only a few,[124–126] probably because there have been fewer studies of NIPPV than on CPAP. These meta-analyses have also compared NIPPV and CPAP, finding no differences between the two modalities with respect to intubation and mortality rates as well as occurrence of myocardial infarction. These findings have held up, even when meta-analyses were performed after publication of the Gray study.[125,126]

Deciding which patients with acute cardiogenic pulmonary edema should receive NIPPV can be challenging because they may respond rapidly to conventional therapy. Using their single-center registry, Masip et al[127] obtained data on eighty conventionally treated patients with cardiogenic pulmonary edema to identify those at risk for intubation. Patients with a pH of less than 7.25 or hypercapnia and a systolic blood pressure of less than 180 mm Hg were found to be at high risk. The authors recommended that such patients should be "promptly considered" for NIV. Because studies have not shown definitively that NIV is more effective than CPAP, however, the most sensible current recommendation is to use CPAP (10 cm H_2O) initially, and consider switching to NIPPV if the patient has unrelenting dyspnea or persisting tachypnea or hypercapnia. Furthermore, either CPAP or NIPPV should be used with great caution, if at all, in patients with acute myocardial infarction or active ischemia. These recommendations are in line with those of a Cochrane analysis that deemed NIV, especially CPAP, as "safe and effective" for the treatment of cardiogenic pulmonary edema in adults.[128]

Prehospital Use of CPAP for Cardiogenic Pulmonary Edema. An important trend in the application of CPAP for acute cardiogenic pulmonary edema has been the use in the field by ambulance crews to treat patients before hospitalization. The experience with this practice has been favorable thus far. Plaisance et al[129] observed a strong trend for reduced intubation and mortality rates among 124 patients with cardiogenic pulmonary edema randomized to "early" (started immediately on site) versus "late" (delayed by 15 minutes) CPAP (7.5 cm H_2O). In another randomized, controlled trial, Thompson et al[130] observed an absolute reduction of 30% in intubation rate (seventeen of thirty-four patients [50%] vs. seven of thirty-five [20%]) and absolute mortality fell by 21% among patients with cardiogenic pulmonary edema treated with CPAP compared to usual therapy with oxygen, including intubation and bag-valve-mask-ventilation if needed.

A pilot study by Duchateau et al[131] reported an improved respiratory status in twelve "do not intubate" patients when offered NIPPV out-of-hospital by emergency medical services. Respiratory rate decreased from 34 to 27 breaths/min ($p = 0.009$) and pulse oximetry improved from 86% to 94% ($p < 0.01$) with only one intolerant patient. These studies suggest that outcomes of patients with cardiogenic pulmonary edema can be improved by very early initiation of noninvasive positive-pressure therapy in the field and adoption of this as a routine practice for emergency medical services seems likely. A recent Cochrane analysis concluded that prehospital NIV "appears to be a safe and feasible therapy" that may lower the need for intubation compared to initiation in the emergency department.[132] The authors of the Cochrane analysis cautioned, however, that the evidence is preliminary and that cost-effectiveness analyses have not been performed.

PNEUMONIA

An earlier retrospective study found that acute severe pneumonia is a predictor of NIV failure, perhaps because NIPPV does little to facilitate the clearance of secretions.[133] Confalonieri et al[134] randomized fifty-six patients with severe community-acquired pneumonia to receive NIPPV or standard O_2 therapy. The NIPPV group had fewer intubations (21% vs. 50%) and shorter ICU lengths of stay (1.8 vs. 6 days) than controls (both $p < 0.05$). In addition, NIPPV-treated patients with COPD had significantly better survival at 2 months, thought to be related to fewer late complications of intubation. The most important observation, though, was that all the benefit was attributable to the subgroup with COPD, and no clear benefit of NIPPV was seen in patients without COPD patients. More recently, a prospective study on NIPPV to treat patients with severe community-acquired pneumonia but without COPD found that oxygenation and respiratory rates improved initially in twenty-two of twenty-four patients after starting NIPPV, but 66% eventually required intubation.[135] Based on the preceding evidence, initiation of NIPPV is justifiable in appropriate patients with pneumonia and

COPD. The benefit of NIPPV in patients with pneumonia but without COPD has not been established. As such, NIPPV should be used selectively and with caution in such patients.

The severe acute respiratory syndrome epidemic was characterized by a high rate of respiratory failure among afflicted individuals, many of whom were otherwise healthy health care workers. Initially, use of NIPPV was discouraged because of concerns about aerosolization and transmission of the highly contagious coronavirus to other health care workers. Two retrospective studies, however, one from Beijing on twenty-eight patients treated with NIPPV[139] and the other from Hong Kong on twenty patients,[140] suggest that NIPPV is effective in avoiding intubation in some patients. Intubation was required in only 33% and 30% of NIPPV-treated patients in the two studies, respectively. Stringent infection-control measures, including the use of a face mask, an inline viral/bacterial filter in the bilevel ventilator tubing, and a high-efficiency particulate accumulator mask by all health care workers having contact with the patients, prevented transmission of severe acute respiratory syndrome to any caregivers. Both studies reported high rates of barotraumas, 22% and 20%, respectively; it was unclear that this was related to NIPPV. Given the lack of controls, these studies cannot be used to assess the efficacy of NIPPV in severe acute respiratory syndrome, although the lack of transmission to health care workers should allay fears about NIPPV spreading the virus so long as stringent isolation and prevention measures are employed.

More recently, the use of NIPPV to treat influenza pneumonia during the H1N1 epidemic was controversial.[138] Based on the 1 m dispersion of aerosol beyond the mask demonstrated during NIPPV applied to a human-like mannequin,[139] some advised against use of NIPPV for influenza pneumonia, although actual transmission by this route was never demonstrated, nor was it compared to dispersion occurring during invasive mechanical ventilation or even spontaneous breathing.

IMMUNOCOMPROMISED PATIENTS

The use of NIPPV to avoid endotracheal intubation in immunocompromised patients is appealing because, by assisting ventilation without having to invade the airway, it reduces infectious and hemorrhagic complications. Encouraging results derived from an uncontrolled series that reported NIPPV success rates as high as 67% (in forty-eight patients with AIDS and *Pneumocystis carinii* pneumonia).[140] Conti et al[141] avoided intubation in fifteen of sixteen patients treated with NIPPV with acute respiratory failure complicating hematologic malignancies, although patients were excluded if they had more than two organ-system failures or were responding poorly to antineoplastic therapy. More recently, Antonelli et al[142] randomized forty patients with acute respiratory failure of various etiologies following solid-organ transplantation to receive NIPPV or standard therapy. NIPPV reduced the need for intubation and lowered ICU mortality rate (both 20% vs. 50% in controls, $p < 0.05$), but total hospital mortality was similar. Trends for fewer health care–associated pneumonias and episodes of severe sepsis also were apparent among NIPPV-treated patients. In a subsequent study of fifty-two immunocompromised patients with respiratory failure, 58% with hematologic malignancies, randomized to receive NIPPV for at least 2 hours three times daily or standard O_2 therapy, those treated with NIPPV had fewer intubations (46% vs. 77%) and mortalities (50% vs. 81%, both $p < 0.05$).[143]

The sizable reductions in mortality among these high-risk patients strongly supports the use of NIV as the ventilatory modality of first choice in selected immunocompromised patients with acute respiratory failure. Patients developing respiratory insufficiency should be started on NIPPV relatively early,[133] before progression to severe respiratory failure, watched closely, and intubated without delay if needed. The need to perform invasive diagnostic procedures sometimes requires intubation in these patients although NIPPV can be used to support patients during fiber-optic bronchoscopy (see below).

ACUTE RESPIRATORY DISTRESS SYNDROME

The use of NIPPV to treat ARDS has been controversial, some considering it the "last frontier." One early cohort series reported that NIPPV maintained adequate oxygenation and averted intubation in six of twelve episodes of ARDS in ten patients.[144] In an observational cohort of seventy-nine patients with acute lung injury, Rana et al[145] found that shock, metabolic acidosis, and profound hypoxemia were predictors of NIV failure and cautioned against use in such patients. A more recent study used NIPPV as a "first-line" therapy of ARDS.[146] Of 479 patients presenting with ARDS, 147 had not been intubated upon admission to the ICU. These were begun on NIPPV and 54% avoided intubation. Not unexpectedly, outcomes were much better in those who avoided intubation than in those who failed NIPPV and required intubation: 2% versus 20% rate of ventilator-associated pneumonia and 6% versus 53% mortality rate, respectively. A simplified acute physiology score of equal to or less than 34 at baseline and a Pa_{O_2}/FI_{O_2} greater than 175 after the first hour of NIPPV predicted success. Although not controlled, the trial suggests that a small minority (15% in this trial) of patients with ARDS can be managed successfully with NIPPV, but they must be chosen carefully and monitored very closely in an ICU. If their oxygenation fails to improve substantially within the first hour, urgent intubation should be considered.

Recently, a randomized controlled trial of NIPPV in patients with acute lung injury ($200 > Pa_{O_2}/FI_{O_2} < 300$ showed reductions in the need for intubation one of twenty on NIPPV pts and seven of 19 control patients) and actual intubations (one of twenty-one versus four of nineteen) as well as occurrence of organ failure (three of twenty-one versus fourteen of nineteen) (all $p < 0.05$), with a trend toward reduced mortality.[147] These studies suggest that NIPPV may have a role in

the management of some patients with acute lung injury and ARDS, but it should be avoided in those with multiorgan system failure and very severe oxygenation defects who are likely to require prolonged ventilator support using sophisticated modes. If a trial of NIPPV is initiated, patients should be intubated without undue delay if they deteriorate or even fail to improve sufficiently.

TRAUMA

Traumatic chest wall injuries such as flail chest or mild acute lung injury might respond favorably to NIPPV, but other etiologies might not. In a retrospective survey on forty-six trauma patients with respiratory insufficiency treated with NIPPV, Beltrame et al[148] found rapid improvements in gas exchange and a 72% success rate, but burn patients responded poorly. More recently, a controlled trial that randomized thoracic trauma patients with $Pa_{O_2}/FI_{O_2} < 200$ to NIPPV or high-flow oxygen was stopped early after enrollment of fifty patients because of significant reductions in intubation rate (12% vs. 40%) and hospital length of stay (14 vs. 21 days) in the NIPPV group.[149] These results support the use of NIPPV for hypoxemic respiratory failure in postthoracic trauma cases, but it is well to remember that these were carefully selected patients.

NONINVASIVE POSITIVE-PRESSURE VENTILATION FOR CATEGORIES OF PATIENTS WITH ACUTE RESPIRATORY FAILURE

Do-Not-Intubate Patients

Some argue that there is little to lose by using NIPPV in almost any terminal patient. NIPPV could be used to lessen dyspnea, preserve patient autonomy, and permit verbal communication with loved ones during a terminal patient's final hours.[150] Some patients might be salvaged in the near term who otherwise would die without ventilatory assistance. This application is controversial, however, with some arguing that it could merely prolong the dying process, diminish patients' comfort in their waning hours, and promote excessive resource utilization.[151]

Among reports on NIPPV to treat patients who have declined or are reluctant to undergo intubation, Benhamou et al[152] retrospectively studied thirty such patients, mostly elderly men (mean age: 76 years) with COPD. Despite severe respiratory failure (mean PA_{O_2} of 43 mm Hg and Pa_{CO_2} of 75 mm Hg), NIPPV was successful initially in 60% of patients. The authors considered NIPPV to be preferable to endotracheal intubation because short-term prognosis was better, and the modality appeared to be more comfortable with fewer complications. In another uncontrolled series, Meduri et al[153] observed a similar response to NIPPV among twenty-six patients with acute hypercapnic and hypoxemic respiratory failure who refused intubation.

In a prospective survey of 113 do-not-intubate patients treated with NIV,[154] amounting to 10% of all patients treated with NIPPV, survival to hospital discharge was 72% and 52% for patients with acute pulmonary edema and COPD, respectively, whereas it was less than 25% for patients with pneumonia or cancer. In addition, the absence of an effective cough and the inability to be awakened were significantly associated with hospital mortality. Similar findings were reported by Schettino et al.[15] Thus, the use of NIV may be justifiable in do-not-intubate patients who have a high likelihood of surviving the hospitalization. Longer-term survival of these hospital survivors, however, is poor; Chu et al[156] found a 30% 1-year survival for do-not-intubate patients with COPD as compared with 65% for patients desiring intubation. Also, no studies have yet assessed effects on patient comfort or family satisfaction.

NIV can also be used for palliation in patients whose prognosis is poor for surviving an admission to hospital, with the possible aims of alleviating dyspnea or prolonging survival long enough to enable a patient time to settle affairs or say goodbye to loved ones. As recommended by a consensus statement by a task force of the Society of Critical Care Medicine on NIV,[157] it is necessary for the patient, family, and caregivers to agree on these goals and to cease NIPPV promptly if it seems to be adding to suffering (via mask discomfort, for example) rather than alleviating it.

Postoperative Patients

Several early case series on the use of NIPPV to treat respiratory insufficiency in postoperative patients with Pa_{CO_2} values of greater than 50 mm Hg, PA_{O_2} values of less than 60 mm Hg, or evidence of respiratory muscle fatigue reported prompt reductions in respiratory rate and dyspnea scores, improvement in gas exchange, and high success rates (roughly 75%) in avoiding the need for reintubation.[158,159] Subsequent studies found that NIPPV was more effective than CPAP or chest physiotherapy in improving lung mechanics and oxygenation after coronary artery bypass surgery,[160] and better than O_2 therapy alone in improving oxygenation after lung-resection surgery.[161] NIPPV also ameliorated postgastroplasty pulmonary dysfunction in morbidly obese patients.[162]

These earlier studies heightened interest in the prophylactic use of CPAP or NIPPV after high-risk surgeries such as major abdominal surgery[162–165] or thoracoabdominal aneurysm repair.[166] These studies, using CPAP (10 cm H_2O) for 24 hours postoperation, observed reductions in the incidence of hypoxemia, pneumonia, atelectasis, and intubations compared with standard treatment.

Few studies have examined the postoperative role of NIPPV in patients with frank respiratory failure, but a randomized trial of NIPPV in forty-eight post–lung-resection patients with acute respiratory insufficiency, most with COPD, showed significant improvements in oxygenation and reductions in the need for intubation (21% vs. 50%) and

mortality rate (13% vs. 38%) compared with conventionally treated controls (both $p < 0.05$).[167]

These studies strongly support the idea that both CPAP and NIPPV should be considered to prevent and treat postoperative respiratory complications and failure, especially in high-risk surgeries, but only a few studies have examined each of the various surgeries and positive-pressure techniques possible, so more specific recommendations cannot currently be made.

Facilitation of Weaning

Nava et al[168] tested the hypothesis that NIPPV could be used to shorten the duration of invasive ventilation and reduce the occurrence of associated complications in a randomized, controlled trial of fifty patients intubated for acute respiratory failure secondary to COPD. If they failed a T-piece weaning trial performed 48 hours after intubation, patients were randomized to extubation followed by facemask PSV or continued intubation and routine weaning. The NIPPV patients had higher overall weaning rates (88% vs. 68%), shorter durations of mechanical ventilation (10.2 vs. 16.6 days), briefer stays in the ICU (15.1 vs. 24 days), and improved 60-day survival rates (92% vs. 72%) (NIPPV-treated versus controls, all $p < 0.05$). In addition, no NIPPV-treated patients had nosocomial pneumonia compared with seven pneumonias among the controls. In a similar trial, Girault et al[169] randomized thirty-three patients with acute-on-chronic respiratory failure to remain intubated or to be extubated to NIPPV after failure of a 2-hour T-piece trial. The NIPPV group had a shorter duration of endotracheal intubation (4.6 vs. 7.7 days, $p = 0.004$), but the total duration of mechanical ventilation was longer in the NIPPV group, and weaning and mortality rates and ICU and hospital lengths of stay were similar between the groups.

More recently, Ferrer et al[170] randomized forty-three patients with "persistent" weaning failure (three consecutive failed T-piece trials) to be extubated to NIV or to remain intubated and be weaned using conventional methods. Patients randomized to NIV had shorter periods of intubation (9.5 vs. 20.1 days), shorter ICU (14 vs. 25 days) and hospital stays (14.6 vs. 40.8 days), a lower rate of nosocomial pneumonia (24% vs. 59%), and improved ICU and 90-day survivals (roughly 80% vs. 50%, all $p < 0.05$). This study lends strong support to the use of NIV to facilitate extubation, but it is worth noting that two-thirds of the patients had COPD or congestive heart failure.

In the most recent randomized (VENISE) trial that included 208 patients who had failed a spontaneous breathing trial, 69% of whom had COPD, the investigators included not only invasively ventilated and NIV groups, but also a group extubated early to oxygen therapy alone.[171] There were no differences in the main outcome variable: reintubation within 7 days (around one-third of patients in each group), or in most secondary outcome variables including mortality and lengths of stay in the ICU and hospital, complications and need for tracheostomy. Duration of intubation, however, was 1.5 days longer in the invasively ventilated group by design and the rate of postextubation acute respiratory failure was significantly less in the NIV group because NIV rescue was used after extubation in 57% and 45% of the oxygen therapy and invasively ventilated patients ($p > 0.05$), respectively, with an overall NIV rescue success rate of 52%. The authors concluded that, based on the reduction in postextubation acute respiratory failure, their results should "support the implementation of NIV" in difficult-to-wean patients, but recommended further study.

Thus, overall, the evidence favors the use of NIPPV to facilitate weaning and extubation in difficult-to-wean patients with COPD, mainly to reduce the occurrence of postextubation respiratory failure. In the absence of overwhelmingly favorable evidence, however, the following caveats should be borne in mind: (a) This approach should be reserved mainly for patients with COPD; (b) patients should be selected carefully, ascertaining that they are good candidates for NIPPV (see "Selection Guidelines" below); (c) patients should not have been difficult intubations; and (d) patients should be comfortable on levels of PSV that can used via mask after extubation.

Treatment of Extubation Failure

Another potential application of NIPPV in the weaning process is to avoid reintubation in patients who fail extubation. Epstein et al[172] reported that extubation failure is associated with much higher morbidity and mortality rates (43%) than successful extubations (approximately 10%). Some investigators have used NIPPV prophylactically to see if extubation failure can be avoided. Jiang at al[173] randomized consecutive extubated patients to receive NIPPV or conventional therapy and found a trend for a higher reintubation rate in the NIPPV group (28% vs. 15%), suggesting that indiscriminate use of NIPPV is not effective for preventing extubation failure. Other investigators have attempted to prevent extubation failure by initiating NIPPV when patients develop risk factors for extubation failure. Esteban et al[174] tried this approach in a multicenter, multinational randomized trial of 221 patients developing risk factors for respiratory failure within 48 hours after they were extubated, including hypercapnia, tachypnea, or hypoxemia. Reintubation rates (48%) and ICU lengths of stay (18 days) were identical in both groups, and the study was terminated prematurely because of a significantly increased ICU mortality in the NIV group (25% vs. 15%, $p = 0.048$). The mortality difference was attributable to a higher mortality in the reintubated NIV patients, reintubation occurring almost 10 hours later than in the standard-therapy group. The authors concluded that NIV is not effective in unselected patients at risk for extubation failure and speculated that the greater delay in reintubation was responsible for the higher mortality rate. It is worth noting, however, that twenty-eight patients in

the control group crossed over to NIPPV when they met failure criteria. Thus, the controls likely would have had a substantially higher reintubation rate had they not crossed over to NIPPV. Also, only 10% of patients enrolled in the study had COPD.

Another approach to treating extubation failure is to await the development of overt respiratory failure before initiating NIPPV. Hilbert et al[175] found that NIPPV used in this fashion lowered reintubation rate (20% vs. 67%) and shortened ICU lengths of stay in thirty patients with COPD and postextubation hypercapnic respiratory insufficiency compared with thirty historically matched controls. Keenan et al[176] randomized eighty-one patients to receive NIPPV or conventional therapy if they developed respiratory failure within 48 hours of extubation. The reintubation rate in this trial was roughly 70% in both the NIPPV group and controls, and no significant differences were found in hospital length of stay or survival. Patients with COPD, however, were excluded after the first year for ethical reasons, and only 12% of the patients had COPD. Furthermore, the pressures used (10 cm H_2O inspiratory and 5 cm H_2O expiratory) may have been insufficient to provide adequate ventilatory assistance.

Two subsequent randomized trials (consisting of ninety-seven and 162 patients, respectively,[177,178] approximately 30% to 40% of whom had COPD or congestive heart failure [CHF]) enrolled patients deemed to be at "high risk" for extubation failure. Both studies found that NIV reduced the need for reintubation, ICU mortality, and hospital length of stay, but hospital mortality was decreased only in the hypercapnic subgroup of the second study.[178] A more recent randomized trial of 106 patients with postextubation hypercapnia (Pa_{CO_2} > 45 mm Hg) showed a significant reduction in postextubation respiratory failure as well as 90-day mortality in the group randomized to NIPPV compared to oxygen-treated controls.[179] The main effect of NIPPV in this study was to prevent greater retention of CO_2. The reason for the reduced 90-day mortality when mortality was not significantly reduced at earlier time points was not apparent.

These more recent studies support the use of NIV for patients who are at "high risk" for extubation failure, particularly if they have COPD, CHF, and/or hypercapnia. A Cochrane systematic review concluded that for patients who mainly have COPD, the evidence "demonstrated a consistent, positive effect on mortality and ventilator-associated pneumonia."[180] Based on the Esteban study,[174] however, NIPPV to prevent extubation failure should be used very cautiously in at-risk patients who do not have COPD or other favorable characteristics because of the higher risk of NIPPV failure and its attendant morbidity and mortality. Such patients failing to improve promptly with NIPPV should be reintubated without delay.

Pediatric Applications

Use of NIPPV in the pediatric population has been increasingly reported in the medical literature,[181] but most studies are retrospective and very few randomized controlled trials have been performed. For more detailed assessments of this literature, the reader is referred elsewhere.[181,182] Pediatric applications of NIPPV parallel those in the adult, but the etiologies of respiratory failure, of course, reflect those encountered in children. In earlier reports, Fortenberry et al[183] found that respiratory rate, Pa_{CO_2}, and oxygenation improved promptly after initiation of nasal bilevel NIPPV in a retrospective series of twenty-eight children with acute hypoxemic respiratory failure, only three of whom required intubation. Padman et al[184] subsequently reported similar results in a prospective series of thirty-four pediatric patients with both hypoxemic and hypoventilatory respiratory insufficiency, again with only three patients requiring intubation. More recent applications have been reported in children with status asthmaticus[185] and atelectasis[186] and randomized, controlled trials have been performed in children with bronchiolitis[187] and tracheomalacia.[188] These studies consistently show more rapid improvements in vital signs and gas exchange with NIPPV compared to controls.

These favorable responses to NIPPV in children are not surprising, particularly when they are suffering from conditions reported to be treated successfully by NIPPV in adults. Concerns have been raised, however, about treating very young children and infants with NIPPV because of increased nasal resistance[189] and inability to cooperate.[182] In the series of Fortenberry et al[183] of twenty-eight patients, NIPPV was successful in avoiding intubation in the ten children who were younger than 5 years of age. More recently, a retrospective trial observed successful application of NIPPV in infants following liver transplantation.[190] In a randomized, prospective trial on infants (median age: 9.5 months) with various causes of upper airway obstruction, CPAP and BiPAP proved to be equally efficacious in reducing respiratory rate and breathing effort; both were well tolerated, although BiPAP was associated with more asynchrony.[188] The lack of controlled trials makes it difficult to formulate specific guidelines for NIPPV in children, although reported success rates appear to be comparable to those in adults, and tentative guidelines have been proposed[182] that are based on those used for adults.

NONINVASIVE VENTILATION FOR PATIENTS UNDERGOING PROCEDURES

Bronchoscopy and Endoscopy

NIPPV administered via T connector attached to a face mask can be used to assist ventilation and enhance oxygenation during fiber-optic bronchoscopy in high-risk patients. First reported to improve oxygenation and be well tolerated in a small series of immunocompromised hypoxemic patients,

NIPPV was shown subsequently to improve and sustain oxygenation better than conventional O_2 supplementation in a randomized, prospective trial in twenty-six patients with Pa_{O_2}/FI_{O_2} ratios of 200 or less and suspected nosocomial pneumonia.[191] More recently, NIPPV to assist ventilation during fiber-optic bronchoscopy was administered successfully using a "helmet" device (see techniques section below).[192] NIPPV also has been used to assist ventilation during upper endoscopy for gastric tube placement in patients with neuromuscular disease[193] and during performance of transesophageal echocardiography.[194]

Preoxygenation before Intubation

NIPPV can be used to improve O_2 saturation during and after intubation and decrease the incidence of O_2 desaturations below 80% during intubation according to a randomized trial in critically ill patients with hypoxemic respiratory failure.[195] This approach is promising but needs further evaluation before routine use can be recommended. This also begs the question whether, if NIV improves oxygenation substantially, intubation could be avoided in some of these patients.

SELECTION OF PATIENTS FOR NONINVASIVE POSITIVE-PRESSURE VENTILATION IN THE ACUTE CARE SETTING

Determinants of Success

Retrospective[133,196] and prospective[197–199] studies have identified predictors of NIPPV success (Table 18-2). Patients with baseline hypercapnia fare better than those with hypoxemia alone, but successful patients have lower baseline Pa_{CO_2} values (79 vs. 98 mm Hg) and higher pH values (7.28 vs. 7.22) than failure patients.[105] Pneumonia predisposes to failure whether alone or in combination with COPD (odds ratio [OR] 5.63 for COPD).[197,199] The strongest predictor of success, though, is prompt improvement in gas exchange and heart and respiratory rates within 1 to 2 hours of NIPPV initiation.[133,196–199] Confalonieri et al[198] have incorporated some of these predictors (Acute Physiology and Chronic Health Evaluation [APACHE] II score ≥ 29, pH < 7.25, Glasgow Coma Score ≤ 11, and respiratory rate ≥ 35 breaths/min) into two risk charts for NIPPV failure, one to be used at baseline and the other at 2 hours (Fig. 18-2). If these abnormalities were all present at baseline, the likelihood of failure was 82% and rose to 99% if they persisted at 2 hours.

Timing of initiation is another determinant of success. Ambrosino et al[133] advised that NIPPV "should be instituted early in every patient before a severe acidosis ensues." Initiation of NIPPV should be viewed as taking advantage of a "window of opportunity." The window opens when acute respiratory distress occurs and shuts when the patient deteriorates to the point of necessitating immediate intubation. In this context, it should be emphasized that NIPPV is used as a way of preventing intubation, not replacing it.

TABLE 18-2: PREDICTORS OF SUCCESS DURING ACUTE APPLICATIONS OF NONINVASIVE POSITIVE-PRESSURE VENTILATION

Younger age
Lower activity of illness (APACHE score)
Able to cooperate, better neurologic score
Able to coordinate breathing with ventilator
Less air leaking, intact dentition
Tachypnea, but not excessively rapid (> 24 but < 35 breaths/min)
Hypercarbia, but not too severe (Pa_{CO_2} > 45 but < 92 mm Hg)
Acidemia, but not too severe (pH < 7.35 but > 7.10)
Improvements in gas exchange, heart and respiratory rates within first 2 hours*

*Most powerful predictor.

Source: Adapted, with permission, from Ambrosino et al,[133] Soo Hoo et al,[196] and Antonelli et al.[199]

Selection Guidelines

The preceding predictors of success and failure and the entry criteria used for enrollment of patients into the many studies have served as a basis for consensus guidelines on the selection of patients to receive NIPPV for acute respiratory failure.[200] These guidelines use a simple three-step approach outlined in Table 18-3. The first step asks whether the patient needs ventilator assistance. Patients with mild or no respiratory distress are excluded from consideration because they should do well without ventilator assistance. Those needing ventilator assistance are identified using clinical indicators of acute respiratory distress and gas-exchange derangement, as listed in Table 18-3. These criteria are most applicable to patients with COPD but can be used to screen those with other forms of expiratory failure, although some modifications are advisable. For example, studies on NIPPV in acute pulmonary edema and acute hypoxemic respiratory failure have used higher respiratory rates as enrollment criteria (> 30 to 35 instead of > 24 breaths/min) and a P_{CO_2}/FI_O ratio of less than 200.[111–114]

The second step is to screen out patients in whom use of NIPPV is contraindicated (see Table 18-3). Most are relative contraindications, and judgment should be exercised in implementing them. Also, some conditions that have been listed as contraindications in the past no longer preclude the use of NIPPV. For example, patients with coma, if related to hypercapnia, may be managed successfully with NIPPV. Diaz

Admission

		pH admission < 7.25		pH admission 7.25–7.29		pH admission > 7.30	
	RR	Apache ≥ 29	Apache < 29	Apache ≥ 29	Apache < 29	Apache ≥ 29	Apache < 29
GCS 15	<30	29	11	18	6	17	6
	30–34	42	18	29	11	27	10
	≥35	52	24	37	15	35	14
GCS 12–14	<30	48	22	33	13	32	12
	30–34	63	34	48	22	46	21
	≥35	71	42	57	29	55	27
GCS ≤11	<30	64	35	49	23	47	21
	30–34	76	49	64	35	62	33
	≥35	82	59	72	44	70	42

1 Hour

		pH after 2 h < 7.25		pH after 2 h 7.25–7.29		pH after 2 h ≥ 7.30	
	RR	Apache ≥ 29	Apache < 29	Apache ≥ 29	Apache < 29	Apache ≥ 29	Apache < 29
GCS 15	<30	72	35	27	7	11	3
	30–34	88	59	49	17	25	7
	≥35	93	73	64	27	38	11
GCS 12–14	<30	84	51	41	13	19	5
	30–34	93	74	65	28	39	12
	≥35	96	84	78	42	54	20
GCS ≤11	<30	93	74	65	28	39	12
	30–34	97	88	83	51	63	26
	≥35	99	93	90	66	76	40

FIGURE 18-2 Charts showing percentage likelihood of noninvasive positive-pressure ventilation (*NIPPV*) failure in patients with chronic obstructive pulmonary disease (*COPD*) based on pH and Acute Physiology and Chronic Health Evaluation (*APACHE*) score and Glasgow coma score (*GCS*). Chart on top refers to values at the time of admission, and bottom chart is at 2 hours. Numbers in boxes are percentages for likelihood of failure. At 2 hours, the combination of an APACHE score of less than 11, APACHE score of 29 or greater, and a Glasgow coma score of less than 11 predicts failure with a likelihood of 99%. Based on 1033 patients with COPD treated with NIPPV in thirteen different experienced units. (Used, with permission, from Antonelli, et al. Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: a multi-center study. *Intensive Care Med.* 2001;27:1718–1728. With kind permission from Springer Science and Business Media.)

et al[201] demonstrated that patients (mainly with COPD) with hypercapnic coma (Glasgow coma scores ≤ 8) had outcomes just as good as those with higher Glasgow coma scores. In another report,[152] nearly half the patients were obtunded or somnolent initially, yet most were managed successfully with NIPPV.

The underlying etiology and potential reversibility of acute respiratory failure are also important considerations in patient selection. As discussed previously, the strongest evidence supports the use of NIPPV for COPD and either NIPPV or CPAP for acute cardiogenic pulmonary edema. As illustrated in Figure 18-3, a reversible etiology permits the use of NIPPV as a "crutch" that assists the patient through a critical interval, allowing time for other therapies such as bronchodilators, steroids, or diuretics to reverse the underlying condition. More severe, less easily reversed forms of respiratory failure that will require prolonged periods of ventilatory support, such as status asthmaticus requiring controlled hypoventilation, complicated pneumonias, or ARDS, are best managed using invasive ventilation. Marginal patients might be considered for a trial of NIPPV but should be watched closely for further deterioration so that needed intubation is not delayed unduly.

NONINVASIVE POSITIVE-PRESSURE VENTILATION FOR CHRONIC RESPIRATORY FAILURE

Evidence for Efficacy

RESTRICTIVE THORACIC DISEASES

Restrictive thoracic disorders limit expansion of the thoracic cage either because of increased elastance (as with chest wall deformity), muscle weakness (as with neuromuscular diseases), or both. Experience gained during the polio epidemics of the 1930s through 1950s and subsequently with other neuromuscular disorders demonstrated that "body ventilators," even when used intermittently, were effective at stabilizing or even reversing chronic respiratory failure secondary to restrictive thoracic disorders.[202,203] Although NIPPV had been available for the therapy of restrictive thoracic diseases for decades,[204] its use beyond a few centers with special expertise was quite limited until the late 1980s. Mouthpieces or full-face masks designed mainly for administration of anesthesia were the only interfaces available, posing challenges for patient adaptation. Despite this, one center reported remarkable success with mouthpiece ventilation in

TABLE 18-3: SELECTION GUIDELINES: NONINVASIVE VENTILATION FOR PATIENTS WITH ACUTE RESPIRATORY FAILURE

Step 1. Identify patients with reversible causes for acute respiratory failure (ARF) in need of ventilator assistance
- a. Reversible cause for ARF such as COPD or acute cardiogenic pulmonary edema
- b. Symptoms and signs of acute respiratory distress:
  - i. Moderate to severe dyspnea, increased over usual
  - ii. Rate > 24 for COPD, rate > 30 for hypoxemic ARF
  - iii. Accessory muscle use, paradoxical breathing
- c. Gas-exchange abnormalities:
  - i. Pa_{CO_2} > 45 mm Hg, pH < 7.35
  - ii. Pa_{O_2}/FI_{O_2} < 200

Step 2. Exclude those at increased risk with noninvasive ventilation:
- a. Respiratory arrest
- b. Medically unstable (hypotensive shock, uncontrolled cardiac ischemia or arrhythmias)
- c. Unable to protect airway (impaired cough or swallowing mechanism)
- d. Excessive secretions
- e. Agitated or uncooperative
- f. Facial trauma or burns or anatomic abnormalities interfering with mask fit

Source: Reprinted with permission of the American Thoracic Society. Copyright © 2012 American Thoracic Society. From Mehta S, Hill NS. Noninvasive ventilation: state of the art. *Am J Respir Crit Care Med.* 2001;163:540–577. Official Journal of the American Thoracic Society.

a cohort of 257 patients with neuromuscular disease and chronic respiratory failure that was treated for an average of 9.6 years.[205] Bulbar function was intact, including speech and swallowing, but the patients were otherwise severely compromised. Of these patients, 144 required 20 to 24 hours of ventilator support daily and had vital capacities of only 10.5% of predicted. Nonetheless, sixty-seven were switched successfully from tracheostomies to NIPPV, and only thirty-eight died during the follow-up interval of up to 37 years. Although the study was uncontrolled, the authors concluded that mouthpiece NIPPV prolonged survival and enhanced convenience and communication in these severely compromised patients.

Despite this favorable experience, however, wider use of NIPPV awaited further developments during the early 1980s. One was the development of nasal CPAP for therapy of obstructive sleep apnea that encouraged the creation of more comfortable commercially available nasal masks.[206] Another was the suggestion by French investigators that nasal ventilation could be used in patients with muscular dystrophy to halt progression of the disease.[23] In 1987, several small series and case reports appeared describing successful management with nocturnal nasal ventilation of patients with chronic respiratory failure secondary to a variety of restrictive thoracic disorders.[207–208] Subsequently, additional small series have confirmed the earlier findings, but no prospective, randomized series have been performed, mainly for ethical reasons. Despite this, NIPPV has gained wide acceptance as the modality of first choice to treat patients with chronic respiratory failure.[200] Because most series have combined patients with different etiologies, the following will discuss evidence for benefits attributed to NIPPV for restrictive thoracic diseases in general, making reference to individual diagnoses as appropriate. Table 18-4 lists individual diagnoses of neuromuscular diseases reported to benefit from NIPPV.

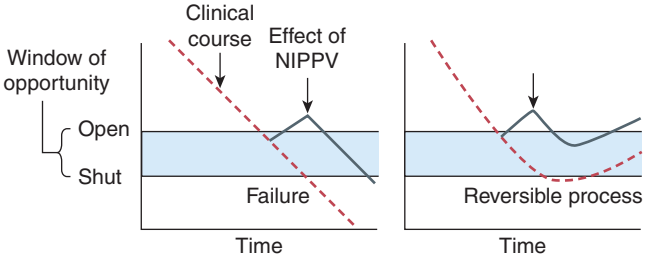

FIGURE 18-3 Schema to illustrate importance of reversibility in success of noninvasive positive-pressure ventilation (*NIPPV*) for acute respiratory failure. *Left:* Relentless downhill clinical course of underlying process (severe acute respiratory distress syndrome). NIPPV initiated when window of opportunity opens still fails because it is not sufficient to support the patient when the underlying process has progressed too far. *Right:* NIPPV succeeds when medical therapy reverses the underlying process (chronic obstructive pulmonary disease exacerbation).

EFFECTS ON SYMPTOMS AND DAYTIME GAS EXCHANGE

Numerous studies on the efficacy of NIPPV in a wide variety of neuromuscular and chest wall disorders have shown that intermittent NIPPV consistently improves symptoms

TABLE 18-4: RESTRICTIVE THORACIC DISEASES TREATED WITH NONINVASIVE VENTILATION

Recommended for the following diagnoses:
- Chest wall deformity
  - Kyphoscoliosis
  - Postthoracoplasty for tuberculosis
- Slowly progressive neuromuscular disorders
  - Postpolio syndrome
  - High spinal cord injury
  - Spinal muscular atrophy
  - Slowly progressive muscular dystrophies
    - Duchenne muscular dystrophy
    - Limb-girdle muscular dystrophy
    - Myotonic dystrophy
  - Multiple sclerosis
  - Bilateral diaphragmatic paralysis
- More rapidly progressive neuromuscular disorders*
  - Amyotrophic lateral sclerosis

Not recommended for†:
- Rapidly progressive neuromuscular disorders
  - Guillain-Barré syndrome
  - Myasthenia gravis

*Tracheostomy ventilation should be considered in far-advanced cases.

†Unless upper airway protective mechanisms intact.

of fatigue, daytime hypersomnolence, and morning headache.[210–213] Daytime gas exchange also improves, Pa_{CO_2} dropping on average from 63 mm Hg to 48 mm Hg and PA_{O_2} increasing from 54 to 71 mm Hg among multiple studies.[1] The improvement in gas exchange is gradual, usually occurring over a period of weeks, as patients increase their hours of use, mainly at night. In addition, nasal NIPPV has been shown to ameliorate chronic hypoventilation in patients with severe kyphoscoliosis who fail to improve with nasal CPAP alone.[214]

EFFECTS ON NOCTURNAL GAS EXCHANGE AND SLEEP

Neuromuscular and chest wall disorders cause protean sleep-related breathing disturbances depending on the specific syndrome and the involvement of respiratory muscles.[215] Abnormalities include obstructive and central sleep apneas, intermittent desaturations, particularly during rapid eye movement sleep in patients with diaphragmatic weakness, and sustained hypoventilation as global weakness and/or chest wall restriction advances. These abnormalities often lead to sleep disruption, characterized by diminished sleep duration, fragmentation related to arousals, and poor sleep quality secondary to diminished slow-wave and rapid eye movement sleep.

NIPPV ameliorates nocturnal hypoventilation and has been shown to eliminate the intermittent obstructive apneas and severe O_2 desaturations that occur during negative-pressure ventilation, particularly during rapid eye movement sleep.[215] Although no randomized, prospective trials have been performed to investigate effects of NIPPV on sleep, investigators have evaluated efficacy using temporary withdrawal of nocturnal nasal NIPPV from long-term users with restrictive thoracic diseases whose gas exchange had been improved by prior NIPPV use.[216,217] Temporary withdrawal of NIPPV caused a deterioration of nocturnal oxygenation and ventilation[215] (Fig. 18-4) and increased frequency of arousals.[216] All changes were reversed promptly on resumption of NIPPV. These findings indicate that NIPPV is important in preventing deterioration of nocturnal gas exchange that is thought to predispose to chronic hypoventilation and contribute to frequent arousals and fragmented sleep. Stabilization of nocturnal gas exchange and improved sleep quality are thought to be major reasons for the improvement in symptoms associated with NIPPV use. Although sleep quality is improved compared to no ventilator assistance, air leaking during NIPPV, however, can contribute to sleep fragmentation.[218] Atkeson et al[219] found that asynchrony with the ventilator was very prevalent in patients with amyotrophic lateral sclerosis (ALS) using NIPPV nocturnally. Twenty-three patients had an average asynchrony index of 69/hour constituting 17% of sleep time.

EFFECTS ON QUALITY OF LIFE

NIPPV improves health-related quality of life in patients with restrictive thoracic disorders.[220,221] The nature and duration of improvement, however, depend on the natural history of the underlying disorder. Among patients with

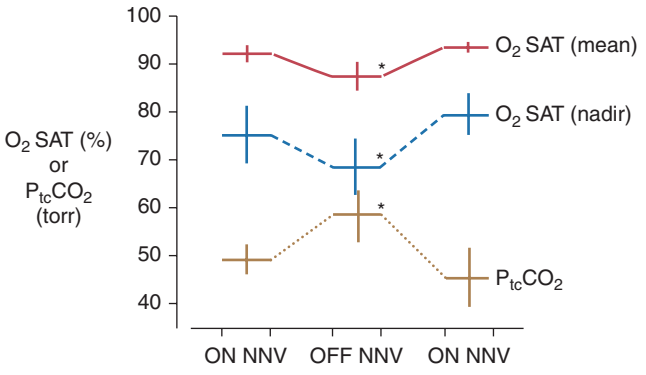

FIGURE 18-4 Effect of withdrawal of nocturnal nasal ventilation (*NNV*) on mean and nadir O_2 saturations and mean transcutaneous P_{CO_2} levels obtained during nocturnal monitoring. Values on the left labeled "on NNV" were obtained during NNV use on the night before NNV withdrawal, values in the middle were obtained on the last night of the NNV withdrawal period, and values on the right labeled "on NNV" were obtained a week after NNV was resumed. Data are mean ± standard error (SE). Asterisk indicates $p < .05$ compared with "on NNV" values ($n = 6$). (Used, with permission, from Hill NS, Eveloff SE, Carlisle CC, Goff SG. Efficacy of nocturnal nasal ventilation in patients with restrictive thoracic disease. *Am Rev Respir Dis.* 1992;145:365–371.)

ALS, the mental component summary score[222] and the vitality score[223] on the SF (short form)-36 questionnaire register sustained improvements. These improvements are seen even when the functional rating declines (Fig. 18-5), but attrition rates are high over time related to the high mortality of the underlying condition.[224] Bourke et al performed a randomized, controlled trial in forty-one patients with ALS, demonstrating improved quality of life in patients with normal or only mild to moderately impaired bulbar dysfunction, which was sustained for up to 2 years.[225] Even more sustained would be expected, of course, in conditions with lower rates of progression. Likewise, musculoskeletal functional gains would not be expected unless the underlying condition offers the potential for improvement (i.e., no quadriplegia).

Some studies have compared quality of life during use of NIPPV with that during use of tracheostomy positive-pressure ventilation among patients with restrictive thoracic diseases.[226–228] Both groups have high levels of satisfaction, but NIPPV was rated as preferable to ventilation via a tracheostomy with regard to comfort, convenience, portability, and overall acceptability.[226] Although tracheostomy ventilation received higher scores for quality of sleep and providing a sense of security, the vast majority of patients preferred NIPPV. Another survey of thirty-five ventilator users, with twenty-nine NIPPV users and six with tracheostomy ventilation, found satisfactory levels of psychosocial functioning and mental well-being, as determined by standard questionnaires.[227] The ratings compared favorably with those of a general population, and NIPPV and tracheostomy ventilation received similar scores. In another survey of home mechanical ventilation users, patients with scoliosis receiving tracheostomy ventilation had higher health-index ratings than those receiving NIPPV.[228] Thus, NIPPV offers many advantages over invasive mechanical ventilation, including

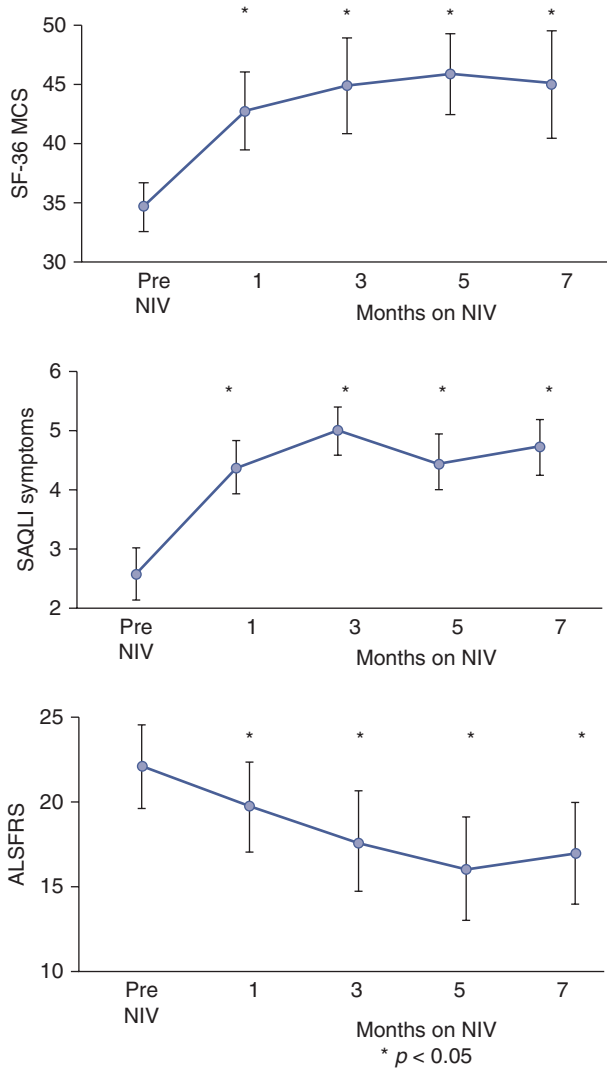

FIGURE 18-5 Serial data for the Short Form-36 Mental Component Summary (*SF-36 MCS*), Sleep Apnea Quality of Life Index (*SAQLI*) symptoms domain, and ALS Functional Rating Scale (*ALSFRS*) immediately before starting noninvasive ventilation (*NIV*) and after 1, 3, 5, and 7 months of NIV. The slight improvement in the ALSFRS score at 7 months is secondary to a survivor effect. (Used, with permission, from Lyall, et al. A prospective study of quality of life in ALS patients treated with noninvasive ventilation. *Neurology.* 2001;57:153–156.)

comfort, portability, cost, and convenience, but some ratings, including overall health and sense of security, may favor invasive mechanical ventilation.

EFFECT ON HOSPITAL UTILIZATION

In their long-term follow-up study of patients with kyphoscoliosis, sequelae of tuberculosis, and Duchenne muscular dystrophy, Leger et al[229] observed significant reductions in hospital days per patient per year from 34, 31, and 18 days for the year before starting NIPPV to 6, 10, and 7 days for the year after, respectively. These findings suggest that NIPPV may cut health care resource utilization in these patients, with the potential for substantial cost savings. More recently, Janssens et al[230] observed a similar reduction in hospital days per patient per year (median of 17 days for the year before and 6 days for the year after NIPPV) for patients with restrictive thoracic disorders in a long-term retrospective study from Switzerland. Although these uncontrolled studies do not preclude the possibility that changes in hospitalization practices over time could have been responsible for the reductions, it appears highly likely that NIPPV reduces the need for hospitalization among these patients.

EFFECT ON SURVIVAL

Long-term cohort series provide strong evidence that NIPPV prolongs survival in comparison with unventilated patients. The ability to prolong survival is obvious in patients using NIPPV continuously who would die if ventilator assistance stops for more than a few minutes.[205] Studies from France[229] and England[231] report on several hundred patients with chronic respiratory failure of various etiologies treated with intermittent nasal NIPPV for periods of up to 5 years (Fig. 18-6). Rather than survival rates, these studies used the rate for continuation of NIPPV, thought to correspond closely with survival for most diagnoses. The studies found very favorable continuation rates for postpolio and kyphoscoliosis patients (approximately 100% and 80%, respectively, after 5 years). Patients with sequelae of old tuberculosis had higher continuation rates in the British study compared with the French study (94% vs. 60%, respectively), perhaps reflecting the greater morbidity of the French patients at the time of enrollment. Also, patients with Duchenne muscular dystrophy in the French study had lower continuation rates (47%) than did those with other neuromuscular diseases, with 28% undergoing tracheostomy and the remaining 25% dying. A more recent follow-up on the English cohort observed much better survival rates for patients with Duchenne muscular dystrophy treated with NIPPV than those previously reported by the French group: 85% for 1 year and 73% for 5 years.[232] This disparity may reflect differences in the severity of illness between patients when begun on NIPPV, how cough was assisted, or practices on switching to tracheostomy. Overall, the continuation rates from these long-term follow-up studies are similar to those observed for patients treated with invasive ventilation reported earlier by the French group.[233]

Survival would be anticipated to be shorter in patients with ALS than in those with more slowly progressive neuromuscular diseases. In a prospective, nonrandomized trial on twenty consecutive patients, Pinto et al[234] treated the first ten with medical therapy alone and the next ten with NIPPV. After 2 years, 50% of the NIPPV patients were alive, whereas all the medical therapy patients had died. Aboussouan et al[235] compared the survival of thirty-one patients with ALS who continued NIPPV with that of twenty-one patients who were intolerant of NIPPV. The intolerant patients had a significantly greater risk of dying over the 3-year study period than were those who remained on NIPPV (relative risk: 3.1). As might be anticipated, patients with bulbar involvement were

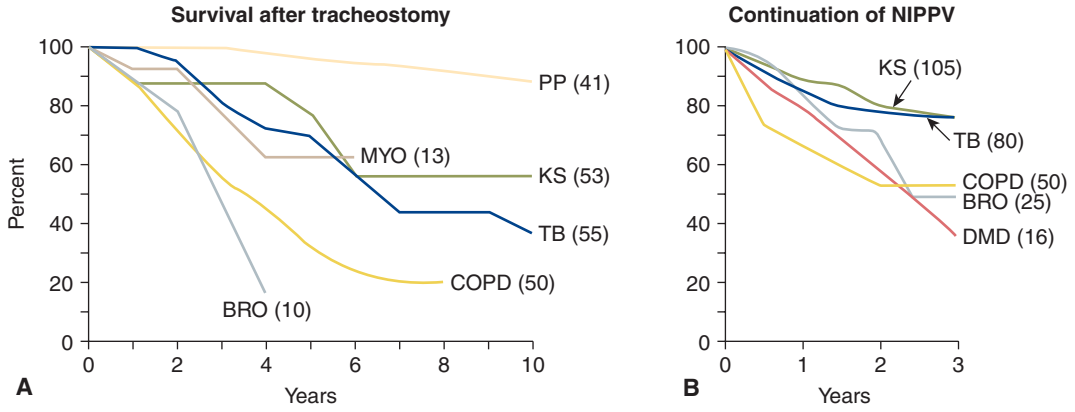

FIGURE 18-6 **A.** Survival after tracheostomy in 222 patients with chronic respiratory failure of various etiologies followed for as long as 10 years. (Redrawn, with permission, from Robert et al.[233]) **B.** Likelihood of continuing noninvasive positive-pressure ventilation (*NIPPV*) in 276 patients with chronic respiratory failure followed for as long as 3 years. (Redrawn, with permission, from Leger et al.[229]) *BRO*, bronchiectasis; *COPD*, chronic obstructive pulmonary disease; *DMD*, Duchenne muscular dystrophy; *KS*, kyphoscoliosis; *MYO*, myopathy; *PP*, postpolio syndrome; *TB*, history of tuberculosis.

unlikely to be tolerant of NIPPV (only six of twenty); if they could tolerate the therapy, however, it imparted an apparent survival advantage. Bach[236] has reported that NIPPV prolongs survival and postpones the need for tracheostomy in ALS. In the randomized, controlled trial on ALS by Bourke et al, patients without severe bulbar involvement had an average 205-day prolongation of survival.[225] Those with severe bulbar involvement tolerated NIPPV much less well than did those without, and had no survival benefit, but they did have some improvement of sleep-related symptoms if they were tolerant.

Based on the above observations, NIPPV is now used in approximately 15% of patients with ALS compared with only 2% using invasive mechanical ventilation, according to one recent cross-sectional U.S. survey.[237] On the other hand, Bach[236] also found that after 5 years of follow-up, only eight of twenty-five (32%) patients with ALS using NIPPV were alive compared with twenty-seven of fifty (54%) patients receiving tracheostomy ventilation. This suggests that NIPPV is less effective at prolonging survival than tracheostomy ventilation in ALS, as might be anticipated among patients with a neuromuscular disease that impairs bulbar function.

Selection of Patients with Restrictive Thoracic Disease to Receive Noninvasive Positive-Pressure Ventilation

Table 18-5 lists guidelines for the selection of patients with restrictive thoracic disorders to receive NIV based on American College of Chest Physicians consensus,[238] Canadian Thoracic Society clinical practice guideline,[239] and Medicare guidelines in the United States. Patients should have symptomatic nocturnal hypoventilation manifested by poor sleep quality, such as morning headache, daytime hypersomnolence, and low energy in combination with demonstrable daytime or sustained nocturnal hypoventilation. The duration of nocturnal O_2 desaturation used as an indicator of nocturnal

TABLE 18-5: SELECTION GUIDELINES: LONG-TERM NONINVASIVE VENTILATION FOR RESTRICTIVE THORACIC DISORDERS OR OBESITY HYPOVENTILATION

Indications

1. Symptoms: fatigue, morning headache, hypersomnolence, nightmares, enuresis, dyspnea, and so on
2. Signs: cor pulmonale
3. Gas-exchange criteria:
   - Daytime Pa_{CO_2} ≥ 45 mm Hg
   - Nocturnal oxygen desaturation (Sa_{O_2} ≤ 88% for more than 5 minutes sustained or >10% of total monitoring time)
4. Sleep evaluation:
   - Unnecessary in restrictive thoracic disorders if other criteria met
   - Should be obtained for obesity hypoventilation to assess obstructive sleep apnea*
5. Other possible indications
   - Recovering from acute respiratory failure with persistent CO_2 retention
   - Repeated hospitalizations for acute respiratory failure

Contraindications

- Inability to protect airway
  - Impaired cough
  - Impaired swallowing with chronic aspiration
- Copious secretions
- Need for continuous or nearly continuous ventilatory assistance
- Anatomic abnormalities that interfere with mask fitting
- Poorly motivated patient or family
- Inability to cooperate or comprehend therapy
- Inadequate financial or caregiver resources

*If obstructive sleep apnea is present, trial of continuous positive airway pressure may be warranted (see Table 18-6).

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hypoventilation (< 88% for more than 5 consecutive minutes) was suggested by consensus,[238] but has never been validated. Even if symptoms are minimal or lacking, patients with severe CO_2 retention (> 50 mm Hg) and those recovering from bouts of acute respiratory failure are considered for long-term NIV, particularly if there is persistent CO_2 retention or a history of repeated hospitalizations. The consensus group of the American College of Chest Physicians as well as the Canadian Thoracic Society also recommended NIPPV for patients with severe pulmonary dysfunction (FVC < 50% of predicted or maximal inspiratory pressure < 60 cm H_2O), even in the absence of CO_2 retention, despite the lack of evidence from clinical studies to support the initiation of NIV on the basis of pulmonary function alone. Simonds also suggests that other possible indications for NIV in patients with chronic respiratory insufficiency include infectious complications, pregnancy, and the perioperative state.[240]

Relative contraindications to the use of NIPPV for chronic respiratory failure (see Table 18-5) include inability to protect the upper airway because of impaired cough or swallowing or excessive secretions. Aggressive treatment with techniques or devices to assist cough[241] may permit the use of NIPPV in such patients who otherwise would not be candidates, but if the condition is too severe, tracheostomy is indicated if the patient desires maximal prolongation of life. Tracheostomy ventilation has been recommended when the need for ventilator assistance exceeds 16 hours daily,[242] although many patients still prefer NIPPV.[226] Table 18-5 lists other relative contraindications to NIPPV. The clinician must render a judgment as to whether these are sufficient to preclude a trial of NIV.

The natural history of the restrictive thoracic disorder also should be considered when deciding about NIPPV. Patients with chest wall deformities and stable or slowly progressive neuromuscular disorders respond well to NIPPV and remain stable for long periods of time.[229,231] Patients with more rapidly progressive neuromuscular disorders such as ALS may respond well temporarily, but as debility progresses and bulbar function deteriorates, NIPPV loses its efficacy. Those who wish to optimize their chances for survival may prefer invasive ventilation, and others may desire hospice care. Patients with rapidly progressive neuromuscular conditions such as Guillain-Barré syndrome or myasthenia gravis in crisis usually are poor candidates for NIV because swallowing frequently is impaired when ventilatory dysfunction becomes severe.

When to Start Long-Term Noninvasive Positive-Pressure Ventilation for Restrictive Thoracic Disorders

NIPPV to treat chronic respiratory failure secondary to restrictive thoracic diseases has gained wide acceptance, but the optimal time for initiation has been debated. Prophylactic initiation in progressive neuromuscular diseases, before the onset of symptoms or daytime hypoventilation, has been proposed to retard the progression of respiratory dysfunction. Raphael et al[243] tested this hypothesis in seventy-six patients with Duchenne muscular dystrophy who had not yet developed symptoms or daytime hypoventilation, randomizing them to receive nasal NIPPV or standard therapy. Not only did NIPPV fail to slow disease progression, it also was associated with greater mortality, leading to premature termination of the trial. The authors surmised that mortality was increased because NIPPV gave patients a false sense of security that caused them to delay seeking medical attention when they developed respiratory infections. The study had numerous shortcomings, including failure to document patient adherence or to consistently use techniques to assist cough, but it has stemmed any enthusiasm about using prophylactic NIPPV in patients with Duchenne muscular dystrophy. Ward et al[244] randomized twenty-six patients with neuromuscular disease and nocturnal hypoventilation to start NIPPV right away or to await the onset of daytime hypercapnia before starting. Patients starting promptly had better gas exchange and quality of life, and a trend toward fewer hypercapnic crises compared to those starting later. The authors concluded that NIPPV is best started with the onset of symptomatic nocturnal hypoventilation and before the onset of diurnal hypercapnia.

Early initiation of NIPPV also has been proposed to treat patients with ALS.[245] Current guidelines based on expert consensus recommend starting NIPPV if FVC drops below 50% of predicted[246] or maximal inspiratory pressure drops below 60 cm H_2O. In a preliminary study,[247] twenty patients with ALS and FVC values ranging between 70% and 100% of predicted were randomized to receive NIPPV if they had an SaO_2 of less than 90% for more than 1 minute during nocturnal oximetry ("early intervention") or to await a drop in FVC to less than 50% of predicted ("standard of care"). The early intervention group had a significant increase in the vitality subscale on the SF-36, suggesting that earlier intervention might offer some benefit in patients with ALS, but more research is necessary.

Presently, awaiting the onset of symptoms of nocturnal hypoventilation before initiation of NIPPV is the most pragmatic approach because adherence to therapy is often poor unless patients are motivated by the desire for symptom relief. Symptomatic patients who have only nocturnal but no daytime hypoventilation, as demonstrated by frequent, sustained nocturnal O_2 desaturations, are good candidates for initiation. Masa et al[247] showed improvements in dyspnea scores, morning headache, and confusion after 2 weeks of nocturnal NIPPV in twenty-one such patients, whose proportion of sleep time with an SaO_2 of less than 90% averaged 40% to 50% on room air before initiation of NIPPV and fell to 6% afterward. The timing of initiation requires a judgment based on the anticipated progression of the disease (sooner for more rapid progression), the patient's symptoms, pulmonary function, and daytime and nocturnal gas exchange. The aim is to begin when there are symptoms with significant pulmonary function and/or gas-exchange abnormalities,

which is when the patient still has time to adapt but well before the occurrence of a respiratory crisis.

Central Hypoventilation/ Obstructive Sleep Apnea

The first case reports describing the use of nasal ventilation for chronic respiratory failure were in young children with central hypoventilation, who had resolution of gas-exchange abnormalities and symptoms after initiation of therapy.[248,249] No controlled studies have examined this application, but enough anecdotal evidence has accrued that consensus groups consider therapy of central hypoventilation as an appropriate indication for NIPPV.[200,238]

Nasal CPAP is considered the therapy of first choice for obstructive sleep apnea. NIPPV, however, may be successful in improving daytime gas exchange and symptoms in hypoventilating patients with obstructive sleep apnea who have persistent CO_2 retention after use of nasal CPAP alone. Among thirteen patients with severe obstructive sleep apnea whose hypercapnia (average Pa_{CO_2} of 62 mm Hg) was unresponsive to CPAP, NIPPV using volume-limited ventilators lowered the Pa_{CO_2} to 46 mm Hg, and nine of the patients eventually stabilized on CPAP alone.[250]

Independently adjusted inspiratory and expiratory pressure or "bilevel" positive-pressure ventilation was first developed as a way of controlling obstructive sleep apnea while using lower expiratory pressures than with CPAP alone, thus potentially enhancing comfort and adherence with therapy.[251] Reeves-Hoche et al[252] were unable to demonstrate improved adherence rates in patients with obstructive sleep apnea treated with bilevel ventilation compared with CPAP alone. Even so, bilevel devices are still used commonly to treat patients intolerant of CPAP alone, but a stronger rationale supports the use of bilevel NIPPV for obstructive apnea if patients have persisting hypoventilation despite adequate CPAP therapy.

Obesity-Hypoventilation Syndrome

Respiratory impairment is common among obese patients, including those with restricted lung volumes secondary to increased chest wall and lung elastance, abnormal blood gases, and breathing disturbances during sleep. When obese patients hypoventilate, the term *obesity-hypoventilation syndrome* is applied, a condition that is multifactorial in etiology. The altered chest wall mechanics are accompanied by reductions in respiratory drive (either acquired or congenital), as well as obstructive sleep apnea (in 80% to 90% of patients), giving rise to the hypoventilation.[253] This is a morbid condition associated with cor pulmonale and a high mortality rate over time, but it responds favorably to NIV.

Morbidly obese subjects have significantly increased work of breathing at baseline, and NIPPV (inspiratory pressure of 9 to 12 cm H_2O, expiratory pressure of 4 cm H_2O) lowers that work.[254] NIPPV also raises tidal volumes and lowers end-tidal P_{CO_2} more in patients with obesity hypoventilation than in obese patients without sleep-disordered breathing or in nonhypoventilating subjects with obstructive sleep apnea.[254] NIPPV lowers and improves symptoms as effectively in patients with obesity hypoventilation as in those with severe kyphoscoliosis,[255] associated with an increase in respiratory drive.[255] CPAP alone, however, may be as effective as NIPPV in some patients.[253] Some investigators also have started with NIPPV and converted to CPAP once hypoventilation has been controlled.[250] In a recent randomized controlled trial of thirty-seven patients with obesity hypoventilation and mild hypercapnia, 1 month of NIV (inspiratory and expiratory pressures 18 and 11 cm H_2O, respectively; backup rate: 13 breaths/min), eighteen NIV patients had improved sleep architecture and gas exchange, but indices of inflammation, endothelial function, and arterial stiffness did not improve compared to a control group given lifestyle advice.[256] These studies support the use of NIPPV for obesity hypoventilation to improve symptoms, sleep quality, and gas exchange.

As obesity has become an increasingly prevalent problem, obesity-hypoventilation syndrome has become an increasingly common indication for using long-term NIPPV. The Swiss survey found that during the 1990s it became the most common diagnosis among patients using long-term NIPPV at home in the Geneva region (Fig. 18-7).[230] Adherence was excellent with the therapy, exceeding 70%, average Pa_{CO_2} normalized, and hospital days fell significantly following NIPPV initiation. A subsequent large cohort of obesity-hypoventilation patients from France was followed long term and manifested favorable sustained responses to NIPPV, with a 3-year continuation rate of 80%, sustained improvements in gas exchange, and a 5-year survival of 77.3%.[257]

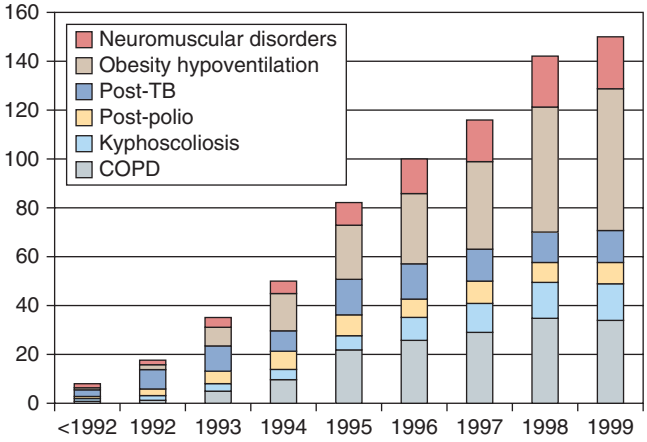

FIGURE 18-7 Yearly count of the cumulative population of patients treated by noninvasive positive-pressure ventilation during the study period (1992 to 2000) according to diagnostic category. (Reproduced with permission from the American College of Chest Physicians from Janseens, et al. Changing patterns in long-term noninvasive ventilation: a 7-year prospective study in the Geneva Lake area. *Chest.* 2003;123:67–79.)

Selection of Patients with Central Sleep Apnea/Obesity-Hypoventilation Syndrome for Noninvasive Positive-Pressure Ventilation

Firm indications and selection guidelines for central hypoventilation/central sleep apnea/obesity-hypoventilation syndrome have not been established although the Canadian Thoracic Society consensus is that NIPPV is the treatment of choice unless CO_2 retention is no more than mild, in which case CPAP alone might suffice.[239] Patients who are symptomatic with frank hypoventilation or who have prolonged central apneas clearly are good candidates for NIPPV. The more severe the hypoventilation, the more important it would be to start with a mode that augments minute volume, and using a backup rate would be important for those with prolonged central apneas. Medicare guidelines in the United States (Table 18-6) require a polysomnogram to document the central apneas, prolonged O_2 desaturations (≤88% for more than 5 minutes) as evidence of nocturnal hypoventilation and, if the patient has obstructive sleep apnea, evidence of CPAP failure with improvement on NIPPV, as determined by oximetry or a repeat polysomnogram.

OBSTRUCTIVE LUNG DISEASES

Chronic Obstructive Pulmonary Disease

During the 1960s, McClement et al[258] speculated that improved ventilation–perfusion relationships, reduced O_2 consumption, and mobilization of secretions would benefit patients with COPD who were treated with negative-pressure ventilators. During the early 1980s, Braun and Marino[259] tested the theory that respiratory muscles are chronically fatigued and will benefit from intermittent rest. They treated sixteen patients with severe COPD using wrap negative-pressure ventilators for 5 hours daily over 5 months and observed improvements in vital capacity, maximal inspiratory and expiratory pressure, and daytime Pa_{CO_2} during spontaneous breathing. Although these results were interpreted as supporting the "muscle rest" hypothesis, controls were lacking, and other aspects of rehabilitation or passage of time alone could have been responsible for the improvements.

Subsequently, several controlled studies showed improvement in respiratory muscle strength after short-term (days to a week) use of negative-pressure ventilation.[260–262] These studies documented respiratory muscle rest by showing significant reductions in the diaphragmatic electromyographic signal. Subsequent controlled trials, however, of longer duration (up to several months) showed no benefit.[263–265] Notably, baseline Pa_{CO_2} among the latter unfavorable trials was approximately 47 mm Hg, substantially lower than that in the favorable studies (57 mm Hg). This raises the possibility that respiratory muscles in patients with severe CO_2 retention are more likely to benefit from intermittent negative-pressure ventilation than patients with little or no CO_2 retention, perhaps because of relief of the unfavorable effect of hypercapnia on respiratory muscle function.[266]

Negative-pressure ventilation was tolerated poorly in the preceding trials, so subsequent trials tested NIPPV to see if better tolerance might achieve more consistent benefits. In addition, patients with severe COPD are known to have more frequent nocturnal desaturations related to hypoventilation than normal subjects. These desaturations are associated with arousals that shorten the duration and diminish the quality of sleep, an effect that can be ameliorated by O_2 supplementation, at least in "blue and bloated" patients.[267] Furthermore, patients with COPD have a 32% drop in inspiratory flow rate during rapid eye movement sleep that is associated with a reduced tidal volume.[268] By assisting ventilation, NIPPV offers the potential of restoring inspiratory flow, eliminating episodes of hypoventilation, and improving nocturnal gas exchange, as well as the duration and quality of sleep.

Studies using NIPPV in patients with severe obstructive lung diseases have yielded conflicting results. Initial small uncontrolled cohort series on the use of nasal NIPPV in patients with severe stable COPD lent support to the idea that NIPPV would improve sleep efficiency and daytime and nocturnal gas exchange.[269,270] A 3-month crossover trial by Strumpf et al,[36] however, found improvement only in neuropsychological function but not in nocturnal or daytime gas exchange, sleep quality, pulmonary functions, exercise tolerance, or symptoms. This study also encountered a high dropout rate, with seven patients withdrawing because of mask intolerance and only seven of nineteen entered patients actually completing the trial. In contrast, in a study of nearly identical design, Meecham-Jones et al[271] enrolled eighteen patients with severe COPD, fourteen of whom completed the study. Nocturnal and daytime gas exchange, total sleep time, and symptoms improved during NIPPV use. These salutary effects of NIPPV on sleep duration and efficiency in patients with severe stable COPD also were observed in a 2-night crossover trial in six patients with an initial Pa_{CO_2} of 58 mm Hg.[272] Some of the disparity between these studies may be explained by the observation that patients in the study of Strumpf et al had more severe airway obstruction (FEV_1 of 0.54 vs. 0.81 L) despite having less CO_2 retention

TABLE 18-6: GUIDELINES FOR NONINVASIVE POSITIVE-PRESSURE VENTILATION IN OBSTRUCTIVE SLEEP APNEA/CENTRAL SLEEP APNEA*

1. Polysomnogram demonstrating OSA, CSA, or mixed apneas
2. If OSA, patient failed to improve or tolerate CPAP alone
3. Sustained oxygen desaturation nocturnally (≤88% for >5 min)
4. Significant improvement in nocturnal gas exchange during NIPPV use, as documented by oximetry or polysomnography

Abbreviations: CSA, central sleep apnea; *NIPPV*, noninvasive positive-pressure ventilation; *OSA*, obstructive sleep apnea.

*Based on Center for Medicare and Medicaid Services Guidelines.

(Pa_{CO_2} of 47 vs. 57 mm Hg) than did patients in the study of Meecham-Jones et al. This suggests that different subsets of patients with COPD were entered into the studies and that those with greater CO_2 retention ("blue bloaters") may be more likely to benefit from NIPPV.

Two other randomized, controlled trials failed to substantiate the hypothesis that greater CO_2 retention predicts NIPPV success in patients with severe COPD, despite attempts to enroll hypercapnic subjects. Gay et al[273] screened thirty-two hypercapnic patients, but only thirteen remained after exclusion for obstructive sleep apnea or other terminal illness. Only four of the seven patients randomized to NIPPV completed the trial and, not surprisingly, no significant differences emerged. Lin et al[274] performed an 8-week crossover trial consisting of consecutive, randomized 2-week periods of no therapy, O_2 alone, NIPPV alone, and NIPPV combined with O_2. Among twelve patients with a mean initial Pa_{CO_2} of 50.5 mm Hg, NIPPV not only conferred no added benefit over O_2 alone with regard to oxygenation, ventricular function, or sleep quality, but it also reduced sleep efficiency and total sleep time. The authors, however, used inspiratory pressures of only 12 cm H_2O, which may have provided insufficient ventilator assistance, and 2 weeks may have been too brief to permit adequate adaptation to NIPPV.

Several longer-term controlled trials have been performed subsequently. Casanova et al[275] performed a randomized year-long trial in forty-four patients with severe COPD, finding no improvements in gas exchange, survival, or hospitalization rate, although one test of neuropsychological function improved. This study, however, also used relatively low inspiratory pressures and did not assess sleep quality or health status. In an Italian multicenter trial, Clini et al[276] screened 120 patients with severe COPD and chronic CO_2 retention (Pa_{CO_2} of 50 mm Hg or more). Ninety patients were enrolled. After dropouts and deaths, forty-seven were left, divided between the NIPPV plus O_2 and O_2 alone groups. Patients treated with NIPPV had less of an increase in Pa_{CO_2} over the 2-year period than controls (55 to 56 vs. 55 to 60 mm Hg, respectively, $p < 0.05$), less deterioration in the Maugeri Respiratory Failure (MRF-28) functional score (although the St. George's Respiratory Questionnaire was no different), and a trend toward fewer hospital days per patient per year (20 days before and 14 days after initiation of NIPPV). No differences were detected in the 6-minute walk distance, dyspnea score, sleep symptoms, or mortality rate. An Australian trial of 144 patients with severe COPD and baseline Pa_{CO_2} is in the low 50 to 53 mm Hg randomized patients to NIPPV or long-term oxygen therapy.[277] The NIPPV group had improved adjusted (OR: 0.63; confidence interval [CI]: 0.40 to 0.99) but not unadjusted survival, and a worse score on the St. George's health status scale for general and mental health. There were no differences in gas exchange after the first 6 months. Only forty-one of the seventy-two patients randomized to NIPPV used it for more than 4 hours nightly and were included in the survival analysis, and average inspiratory and expiratory pressures were 12.9 and 5.1 cm H_2O, respectively.

These studies have lacked statistical power and results have been inconsistent, with some showing benefit only for physiologic variables such as respiratory muscle strength and Pa_{CO_2} or total sleep time. Some have shown improved mortality, functional status and quality of life, but most have not. Furthermore, continuation rates have been relatively low compared to neuromuscular or chest wall disorders (see Fig. 18-7). This suggests that patients with COPD are less tolerant of or benefit less from NIPPV than neuromuscular or obesity hypoventilation patients. Criner at al[278] initiated NIPPV in twenty patients with neuromuscular disease and twenty with COPD during a several-week stay in a specialized ventilator unit. Despite these optimal conditions, only 50% of patients with COPD as compared with 80% of those with neuromuscular disease were still using NIPPV after 6 months.

One concern has been that ventilator pressures have been too low in many of the studies to adequately enhance gas exchange. Windisch et al[279] have pioneered the use of "high-intensity" NIPPV to allay these concerns in patients with COPD. In a cohort of seventy-three patients, average inspiratory pressure of 28 mm Hg was used, and patients had a relatively low hospitalization rate (22%) during the subsequent year and higher-than-expected survival at 3 and 5 years (82% and 58%, respectively). In a follow-up study, Dreher et al[280] performed a 6-week crossover trial comparing high-intensity versus low-intensity NIPPV (average inspiratory pressure: 28.6 and 14.6 cm H_2O, respectively). At the end of the trial, the high-intensity group used NIPPV 3.6 hours more per day than did the low-intensity group, and there were significant improvements in exercise-related dyspnea, daytime Pa_{CO_2}, FEV_1, vital capacity, and the Severe Respiratory Insufficiency Questionnaire Summary score.

Overall, the results of these long-term trials testing the efficacy of NIPPV in severe stable COPD have been disappointing, and this application remains controversial.[281] A meta-analysis of the earlier controlled trials concluded that the studies were too small to discern a "clear clinical direction."[282] It should be acknowledged that three subsequent randomized trials[276,277,280] yielded favorable findings, although all have methodologic limitations. Despite controversy about the strength of the evidence for benefit, NIV is used widely in chronic stable COPD in some countries.[283] The high-intensity approach advocated by Windisch et al also shows promise, but requires further validation at other centers.

Noninvasive Positive-Pressure Ventilation to Enhance Rehabilitation in Chronic Obstructive Pulmonary Disease

NIPPV may serve as an adjunct to exercise training in rehabilitation for patients with severe stable COPD. Two different approaches have been used: one employs NIPPV to unload the inspiratory muscles during exercise and to permit a greater exercise intensity to magnify the training effect; the other rests muscles between sessions (mainly at

night) to enhance daytime function during the sessions. Investigations show that CPAP and PSV singly and in combination increase exercise capacity in patients with severe COPD.[284,235] Bianchi et al[286] showed that compared with CPAP or PSV, proportional-assist ventilation brought about the greatest improvement in cycling endurance and reduction in dyspnea in fifteen stable hypercapnic patients with COPD. This enhanced exercise capacity during ventilator use, however, has not yet been shown to translate into a greater training effect or functional improvement during spontaneous breathing.[287] Garrod et al[288] tested the second approach among forty-five patients with severe COPD (FEV_1 < 50% of predicted), showing that nocturnal NIPPV between rehabilitation sessions increased the shuttle-walk distance and improved quality of life compared with standard therapy. Duiverman et al[289] tested a similar approach, randomizing seventy-two patients with severe COPD to nocturnal NIPPV plus rehabilitation and rehabilitation alone. The combination group had greater improvements in some domains of quality of life as well as daytime Pa_{CO_2}, daily step count, and minute ventilation. These studies indicate that NIPPV, used either during or between exercise sessions, has the potential to enhance benefits accruing from pulmonary rehabilitation, but more confirmatory studies are needed.

Cystic Fibrosis and Diffuse Bronchiectasis

Small case series[290,291] have reported stabilization and sometimes even improvement of gas-exchange abnormalities for periods ranging up to 15 months in severely hypercapnic (Pa_{CO_2} > 54 mm Hg) patients with end-stage cystic fibrosis awaiting lung transplantation. Gozal et al[292] observed markedly improved gas exchange in all sleep stages in six patients with cystic fibrosis treated with NIPPV plus O_2 therapy in comparison with patients treated with O_2 therapy alone, although sleep duration and architecture were similar in the two conditions. Cystic fibrosis is now a common reason among children for the use of NIPPV at home, constituting 17% of such children in a French survey.[293]

The mechanism by which NIPPV assists cystic fibrosis patients is not entirely clear. NIPPV reduces the work of breathing significantly,[294] but a study in thirteen hypercapnic patients with cystic fibrosis (average Pa_{CO_2} of 51 mm Hg) found no improvements in sleep quality, daytime arterial blood gases, pulmonary function tests, respiratory muscle strength, or exercise tolerance after 2 months of NIPPV, even though eight of the patients felt improved symptomatically.[295] Madden et al[296] found improved hypoxemia but again no improvement in hypercapnia among 113 patients treated long term with NIPPV; these authors still considered NIPPV useful as a bridge to lung transplantation. NIPPV also can be useful for administration of aerosol to cystic fibrosis patients. Fauroux et al[297] found that it was superior to a standard nebulizer in a small group of cystic fibrosis patients. Thus, NIPPV appears to have a role in supporting deteriorating patients with cystic fibrosis and serving as a bridge to transplantation, even though improvements in gas exchange and sleep parameters are not seen consistently.

In diffuse bronchiectasis patients, Benhamou et al[298] found that the use of NIPPV was associated with improved Karnovsky function scores and a reduction in days of hospitalization from 46 days for the year before to 21 days for the year after starting NIPPV. Compared with a historical control group, however, rates of deterioration in oxygenation were similar, and no survival benefit was apparent. In fact, in the long-term English follow-up study,[231] patients with end-stage bronchiectasis had poorer survivals than other patient subgroups, most dying within 2 years. Dupont et al[299] retrospectively reviewed the outcomes of forty-eight patients with diffuse bronchiectasis following their first ICU admission over a 10-year period; 27% were treated with NIPPV and 54% required intubation. One-year mortality was 40%. Age older than 65 years, a higher simplified acute physiology score II score (>32), and the need for intubation were identified as predictors of mortality. These studies suggest a role for NIPPV in treating patients with cystic fibrosis and diffuse bronchiectasis who have developed severe CO_2 retention, as well as in serving as a bridge to transplantation, but the capacity to prolong life may be limited.

A recent Cochrane analysis[300] concluded that NIPPV may be helpful in facilitating secretion clearance in patients with cystic fibrosis and when combined with O_2 supplementation, may improve nocturnal gas exchange, but cited the lack of controlled trials as a limitation in making recommendations. Lacking such controlled trials, definitive recommendations on how to select patients with cystic fibrosis or diffuse bronchiectasis for NIPPV or when to start are unavailable; most clinicians use guidelines similar to those used for severe COPD (see below), paying particular attention to the inclusion of techniques to aid in secretion clearance.

Selection of Patients with Chronic Respiratory Failure and Obstructive Lung Diseases to Receive Noninvasive Ventilation

An earlier consensus statement noted the discordant results of the available trials and concluded that more study is needed before NIPPV can be recommended in severe stable COPD.[200] A subsequent consensus conference agreed that the data are scanty and conflicting but opined that the available evidence suggests that certain subgroups of patients with COPD may benefit.[238] Most trials that have observed benefit from either negative-pressure or positive-pressure NIV in severe stable COPD have enrolled patients with more CO_2 retention at baseline than trials with negative results. Thus, the consensus opinion was that a trial of NIPPV in severe stable COPD patients is justified if CO_2 retention is severe (i.e., Pa_{CO_2} > 55 mm Hg).

Considering that one of the four controlled trials reporting beneficial effects of NIPPV in severe stable COPD patients[271] enrolled patients with frequent hypopneas

(ten per hour) and O_2 desaturations during sleep, another indication suggested by the consensus group was sustained, severe nocturnal O_2 desaturation (< 88% for more than 5 consecutive minutes). O_2 therapy alone, however, has been shown to improve sleep quality, reduce drowsiness, and improve neuropsychological function in such patients.[267,268] Therefore, the recommendation was made that sleep monitoring be performed during O_2 supplementation and that NIPPV not be initiated unless symptoms fail to respond to a trial of long-term O_2 therapy. If patients have a daytime Pa_{CO_2} between 50 and 54 mm Hg, the consensus group opined that NIPPV should be used if such patients have evidence of nocturnal hypoventilation, as indicated by nocturnal oximetry, or if there is a history of repeated hospitalizations. Patients whose CO_2 retention worsens substantially during O_2 therapy should also be considered for NIPPV, because such patients responded favorably to NIPPV in an uncontrolled trial.[301]

In the absence of more controlled trials with favorable findings, however, these guidelines are tentative. Also, even for patients who meet the criteria, patient tolerance of NIPPV may be poor.[278] To maximize patient compliance, only motivated symptomatic patients, such as those with fatigue or daytime hypersomnolence, who can cooperate and comprehend the purpose of the therapy should be selected. As outlined in Table 18-7, NIV should not be initiated unless other therapies have been optimized, including O_2 supplementation and CPAP (if indicated). These guidelines have led to reduced use of NIPPV for severe stable COPD in the United States since the late 1990s, when certain home respiratory companies were encouraging widespread use. Use is currently more prevalent in certain European countries, such as Switzerland, where a survey found that COPD was the second most common reason for use of NIPPV in the home.[230] A pan-European survey on home mechanical ventilation showed enormous variability between countries in the proportion of patients receiving ventilation for neuromuscular versus lung diseases and between those receiving noninvasive versus tracheostomy ventilation.[283]

TABLE 18-7: RECOMMENDED GUIDELINES FOR SELECTION OF PATIENTS WITH OBSTRUCTIVE LUNG DISEASES TO RECEIVE LONG-TERM NONINVASIVE POSITIVE-PRESSURE VENTILATION*

1. Symptoms: fatigue, hypersomnolence, dyspnea, and so on
2. Failure to respond to optimal medical therapy:
   Maximal bronchodilator therapy and/or steroids
   O_2 supplementation if indicated
3. Gas-exchange abnormalities:
   $Pa_{CO_2} \geq 52$ mm Hg
   $Sa_{O_2} < 88\%$ for more than 5 consecutive minutes nocturnally despite O_2 supplementation
4. Obstructive sleep apnea excluded on clinical grounds or failure to respond to CPAP therapy if moderate to severe obstructive sleep apnea detected on sleep study
5. Reassess after 2 months' therapy; continue if adequate compliance (>4 hours a day) and favorable therapeutic response

*Based on Center for Medicaid and Medicare Services reimbursement guidelines.

CONGESTIVE HEART FAILURE

As discussed earlier, evidence supports the use of NIV (either CPAP alone or NIPPV) in the therapy of acute heart failure, and it also may have a role in chronic CHF. Increases in intrathoracic pressure have long been known to have salutary hemodynamic effects in some patients with congestive heart failure. Naughton et al[21] found that CPAP (10 cm H_2O) reduced both ventilatory work (by minimizing negative intrathoracic pressure swings) and cardiac load (by reducing transmural pressure) in fifteen patients with congestive heart failure. A subsequent study found that longer-term nocturnal CPAP (9 cm H_2O) improved inspiratory muscle strength (maximal inspiratory pressure increased from 79.3 to 90.7 cm H_2O) in a group of eight patients with CHF.[302] One month of nocturnal CPAP also increased left-ventricular ejection fraction (33.8% vs. 25%) and lowered systolic systemic pressure (116 vs. 126 mm Hg) in patients with CHF and obstructive sleep apnea compared with healthy subjects.[303]

Whether NIPPV is better than CPAP alone in these patients has been controversial. Willson et al[304] found dramatic improvements in sleep parameters (apnea-hypopnea index: 49–6; arousal index: 42–17) in patients with CHF and Cheyne-Stokes respiration after treatment with a portable bilevel device. Conversely, Kohnlein et al[305] performed a crossover trial consisting of randomized 2-week periods of NIPPV and CPAP in thirty-five patients with Cheyne-Stokes respiration. Both modalities improved apnea-hypopnea and arousal indexes dramatically, but there was no difference between the two. Teschler et al[306] randomized fourteen patients with CHF and Cheyne-Stokes respiration to control, O_2 alone, CPAP alone, bilevel NIPPV, and adaptive pressure-support servo ventilation on five separate randomly ordered nights. They observed equal reductions in apnea-hypopnea and arousal indexes with O_2 alone and CPAP alone, a greater reduction with bilevel ventilation, and the greatest improvement with adaptive pressure-support servo ventilation. This study supports the idea that customized modes designed to respond to the apneas of Cheyne-Stokes respiration (such as adaptive pressure-support servo ventilation) may be especially effective. But no adequately powered trials addressing important clinical outcomes have yet been performed.

The Canadian CPAP (CanPAP) trial randomized 258 patients with CHF and central sleep apnea to receive CPAP or no CPAP. CPAP attenuated central sleep apnea, improved nocturnal oxygenation, increased the left ventricular ejection fraction, lowered norepinephrine levels, and increased the distance walked in six minutes by 21 meters. It did not,

however, improve quality of life or survival and the authors concluded that their data "do not support the use of CPAP to extend life" in patients with CHF and central sleep apnea.[307] In post hoc analysis, however, these authors subsequently reported that in a subgroup of patients whose apnea-hypopnea index was lowered to below 15/hour by CPAP, transplantation-free survival was significantly improved.[308] Thus, the role of NIPPV in patients with CHF is currently unclear. Most clinicians currently use CPAP alone for patients with CHF and obstructive sleep apnea and optimal medical therapy, including O_2 supplementation, for those with Cheyne-Stokes breathing. Some favor adaptive pressure-support servo ventilation as the preferred noninvasive mode for patients with CHF and "complex" sleep apnea characterized by periodic central apneas (Cheyne-Stokes breathing),[309] but further studies are needed before firm recommendations can be made.

PEDIATRIC USES OF NONINVASIVE POSITIVE-PRESSURE VENTILATION FOR CHRONIC RESPIRATORY FAILURE

Since the first case reports on the successful use of nasal NIPPV in children with central hypoventilation,[199,200] relatively few reports of NIPPV have appeared in the pediatric literature. Nonetheless, some of the experience in adults can be applied to children because such conditions as Duchenne muscular dystrophy or cystic fibrosis may impair respiratory function in older children, and these have been included in a number of the published reports.[248,249] In their experience with fifteen children having neuromuscular disease or cystic fibrosis treated with nasal NIPPV and followed for periods ranging from 1 to 21 months, Padman et al[184] found that average Pa_{CO_2} and hospital utilization fell; only one child required an artificial airway. Fauroux et al[310] undertook a French survey on the use of NIPPV by children at home. Of 102 children followed at fifteen centers, 7% were younger than 3 years of age, 35% were 4 to 11 years of age, and 58% were 12 years of age, and 34% had neuromuscular disease, 30% had obstructive sleep apnea or craniofacial abnormalities, 17% had cystic fibrosis, 9% had central hypoventilation, and 8% had scoliosis. In a subsequent report, Fauroux et al[311] described flattening of the face in 48% of patients. Nevertheless, pediatric patients appear to respond as well to NIPPV as most adults with chronic respiratory failure. In a long-term follow-up study of thirty pediatric patients (average age: 12.3 years) with mainly non-Duchenne neuromuscular syndromes, Mellies et al[312] observed clinical stability exceeding an average of 2 years in duration. Nocturnal and diurnal gas exchange, quality of sleep, and symptoms were improved, and these deteriorated promptly on temporary withdrawal of NIPPV. The authors concluded that NIPPV is effective and should be used in children with symptomatic sleep-disordered breathing associated with neuromuscular syndromes.

PRACTICAL APPLICATION OF NONINVASIVE POSITIVE-PRESSURE VENTILATION

Despite the accumulating evidence on NIPPV indications that helps in selecting appropriate patients, the delivery of NIPPV remains very much an art. After the decision is made to treat a patient with NIPPV, the clinician must decide on a mask (or interface), ventilator, settings, and adjuncts. NIPPV must be delivered in a safe and adequately monitored location. Implementation of each step requires knowledge and experience. More than with invasive ventilation, the interaction between patient and clinician is central to success. The following will provide an overview of the steps in this process.

Initiation

Although little scientific evidence is available to guide the decisions surrounding initiation, they should be made carefully because success or failure depends on them. Focusing on the major goals of NIV may help (Table 18-8). NIV shares with invasive ventilation the goals of improving gas exchange, either nocturnal, daytime, or both, and minimizing complications. Even more than with invasive ventilation, though, NIV seeks to alleviate symptoms and optimize comfort. Because of the open-circuit design of noninvasive positive-pressure ventilators, success depends largely on patient cooperation and acceptance. Patient tolerance is an important goal because the other goals are not achievable unless the patient accepts the therapy. The goals of acute and long-term applications are overlapping, but alleviation of increased work of breathing is an important goal in acute applications, whereas improvement in sleep duration and quality is more important during long-term applications.

TABLE 18-8: GOALS OF NONINVASIVE VENTILATION

Acute applications
Relieve dyspnea
Optimize patient comfort
Reduce work of breathing
Improve or stabilize gas exchange
Minimize complications
Avoid intubation
Avoid delay of needed intubation
Long-term applications
Ameliorate symptoms
Improve or stabilize gas exchange
Improve sleep duration and quality
Maximize quality of life
Enhance functional status
Prolong survival

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The following gives recommendations for initiation, citing evidence when available, pointing out controversy where it exists, and offering opinion where necessary. Most sections offer comments on both acute and long-term applications.

Location

ACUTE

NIV can be initiated wherever the patient presents with acute respiratory distress—in the emergency department,[60,313] ICU,[17,61] intermediate-care or respiratory-care unit, or hospital ward.[62,314] A survey of acute care hospitals in Massachusetts and Rhode Island found that a third of NIPPV initiations were in the emergency department, and half were in the ICU.[315] Following initiation, transfer to a location that offers continuous monitoring is recommended until the patient stabilizes. The patient's acuity of illness and risk of deterioration if an accidental disconnection occurs should dictate the intensity of monitoring. One study used 15 minutes of stability following discontinuation of NIPPV as a criterion for admission to a regular ward,[316] but a longer period of time (30 minutes for example) may be safer. During transfers, ventilator assistance and monitoring should be continued because rapid deteriorations can occur.

NIPPV is used on regular wards in many hospitals because of the scarcity of ICU beds, but some guidelines have recommended that NIPPV be applied only in the ICU because of concerns about patient safety.[317] Others have suggested that if pH < 7.30 in patients with COPD, ICU transfer is advisable. Farha et al[318] reported on their experience with seventy-six patients treated on a regular ward with NIPPV. Of the sixty-two patients without a do-not-intubate status, 31% required intubation and were transferred to the ICU. The authors considered this comparable to the experience with patients treated in more closely monitored settings, concluding that NIPPV can be administered safely on regular floors. But unless the ward has considerable experience administering NIPPV, only stable patients should be treated there.

CHRONIC

Stable patients with chronic respiratory failure may start NIPPV during an inpatient admission, in a sleep laboratory during the daytime or an overnight stay, in a physician's outpatient office (with therapists from the home respiratory vendor present), or at home. In a randomized controlled trial of twenty-eight patients, mainly with neuromuscular disease, patients initiated at home experienced just as good outcomes after 2 months as those begun as inpatients, including gas exchange and ventilator adherence, except that an average 3.8-day hospitalization was avoided.[319] Thus, routine hospitalization is unnecessary unless warranted by the patient's medical condition. Initial use of a sleep laboratory offers the advantage of precise titration of initial pressure or volume settings during sleep monitoring but adds to costs and may delay implementation because of scheduling problems. Also, no titration protocol has been validated, and selecting pressures to eliminate apneas and hypopneas, as is done with sleep apnea, may not be adequate to reverse hypoventilation in patients with chronic respiratory failure. Until outcome studies demonstrate the superiority of one location over another, the choice of location will be based on practitioner preference. Perhaps more important than the specific location is the availability of skilled, attentive practitioners to help during the initiation and adaptation processes.

Masks (Interfaces)

A daunting array of interfaces has become available to deliver NIPPV, and detailed descriptions can be found elsewhere.[320] In brief, the most commonly used interfaces in both acute and long-term settings are nasal and oronasal (or full-face) masks. Nasal masks usually are triangular clear plastic domes that have soft silicone sealing surfaces. Oronasal (or full-face) masks are similar in appearance but are larger and fit over the nose and mouth. Nasal interfaces offer many modifications, however, including nasal pillows with soft rubber cones that insert directly into the nares, so-called minimasks that fit over the tip of the nose, and gel-filled seals designed to enhance comfort. Various oronasal masks are available, including those with foam-filled or air-filled seals and a chin support. A larger version of the full-face mask is available that seals around the perimeter of the face, potentially enhancing comfort and eliminating the development of nasal bridge ulcers.[321] Oral interfaces also are used occasionally, mainly in the long-term setting in patients with neuromuscular disease.[205]

More recently, a number of studies have evaluated the "helmet," a novel interface for NIV that consists of a clear plastic cylinder that fits over the head and seals on the shoulders. The Food and Drug Administration has not yet approved this application in the United States. It avoids contact with the nose and mouth, eliminating nasal ulceration and potentially enhancing comfort.[322] CPAP delivered via the helmet to patients with acute respiratory failure is better tolerated than the full-face mask in historically matched controls.[323] Compared with the full-face mask used to deliver PSV in patients with COPD in acute respiratory failure[324] the helmet similarly improved vital signs, achieved similar intubation and mortality rates, and reduced complications. A more recent randomized trial showed that the Helmet is less efficient than a full face mask at CO_2 removal and can cause problems with triggering and cycling during pressure-support ventilation.[325] Pa_{CO_2} tends to be higher in patients treated with the helmet, raising concerns about rebreathing. High flow rates must be used to avoid this problem,[326] but this contributes to noise levels that may exceed 100 dB.[327]

Oral interfaces have been used successfully for many years in patients with slowly progressive neuromuscular diseases.[205] Long-term nasal ventilation appears to offer improved tolerance compared with mouthpiece ventilation in some patients.[211] Either may be effective, even in patients with minimal pulmonary reserve, and both may be used in the same patient, nasal ventilation during sleep at night, for

example, with mouthpiece ventilation used as needed during the daytime.[211]

Selection of Interfaces

ACUTE

Ideally, interfaces for the acute setting should be inexpensive and disposable or reusable without sacrificing comfort. A randomized, controlled trial in seventy patients with acute respiratory failure showed that full-face and nasal masks similarly improve dyspnea, vital signs, and gas exchange, but the nasal mask had a higher initial intolerance rate (34% vs. 12%), attributed to air leaking through the mouth.[328] Mouth leaks have been reported to occur in as many as 94% of patients receiving NIPPV for hypercapnic acute respiratory failure and commonly contribute to mask failures.[329] Thus, the full-face mask is usually the first choice in the acute setting, although claustrophobic patients or those with a need to expectorate frequently may fare better with nasal masks. In a recent randomized trial, the larger Total-face mask that seals around the perimeter of the face was equivalent to the standard full-face mask with regard to patient comfort and NIPPV failure rate, but some patients declined early on to use it because of its imposing appearance.[330] Concerns have been raised about the dead space attributable to the large volumes of these face masks, but "streaming" of airflow directly from the inlet to the patient's nose and mouth appears to minimize this problem.[331,332]

The oral interface is used sometimes in the acute setting to facilitate initial patient adaptation.[333] In a comparison study, however, of four different NIPPV interfaces in patients with acute respiratory failure, the mouthpiece had the largest leak, while there was no significant difference between the Total-face mask, oronasal mask, or nasal mask.[334] In a short-term randomized crossover evaluation in healthy volunteers, higher pressures (15 inspiratory, 10 expiratory cm H_2O) were more uncomfortable than lower pressures (10 inspiratory, 6 expiratory cm H_2O) regardless of mask; the Total-face mask avoided nasal bridge discomfort and has less rebreathing, the nasal mask caused less oral dryness, and the standard full-face mask was associated with bothersome air leaking into the eyes.[335]

The above findings emphasize that many different mask types are available, all of which may be acceptable depending on caregiver preferences, proper fitting, ventilator settings, individual patient characteristics, and other factors. Thus, when initiating NIPPV, clinicians should have a variety of interfaces readily available; a "mask bag" can be suspended from the ventilator so that individual patient needs can be accommodated.

CHRONIC

Comfort and tolerance are even more important in the long-term setting because interfaces must be used for months, mainly during sleep, before being replaced. Many different interfaces are available partly because of the demand driven by the large population of patients with obstructive sleep apnea using similar technology. Standard nasal masks are the most commonly used interfaces in the chronic setting, and a short-term controlled trial on naive patients with restrictive and obstructive forms of chronic respiratory failure found that patients rated these nasal masks as more comfortable than nasal prongs or full-face masks.[336] A polysomnographic comparison of the two masks in patients with chronic respiratory failure[337] found that nasal and full-face masks were equivalent with regard to apnea-hypopnea index, gas exchange, and sleep quality, but the nasal mask required chin straps to control mouth leaks, and sleep efficiency was less with the full-face mask.

Once again, clinicians must be prepared to try a number of different interfaces to optimize comfort. Fitting gauges should be used when available to facilitate proper sizing, and strap tension should be the minimum that controls leaks. Headstrap materials, tightness, and attachments to the head and mask are also important for comfort. Many different types of headstraps are available, although they usually are designed for a particular mask.

Selection of a Ventilator

ACUTE

A steadily expanding number of ventilators is available for NIPPV in the acute setting. Bilevel devices are portable PSV ventilators, first developed for home applications, that cycle between higher inspiratory and lower expiratory pressures.[11,25] These ventilators have been used widely in acute settings because of their ease of administration and low cost, but they have been limited by a lack of alarms, monitoring capabilities, and O_2 blenders. Newer bilevel devices have been designed specifically for acute applications of NIPPV. They have features aimed at enhancing leak compensation and patient comfort, such as adjustable triggering and cycling mechanisms and rise times (the time to reach the preset inspiratory pressure). In addition to oxygen blenders, they also include graphic interfaces comparable to standard critical care ventilators, battery backup for in-hospital transport, and a variety of modes including proportional assist ventilation.

"Critical care" ventilators are those designed for invasive ventilation and, by virtue of microprocessor technology, offer a wide variety of modes, extensive alarm and monitoring capabilities, and O_2 blenders. In the past, these devices have been limited by triggering of nuisance alarms and limited leak-compensating abilities when used for NIPPV.[338] Many, however, now offer "NIV modes" that use a PSV mode, silence alarms, and add leak compensation and algorithms that facilitate triggering and cycling, even in the face of leaks. A laboratory study comparing bilevel ventilators with a critical care ventilator found that triggering, cycling, and leak-compensatory mechanisms were superior in several of the bilevel ventilators.[339] A more recent laboratory evaluation of NIV modes on critical care ventilators observed that most

require additional adjustments in the face of leaks to function adequately.[340]

Because they use a single tube for both inspiration and expiration, bilevel ventilators contribute to CO_2 rebreathing unless used with a nonrebreathing exhalation valve that may increase expiratory resistance and expiratory work of breathing.[341,342] This rebreathing can be minimized by using an expiratory pressure greater than 4 cm H_2O[341,342] and masks with an in-mask exhalation valve situated over the bridge of the nose.[331,332] Comparisons of bilevel and critical care ventilators in intubated patients have demonstrated that gas exchange is equivalent, but work of breathing is increased during bilevel ventilation if minimal expiratory pressure levels (2 to 3 cm H_2O) are used.[344] When expiratory pressures of 5 cm H_2O are used, however, the two types perform equally well in supporting gas exchange and reducing work of breathing, presumably because of counterbalancing of auto-PEEP. For delivery of NIV, clinical outcome studies using bilevel ventilators report success rates that compare favorably with those for critical care ventilators,[60,62] although no randomized, controlled trials have compared the two directly. Thus, the selection of either system can be justified, and the choice is often based on availability and financial considerations. Further, recent developments as described above have blurred the distinctions between the various types of ventilators.

CHRONIC

Blower- or turbine-based portable pressure-limited bilevel ventilators are used most often in the long-term setting to deliver NIPPV. In a 9-year Swiss survey,[230] volume-limited devices predominated initially, but pressure-limited devices accounted for more than 90% of ventilator applications during the latter years. This shift has been driven by the low cost, ease of use, and portability of the pressure-limited devices. In addition, manufacturers have been steadily adding features that enhance monitoring. Some now offer wireless Internet connections that permit home monitoring of respiratory rate, oximetry, airway pressures, tidal volumes, and air leaks. Portable volume-limited positive-pressure ventilators are still preferred by some clinicians for specific applications. Because they offer sophisticated monitoring, they are used in patients requiring nearly continuous ventilator support. Because of their high pressure-generating capabilities, they may be preferred in patients with high respiratory system impedances, such those with morbid obesity or chest wall deformity, or they may be used to "stack" breaths to attain a higher inspired lung volume to increase cough flows.[241] Also, because volume-limited ventilators usually are driven by intermittent piston action rather than continuously operating blowers, backup battery life can be considerably longer. On the other hand, pressure-limited ventilators compensate for leaks more effectively than do volume-limited ventilators, although the compensatory flow goes, not surprisingly, mainly into "feeding" the leaks.[345] Studies in the long-term setting have not shown consistently better outcomes with one type of ventilator over the other,[346,347] however, and the choice usually becomes one of clinician and/or patient preference. In addition, a number of more recently introduced ventilators are "hybrid" devices that have the capability of delivering both pressure-limited and volume-limited breaths.

Selection of a Ventilator Mode

ACUTE

Although no studies have demonstrated superior efficacy in terms of avoiding intubation or mortality of one ventilator mode over another in the acute setting, some practitioners have found enhanced patient comfort or compliance with PSV.[348,349] Thus, although either volume-limited or pressure-limited modes can be used with the expectation of similar rates of success, pressure-limited modes appear to be accepted more readily by patients and are more commonly used (>90% of applications in some studies).[315] Some newer hybrid ventilators designed specifically for NIV are able to deliver both volume-limited or pressure-limited modes, with the capability of adjusting triggering and cycling sensitivity, rise time, and inspiratory duration to optimize patient comfort.[350] Proportional-assist ventilation, a unique mode that tracks instantaneous patient airflow, is capable of closely matching patient breathing pattern and hence potentially enhancing synchrony and comfort (see Chapter 13).[351] The flow signal is fed back to the ventilator as a raw signal (flow assist) or integrated over time (volume assist). Gains are imposed on both these signals and on a composite signal (proportional assist) that can be adjusted to assist a "proportion" of the patient's breathing effort. Theoretically, flow and volume assist are adjusted to match resistive and elastic work, respectively, which must be measured. These specific adjustments, however, are unnecessary when proportional-assist ventilation is used to deliver NIPPV clinically. Proportional-assist ventilation has been shown to be as effective and a more comfortable means of administering NIPPV than PSV delivered via a critical care ventilator[352] or a bilevel device.[353]

CHRONIC

In the long-term setting, pressure-support and volume-limited ventilators achieve similar levels of overnight oxygenation.[347] Thirty consecutive patients, mainly with restrictive forms of chronic respiratory failure, received nasal volume-limited ventilation for 1 month followed by pressure-limited ventilation.[346] Only two patients failed to improve with volume-limited ventilation, whereas ten had increased Pa_{CO_2} or symptomatic deterioration when switched to pressure-limited ventilation. Conversely, ten patients in another study had improved daytime blood gases when switched from volume-limited to pressure-limited ventilation.[354] Although these were not prospective, randomized trials, they show no clear advantage of one ventilator mode over the other. Thus, the choice between the two hinges on clinician preference and consideration of specific ventilator properties such as

portability, pressure-generating capabilities, backup-battery life, ability to stack breaths, and other factors. In general, though, volume-limited ventilators have greater pressure-generating and alarm capabilities. A more recent approach has been to use hybrid modes such as volume-assured pressure preset ventilation that automatically adjusts the inspiratory pressure within preset limits to achieve a target minute volume. Thus far, the mode appears to function as well as standard pressure preset modes and may lower CO_2 levels more in patients with obesity hypoventilation than with standard bilevel therapy,[355] but not in patients with COPD and hypercapnia.[356] Similarly, a randomized crossover trial of twenty patients with restrictive thoracic disease showed no advantage of an autotitrating bilevel mode over a standard bilevel mode.[357]

Ventilator Settings

ACUTE

Two strategies have been described: the *high-low approach,* which starts with a higher inspiratory pressure (20 to 25 cm H_2O) and lowers it if patients are intolerant,[17] and the *low-high approach,* which starts with a low inspiratory pressure (8 to 10 cm H_2O) and raises it gradually as tolerated by the patient.[60] The former approach prioritizes rapid alleviation of respiratory distress; the latter aims to optimize patient comfort in an effort to maximize patient tolerance. Paramount with both approaches is the realization that subsequent adjustments are necessary depending on patient response. Higher initial pressure often must be adjusted downward, and it is very important that low initial pressure be raised (usually to 12 to 20 cm H_2O) within the first hour, if possible, to provide adequate ventilator assistance. The high-low approach may be preferable in patients with hypoxemic respiratory failure who often have high minute volumes and are very dyspneic. L'Her et al[358] demonstrated that in patients with acute lung injury treated with NIPPV, higher pressure support levels were effective at relieving dyspnea while increases in PEEP were effective at improving oxygenation.

Expiratory pressure (or PEEP) is used routinely with bilevel ventilators and is optional with volume-limited ventilators. Bilevel ventilators require a bias flow during expiration to flush CO_2 from the single ventilator tube and avoid rebreathing.[341] Minimal expiratory pressure with these ventilators is in the 3 to 4 cm H_2O range. Higher expiratory pressures (typically 4 to 8 cm H_2O) are used to counterbalance intrinsic PEEP during treatment of exacerbations of COPD or to enhance oxygenation. It is important to recall that the difference between inspiratory and expiratory pressure is the level of PSV, so inspiratory pressure must be increased in tandem with expiratory pressure if the same level of ventilatory assistance is to be maintained. Adjusting the rate of pressurization (or rise time) may be useful to enhance comfort; patients with COPD prefer slightly more rapid rise times than restrictive patients. Very rapid pressurization rates minimize the work of breathing in patients with COPD but may be sensed as less comfortable by patients than slightly lower pressurization rates.[359]

CHRONIC

No consensus has been reached on how to select ventilator settings for patients in the long-term setting. In the sleep laboratory, one approach is to increase expiratory pressure until apneas are eliminated and inspiratory pressure until hypopneas are eliminated without inducing excessive arousals. The American Academy of Sleep Medicine has proposed guidelines for achieving this titration.[360] This approach, however, is based largely on expert opinion and does not ensure that the pressures selected will alleviate hypoventilation, nor does it facilitate initial adaptation if the patient finds the recommended initial pressures intolerable. Thus, I prefers a gradual up titration of pressures over weeks or even months as tolerated by the patient. Initial inspiratory pressure is 6 to 10 cm H_2O, with increases weekly by 1 to 2 cm H_2O as tolerated. Expiratory pressure is set at 3 to 4 cm H_2O and rarely is increased above 6 cm H_2O unless sleep apnea is deemed an important contributor. For volume-limited ventilation, an initial tidal volume of 10 to 15 mL/kg has been recommended, in excess of the standard recommendations for invasive ventilation, because of the need to compensate for air leaks.[361] Parreira et al[362] found that a tidal volume of 13 mL/kg optimized assisted minute volume in a group of patients with restrictive thoracic disorders.

A backup rate sufficiently high to control breathing nocturnally has been recommended for patients with neuromuscular disease to maximize respiratory muscle rest and prevent apneas. In patients with severe stable COPD, on the other hand, the need for a backup rate is not clear, considering that one controlled trial of NIPPV found significant benefit using a spontaneous ventilator mode without a backup rate.[332] Compared with a spontaneous mode, these authors found that use of a backup rate had no effect on nocturnal gas exchange in patients with COPD and chronic respiratory failure. On the other hand, Parreira et al[362] found that minute volume was optimized when patients with restrictive thoracic disorders used a relatively high backup rate of 23 breaths/min.

Adjuncts to Noninvasive Ventilation

With bilevel ventilators, supplemental O_2 can be provided directly through tubing connected to a nipple in the mask or to a T connector in the ventilator tubing, with liter flow adjusted to keep SaO_2 above 90% to 92%. Maximal FI_{O_2} using this setup is only 45% to 50%. FI_{O_2} delivered via bilevel ventilators depends on a number of factors, including O_2 flow rate, breathing pattern, ventilator settings, and location of the O_2 connection (connection to the mask gives a higher FI_{O_2}).[363] With critical care ventilators and some bilevel devices designed for acute applications, standard O_2 blenders are used to accurately provide the desired. Thus, these

latter ventilators are preferred for patients with hypoxemic respiratory failure.

Humidification may enhance comfort during NIPPV and is advised if NIPPV is to be used for more than a few hours, although effects on NIV failure rates have not been established.[364] A heated humidifier is preferred over a heat and moisture exchanger because the latter adds to work of breathing[365] and may interfere with triggering and cycling. Also, with excessive air leaking, a heated humidifier lowers nasal resistance.[23] In the long-term setting, humidification usually is provided, particularly during the winter months in colder climates. Nasogastric tubes are not recommended routinely as adjuncts to NIV, even when oronasal masks are used.

Noninvasive Techniques to Assist Cough

Because it provides no direct access to the lower airways, as does invasive ventilation, NIPPV depends on the integrity of airway protective reflexes for its success. In the acute setting, patients with excessive secretions or severe cough impairment are intubated rather than managed noninvasively. In the long-term setting, however, a number of techniques have been developed to enhance secretion removal in patients with compromised secretion-clearance capabilities. These techniques are of greatest value in patients with neuromuscular disease and weakened expiratory muscles. Severe bulbar involvement, such as occurs with ALS, is treated most effectively with invasive ventilation. Secretion retention related to abnormal mucus, such as occurs with cystic fibrosis, is beyond the scope of this chapter.

An effective cough depends on the ability to generate adequate expiratory airflow, estimated at more than 160 L/min.[366] Expiratory airflow is determined by lung and chest wall elasticity, airway conductance, and at least at higher lung volumes, expiratory muscle force. By generating an adequate vital capacity (> 2.5 L) to take advantage of respiratory system elasticity, inspiratory muscle function also contributes to cough adequacy. In addition, an effective cough requires the ability to close the glottis so that explosive release of intrathoracic pressure can generate high peak expiratory cough flows.[367] When patients with severe neuromuscular disease are too weak to take advantage of these mechanisms and have insufficient cough flows, techniques to assist cough should be applied.

The simplest maneuver to augment cough flow is manually assisted or "quad" coughing. This consists of firm, quick thrusts applied to the abdomen using the palms of the hands, timed to coincide with the patient's cough effort.[241] The technique should be taught to caregivers of patients with severe respiratory muscle weakness with instructions to use it whenever the patient has difficulty expectorating secretions. With practice, the technique can be applied effectively and frequently with minimal discomfort to the patient. Peak expiratory flows can be increased severalfold when manually assisted coughing is applied successfully.[368] To minimize the risk of regurgitation and aspiration of gastric contents, the patient should be semi-upright when manually assisted coughing is applied, and the technique should be used cautiously after meals. The technique can be used, though, in patients with gastric feeding tubes.

Although manually assisted coughing may enhance expiratory force, it does not augment inspired volume. Thus, patients with severely restricted volumes may not achieve sufficient cough flows even when assisted by skilled caregivers. To overcome this problem, the inhaled volume should be augmented. One approach is to "stack" breaths using glossopharyngeal breathing[368] or volume-limited ventilation and then to augment the cough using manual assistance. Another is to use a mechanical insufflator–exsufflator, a device that was developed during the polio epidemics to aid in airway secretion removal.[368] This device delivers a positive inspiratory pressure of 30 to 40 cm H_2O via a face mask and then rapidly switches to an equal negative pressure. The positive-pressure ensures delivery of an adequate tidal volume, and the negative pressure has the effect of simulating the rapid expiratory flows generated by a cough. Use of the insufflator–exsufflator has been combined with manually assisted coughing in an effort to further augment cough flows.[369]

The mechanical insufflator–exsufflator increases cough flows in patients with neuromuscular weakness but is less effective in patients with kyphoscoliosis, and in one study, actually decreased cough flows of patients with COPD.[370] In another study, however, mechanical insufflation–exsufflation decreased dyspnea and improved oxygenation not only in neuromuscular patients but also in patients with airflow obstruction.[371] Although no controlled trials have evaluated the efficacy of the cough insufflator–exsufflator, anecdotal evidence suggests that it enhances removal of secretions in patients with impaired cough. It has been reported to reduce failures (need for intubation) in neuromuscular patients in critical care settings,[372] reduce the occurrence of atelectasis and pneumonias in children with neuromuscular disease,[373] and improve cough flows in patients with ALS unless there is bulbar dysfunction, which may predispose to upper airway collapse.[374] It has been particularly useful in patient homes to treat episodes of acute bronchitis, permitting avoidance of hospitalization.[375] One recent European study demonstrated cost savings by staying in telephone contact with patients and using the cough insufflator–exsufflator on an "on-demand" basis to treat exacerbations.[376] Other devices that aid expectoration, such as the percussive ventilator, Hayek oscillator, and vibratory vest, have some theoretical advantages over other techniques for assisting secretion removal.[241] Their use of high-frequency vibrations (up to 15 Hz) may facilitate mobilization of airway secretions. Unfortunately, even anecdotal evidence to support their use is lacking.

Clinicians caring for patients with severely impaired cough should be familiar with the various techniques available to assist expectoration. These are particularly important with NIV because there is no direct access to the airway, and

secretion retention is a frequent complication and common cause for failure. Although controlled data are lacking, these techniques appear to help in maintaining airway patency in patients with cough impairment during use of NIV in both acute and chronic settings.

Role of the Clinician: Time Demands, Importance of Experience, and Guidelines

An experienced clinician conveying an air of assuredness to patients is thought to be crucial to the success of NIPPV. The clinician should motivate the patient, explaining the purpose of each piece of equipment and preparing the patient for each step in the initiation process. Patients should be reassured, encouraged to communicate any discomfort or fears, and coached in ways to coordinate their breathing with the ventilator. When using nasal masks, patients are instructed to keep their mouths shut.

Time demands on medical personnel have been a concern for the delivery of NIPPV. Chevrolet et al[377] were the first to draw attention to this potential problem, reporting large time demands on nurses during administration of NIPPV. Conversely, Kramer et al[60] found that compared with controls, NIPPV patients tended to require more time from respiratory therapists during the first 8 hours, an amount that fell significantly during the second 8 hours. Nava et al[378] also found that respiratory therapists spent more time during the first 48 hours caring for NIPPV patients than invasively ventilated patients. These findings indicate that NIPPV initially requires more time to administer than conventional therapy, for interface fitting and initial ventilator adjustment, although these demands diminish rapidly after the first few hours. Nurses, respiratory therapists, physicians, or some combination of these must spend the additional time, depending on institutional practices.

As might be anticipated, the experience of personnel also appears to be important for the success of NIPPV. Girou et al[15] reviewed the experience of a twenty-six-bed French ICU between January 1994 and December 2001 on 479 patients with either COPD or cardiogenic pulmonary edema requiring ventilator assistance, invasively or noninvasively. Use of NIV increased from approximately 20% to 90% (of the patients) during the course of the study, associated with a decrease in the rate of nosocomial pneumonias from 20% to 8% and in ICU mortality from 21% to 7% (all $p < 0.05$). The authors speculated that a "learning effect" over the course of the study was responsible for the improved outcomes. Over an 8-year period in their ICU, Carlucci et al[379] found that NIPPV success rates increased in patients with COPD despite a worsening of the severity of illness as staff gained experience with the technique. Whether or not guidelines for NIPPV implementation can improve patient outcomes remains to be established. Sinuff et al[380] found that clinician behavior changed after implementation of a guideline at their single academic institution, but overall patient outcomes were not altered. More recently, Kikuchi et al[381] observed a decreased mortality after institution of a NIPPV protocol for acute respiratory failure, although the before/after study design cannot control for other changes related to passage of time.

MONITORING

Patients receiving NIV are monitored to determine whether the goals are being achieved (see Table 18-8).

Subjective Responses

The key aims of NIPPV are alleviation of respiratory distress in the acute setting and of fatigue, hypersomnolence, and other symptoms of impaired sleep in the chronic setting while achieving patient tolerance. Agitation and mask discomfort are challenges during NIPPV. These aspects can be assessed easily using bedside observation and patient queries. Some patients minimize or deny discomfort and still may have great difficulty adapting successfully to NIV, so clinicians not should only query patients but also should observe for nonverbal signs of distress or discomfort.

Physiologic Responses

Evidence of physiologic improvement within the first 2 hours, including decreases in respiratory and heart rates, diminished sternocleidomastoid muscle activity, and elimination of abdominal paradox, portends a favorable NIPPV outcome.[133,196] Patients should be breathing in synchrony with the ventilator, and air leaking should be minimal. Some clinicians also monitor tidal volumes, aiming for delivered volumes in excess of 7 mL/kg.[382] Relying on ventilator monitoring to follow tidal volumes may be misleading, however, particularly during use of bilevel ventilators, because these integrate the inspired flow signal and may be very inaccurate in the face of air leaks.

Gas Exchange

Improvement in gas exchange as determined by continuous oximetry and occasional blood gases is a key aim in acute application of NIPPV, although improvement in ventilation may occur gradually over hours.[17] In chronic stable patients, the improvement in daytime gas exchange occurs even more slowly, over a period of weeks, depending on the duration of daily ventilator use. Some patients adapt slowly and require up to several months before they sleep through the night using the ventilator. Arterial blood-gas measurement should be delayed until the patient is consistently using the ventilator for a period of time likely to improve gas exchange: usually at least 4 to 6 hours a day. No consensus on an ideal level for daytime Pa_{CO_2} has been reached; most investigators target

levels in the middle 40s. In my experience, a daytime Pa_{CO_2} of up to 60 mm Hg, or even higher, may be tolerated without hypersomnolence or evidence of cor pulmonale as long as oxygenation is adequate. Noninvasive CO_2 monitoring may be useful for trending purposes in patients with normal lung parenchyma such as those with neuromuscular disease. Transcutaneous Pa_{CO_2} is probably the most useful because variable air leaks and breathing patterns and dilution secondary to bias flow with some ventilators render end-tidal CO_2 recordings inaccurate, particularly if the patient has parenchymal lung disease.[383]

Sleep

Little is known about sleep during NIPPV in the acute setting, and the role of sleep monitoring in the long-term setting is controversial. As noted earlier, some clinicians prefer to use the sleep laboratory to decide on initial settings for NIPPV. Others begin most patients, particularly those with neuromuscular disease, without a polysomnographic evaluation. If both approaches prove to be equal in achieving the goals of NIV, it would be difficult to argue that routine sleep studies are necessary. The relative utilities of polysomnography, multichannel portable recordings, and nocturnal oximetry are also unclear in follow-up of long-term NIPPV, but one pragmatic approach is to screen patients using home oximetry and to perform more sophisticated studies when the oximetry results indicate the need for further evaluation.

ADAPTATION

Acute

It is critically important to ascertain that the delivered pressures are sufficient to alleviate respiratory distress; a common mistake is to fail to increase pressures quickly enough, and the patient fails because of inadequate ventilator support. The patient also should use the ventilator for more time initially, with increasing periods of time off the ventilator as the underlying condition improves. Some clinicians encourage use most of the time initially, as dictated by the degree of respiratory distress during ventilator-free intervals.[60] Others employ sequential use,[384] wherein periods of use alternate with lengthy ventilator-free periods; total daily use averages only 6 hours, although this would be suitable only for mildly ill patients. When no respiratory distress recurs during ventilator-free intervals, ventilator assistance is discontinued. Total duration of ventilator assistance depends on the speed of resolution of the respiratory failure. Patients with acute pulmonary edema require an average of 6 to 7 hours of ventilator use,[114] whereas patients with COPD average 2 days or more.[60] Some patients may continue nocturnal ventilation after discharge from the hospital, following guidelines for long-term use of NIPPV.

Chronic

Patients start more gradually and increase periods of use as tolerated. Anxious patients may begin with only 1 to 2 hours of daytime use followed by gradually increasing periods of nocturnal use over several weeks or even months. Compared with the acute setting, urgency in the chronic setting is less, and because the intent is to use the ventilator during sleep, great care must be exercised in optimizing patient comfort. During this period, visits from a home respiratory therapist are helpful to assess comfort and address any problems that arise. Criner et al[278] found that 36% of patients required further adjustments in mask or ventilator settings, even after discharge from a several-week stay in an inpatient ventilator unit.

ADVERSE EFFECTS AND COMPLICATIONS

In properly selected patients, NIPPV is safe and well tolerated, and most of the adverse effects are related to the interface or ventilator (Table 18-9). Approximately 10% to 15% of patients fail to tolerate interfaces despite adjustments in strap tension, repositioning, and trials of different sizes and types of interfaces. These patients may have claustrophobia or high levels of anxiety and fail even after multiple attempts at mask readjustment and judicious use of sedation. Other mask-related adverse effects include erythema, pain, and ulceration on the bridge of the nose. Minimizing strap tension and advances in mask technology, with softer silicon seals and routine use of artificial skin on the bridge of the nose, are associated with less frequent nasal bridge ulceration, which had been as high as 40% in earlier studies.[385]

Air pressure-related and flow-related adverse effects include oronasal dryness or congestion that may respond to humidification or decongestants, sinus and ear pain, eye irritation from air leakage under the mask seal on the sides of the nose, and gastric insufflation. Readjusting the mask seal to reduce air leaking or reducing inspiratory pressure, if possible, may help.

Air leaking is ubiquitous during NIV, either under the seal or through the mouth with nasal ventilation. Air leaking adds to discomfort and may interfere with ventilator triggering and cycling, as well as efficacy of ventilation. The leaks usually are tolerated as long as the ventilator compensates adequately, as most bilevel ventilators do. As discussed earlier, bilevel ventilators cannot function properly without a small intentional leak in the tubing, which is necessary for removal of CO_2 to prevent rebreathing. Most volume-limited modes compensate poorly for leaks, but large air leaks may compromise the effectiveness of any form of NIPPV. Attempts to control air leaks should start with a reassessment of mask fit and readjustment of the head straps. To reduce air leaking through the mouth during nasal ventilation, edentulous patients should not be

TABLE 18-9: FREQUENCY OF ADVERSE SIDE EFFECTS AND COMPLICATIONS OF NONINVASIVE POSITIVE-PRESSURE VENTILATION WITH POSSIBLE REMEDIES

Complication	Occurrence (%)*	Possible Remedy
Mask-related		
Discomfort	30% to 50%	Check fit, adjust strap, new mask type
Facial skin erythema	20% to 34%	Loosen straps, apply artificial skin
Claustrophobia	5% to 10%	Smaller mask, sedation
Nasal bridge ulceration	5% to 10%	Loosen straps, artificial skin, change mask type
Acneiform rash	5% to 10%	Topical steroids or antibiotics
Air pressure or flow related		
Nasal congestion	20% to 50%	Nasal steroids, decongestant/antihistamines
Sinus/ear pain	10% to 30%	Reduce pressure if intolerable
Nasal/oral dryness	10% to 20%	Nasal saline/emollients, add humidifier, decrease leak
Eye irritation	10% to 20%	Check mask fit, readjust straps
Gastric insufflation	5% to 10%	Reassure, simethicone, reduce pressure if intolerable
Air leaks	80% to 100%	Encourage mouth closure, try chin straps, oronasal mask If using nasal mask, reduce pressures slightly
Major complications		
Aspiration pneumonia	< 5%	Careful patient selection
Hypotension	< 5%	Reduce pressure
Pneumothorax	< 5%	Stop ventilation if possible, reduce pressure; if not, use thoracostomy tube if indicated

*Occurrences estimated from literature and my experience.

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treated with nasal masks, others are coached to keep their mouths shut, chin straps may be used, or an oronasal mask may be tried.

Major complications, such as pneumothoraces, are unusual, probably because inflation pressures are low compared with those used with invasive ventilation. Lack of patient cooperation interferes with efficacy and may be ameliorated by judicious use of sedation, such as low doses of benzodiazepines. Unremitting agitation should be considered an indication for intubation. Aspiration is a reported complication,[386] but should be unusual if patients with swallowing dysfunction and problems clearing secretions are excluded. Routine insertion of nasogastric tubes has been recommended at some centers to lower the risk of aspiration during use of face masks,[382] but there are no data available to support this practice, and it is no longer recommended. Progressive hypoventilation occurs in a small minority of patients, usually necessitating intubation. Uncooperativeness, lack of synchronization with the ventilator, inability to tolerate adequate inflation pressures, and excessive air leaking are common causes for this predicament, and measures aimed at correcting these may be helpful. Rarely, nasal obstruction contributes and may respond to decongestant sprays.

In the acute setting, NIPPV fails in roughly a third to a quarter of patients, depending on many factors, including skill and experience of the team, occurrence of adverse effects and complications as discussed earlier, and underlying severity of the patient's illness. Progression of the underlying process, such as worsening hypoxemia, also may be responsible for failure. Close monitoring with proactive efforts to address and minimize adverse effects should minimize failure rates.

SUMMARY AND CONCLUSIONS

In the acute setting, evidence now supports NIPPV in the treatment of respiratory failure secondary to acute exacerbations of COPD, acute cardiogenic pulmonary edema (which can be managed with CPAP as well), and immunocompromised states and to facilitate weaning in patients with COPD. Weaker evidence supports NIPPV in the treatment of other forms of respiratory failure, including respiratory insufficiency in patients with asthma, post–lung resection, or those who decline intubation. NIPPV should not be used routinely in patients with ARDS or severe pneumonia. Regardless of the underlying cause of the respiratory failure, patients to receive NIPPV must be selected carefully. Those with mild deteriorations likely will succeed without ventilator assistance, and prompt intubation usually is preferred in severely ill patients. Patients with unstable medical conditions, inability to protect the airway or clear secretions, or uncooperativeness are excluded from consideration. Patients selected according to these guidelines and monitored closely can be managed with NIPPV with the expectation that intubation and its inherent complications will be avoided.

In the chronic setting, NIPPV has long been considered the modality of first choice for patients with respiratory failure secondary to neuromuscular disease or chest wall

deformity. Randomized, controlled trials have not been done because of ethical concerns, but the ability of NIPPV to improve symptoms, gas exchange, quality of life, and survival in these patients is widely accepted. NIPPV for patients with severe stable COPD has been more controversial because of conflicting data, but it may prevent deterioration of gas exchange, improve quality of life, and reduce the need for hospitalization in patients with severe CO_2 retention and nocturnal hypoventilation who adhere to therapy (which is often not the case). In some countries, the obesity-hypoventilation syndrome has become the largest diagnostic category for NIPPV at home, perhaps because of increasing recognition and the obesity epidemic.

In both the acute and chronic settings, experience and skill with the implementation of NIPPV are important. Proper fit and application of the mask are keys to success. Although the type of ventilator is not as important, ventilator mode and settings affect comfort and effectiveness. In carefully selected patients initiated according to current recommendations and monitored in an appropriate setting, NIPPV can be delivered safely with no or minor adverse effects. The failure rate remains substantial at roughly a quarter to a third of patients, but hopefully will decline as clinicians gain experience, selection criteria are refined, and technology improves. NIPPV has assumed an important role in acute and chronic care settings and should be considered a lung-protective strategy for certain forms of respiratory failure. In addition, clinicians caring for patients with respiratory failure should have the necessary skill and experience with NIPPV applications.

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VII

UNCONVENTIONAL METHODS OF VENTILATOR SUPPORT

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19

HIGH-FREQUENCY VENTILATION

Alison B. Froese
Niall D. Ferguson

High-frequency ventilation has been an unconventional option for more than three decades and during that period several varieties of high-frequency ventilators have come and gone. Currently, interest in high-frequency ventilation in adult critical care is part of a larger search for ventilator strategies that can support gas exchange in the severely hypoxemic patient without contributing additional ventilator-induced lung injury. Over the past 30 years, high-frequency ventilators provided an experimental tool that identified many of the mechanisms that contribute to ventilator-induced lung injury. It became clear that ventilator-induced lung injury is minimized by ventilator patterns that achieve homogeneous aeration of as much of the lung as possible, avoiding both injury from overdistension (volutrauma) and that arising from the repetitive opening and closing of lung units in regions of atelectasis (atelectrauma) (Fig. 19-1).[1] Failure to operate in the "safe zone" initiates biotrauma.[2,3]

The concept of a "safe zone" within which to ventilate the atelectasis-prone lung has been reflected in numerous clinical trials of lung-protective ventilation over the last 15 years. Conventional ventilator protocols have found survival benefit from shrinking the tidal volume and minimizing peak or plateau distending pressures.[4] Studies such as that of Roupie et al[5] and Terragni et al[6] suggest that very small tidal volumes—even lower than 6 mL/kg predicted body weight—may be needed in some patients (those with the worst lung injury) to avoid overdistension. Very high levels of positive end-expiratory pressure (PEEP) would be needed in some patients to avoid derecruitment.[7] Concurrently, high-frequency ventilation—both in oscillatory and jet forms—has become an established lung-protective modality in neonatal and pediatric intensive care (see Chapter 23).[8–14] The question, however, persists: in severe acute respiratory distress syndrome in adult patients, will use of a high-frequency device result in clinically important outcome differences compared with lung-protective conventional ventilation, or are newer conventional ventilator protocols now equally able to protect the lung?[15–17]

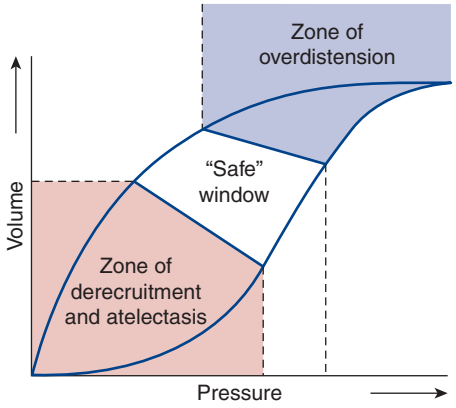


FIGURE 19-1 Pressure-volume curve of a moderately diseased lung, as in a patient with acute lung injury. Ventilator-induced lung injury occurs at both extremes of lung volume. In the zone of overdistension, damage arises from edema fluid accumulation, surfactant degradation, and mechanical disruption. In the zone of derecruitment and atelectasis, lung injury arises from the direct trauma of repeated closure and reexpansion of small airways and alveoli, through accumulation and activation of inflammatory cells with release of cytokines (biotrauma), through interactions with local hypoxemia, by inhibition of surfactant, and through compensatory overexpansion of the rest of the lung as the lung "shrinks." High end-expiratory pressures plus small tidal volume cycles are needed to stay in the safe window. (Reproduced, with permission, from Lippincott Williams & Wilkins, Froese AB, High-frequency oscillatory ventilation for adult respiratory distress syndrome: let's get it right this time. *Crit Care Med.* 1997;25:906–908.)

HISTORICAL OVERVIEW

Several existing reviews detail the history of high-frequency ventilation.[18,19] Early developments often were driven by issues peripheral to pulmonary critical care. Sjöstrand et al[20] wanted to eliminate respiration-related variations in vascular pressures so that they could investigate carotid sinus reflexes and developed high-frequency positive-pressure ventilation. Lunkenheimer et al[21] wanted to use the lungs as a route to deliver oscillatory pressure pulses to the myocardium. They needed apnea for this and were amazed to find gas exchange occurring while they applied their high-frequency flow oscillations. Emerson[22] thought that high-frequency flow oscillations might provide internal physiotherapy and help to mobilize secretions. In Toronto, Bryan[23] initially was curious to see whether an external "shaker" could enhance the gas mixing produced by cardiogenic oscillations. Klain and Smith[24] explored jet ventilation at increasing frequencies to solve the problem of achieving alveolar ventilation in respiratory systems with a big leak, such as a bronchopleural fistula.

These devices often became intriguing phenomena in search of a reason for being. Devices such as high-frequency positive-pressure ventilation and high-frequency jet ventilation were particularly useful for surgical procedures when both anesthesiologist and surgeon needed access to the airway. The notion, however, that high rates and small tidal volumes might be of broader therapeutic value needed a pathophysiologic rationale.

An emerging concept in the 1970s was that many of the pulmonary perturbations that put patients into intensive care units were problems of low lung volume. Low lung volumes were associated with poor lung compliance, increasing airway and vascular resistances, increased work of breathing, airway closure, low ventilation–perfusion ($\dot{V}_A/\dot{Q}$) ratios, atelectasis, hypoxemia, and high oxygen (O_2) exposure. Neonatal outcome was improving simply from the introduction of continuous positive airway pressure to improve alveolar aeration.[25]

A crucial insight occurred early in our experience with high-frequency oscillatory ventilation (HFOV) when we explored a variety of mean airway pressure settings while ventilating an infant with neonatal respiratory distress syndrome (Fig. 19-2).[26] The infant was stable in terms of both hemodynamics and CO_2 elimination over the whole range of mean pressures tested, but oxygenation varied markedly. One could either ventilate with a low mean airway pressure (mPaw) and high fractional inspired oxygen concentration (FI_{O_2}) or a higher mean pressure and low FI_{O_2}. A choice had to be made. We gave priority to the reversal of low lung volumes. We argued that the small-volume cycles of HFOV should allow one to optimize alveolar aeration by using higher mean pressures than were considered safe during conventional mechanical ventilation while still keeping peak pressures less than those needed to eliminate CO_2 at conventional rates. This pathophysiologic rationale continues to guide high-frequency applications to this day.

Many devices invented along the way, such as high-frequency positive-pressure ventilation, have since disappeared from use. High-frequency jet ventilation was explored in many adult intensive care units in the 1980s for difficult cases of bronchopleural fistula or tracheal disruption.[27] It

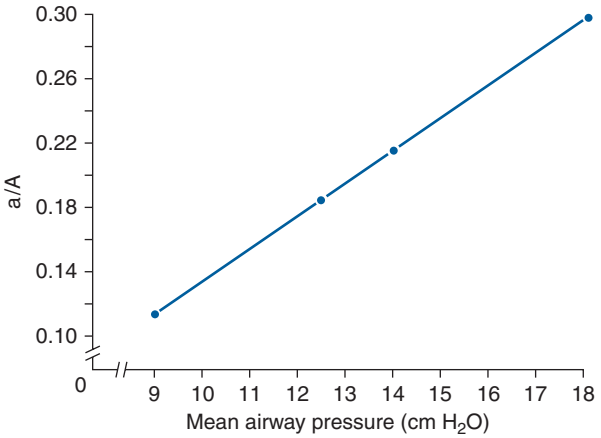


FIGURE 19-2 Relationship of oxygenation, as reflected in the ratio of the arterial and alveolar oxygen tensions (a/A ratio), to the mean airway pressure (mPaw) applied during HFOV, at constant tidal volume and frequency, in an infant with respiratory distress syndrome. No circulatory instability occurred over the entire range of mean pressures. CO_2 elimination could be achieved equally well using a high FI_{O_2} and a low mPaw or a low FI_{O_2} and a higher mPaw. A choice of operating conditions had to be made. (From Marchak, et al. Treatment of RDS by high-frequency oscillatory ventilation: a preliminary report. *J Pediatr.* 1981;99:287–292. Reproduced with permission of Mosby, Inc.)

gradually became clear that any oxygenation benefits occurring during high-frequency jet ventilation resulted from increases in mean lung volume, not from some unusual properties of gas distribution.[28] With an high-frequency jet ventilation device, the end-expiratory lung volume is a complex product of jet diameter and placement, driving pressure, jet frequency, and the time available for expiration.[29,30] Safe use requires accurate intrapulmonary pressure monitoring, which was rarely provided with early devices. Inadvertent hyperinflation could cause problems with both circulatory depression and/or barotrauma. No North American, commercial, adult-sized jet ventilator was ever marketed with a safe, effective humidification system such as that available in Europe.

The largest early comparative trial of high-frequency jet ventilation versus conventional mechanical ventilation in hypoxemic lung disease was performed before the importance of atelectasis reversal was established. Consequently, it was carried out with the goal of supporting gas exchange with the lowest possible peak and mean pressures, and proved of no benefit.[31] For all these reasons, high-frequency jet ventilation in adults has become a rare event. Jet ventilation at high or low frequencies continues to be a useful approach to situations in which airway access must be shared during surgical procedures[32] or alveolar ventilation needs to be maintained in the presence of severe bronchopleural fistulas.[29]

High-frequency jet ventilation has persisted in neonatal and pediatric critical care largely because of the continuous design refinements of the Bunnell Life Pulse device.[13,14] Early problems with poor humidification causing desiccation of tracheal mucosa were corrected, appropriate pressure-monitoring systems were devised, and expert training and technical support were provided.

A hybrid device combining high-frequency ventilation and conventional pressure-cycled ventilation (e.g., the high-frequency percussive ventilation/volume diffusive respirator [Percussionaire 4, Bird Technologies, Sandpoint, ID]) is used in many burn units.[33] Its use was reviewed recently.[34] Currently, the main high-frequency ventilatory options in the critical care of adults or larger children are HFOV or the high-frequency percussive ventilation/volume diffusive respirator Percussionaire. For neonates and small infants, high-frequency oscillatory ventilators, high-frequency jet ventilators, and the high-frequency percussive ventilator remain available. In view of HFOV's increasing role in adult intensive care, this chapter focuses on HFOV.

BASIC PRINCIPLES OF HIGH-FREQUENCY OSCILLATORY VENTILATION

HFOV achieves gas transport with stroke volumes approximating anatomic dead space. Quasi-sinusoidal flow oscillations applied at the airway opening induce rapid gas mixing within the lungs. A number of physical transport mechanisms contribute to this mixing process. They have been reviewed in detail elsewhere.[35]

In practical terms, HFOV can be viewed as a mixing device that rapidly blends high O_2/low CO_2 gas from the top of the endotracheal tube with gas in the alveoli (Fig. 19-3).

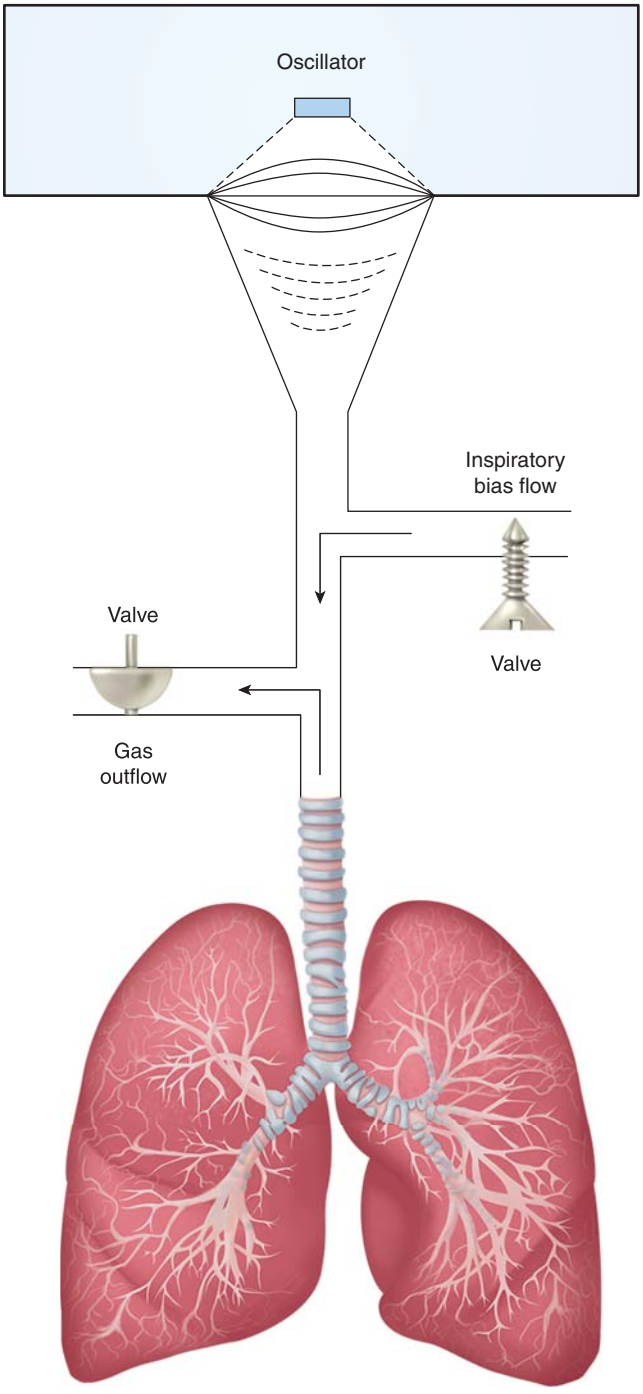


FIGURE 19-3 Schematic of a circuit for delivery of HFOV. Quasi-sinusoidal flow oscillations are generated by a diaphragm or piston pump and directed to the endotracheal tube. A bias flow of humidified gas flushes the CO_2 that is transported out of the lungs out of the circuit. Mean airway pressure is regulated by adjustments of the bias flow and the resistance of the expiratory limb. (From Krishnan, et al. High-frequency ventilation for acute lung injury and ARDS. *Chest.* 2000;118:795–807. Reproduced with the permission of the American College of Chest Physicians.)

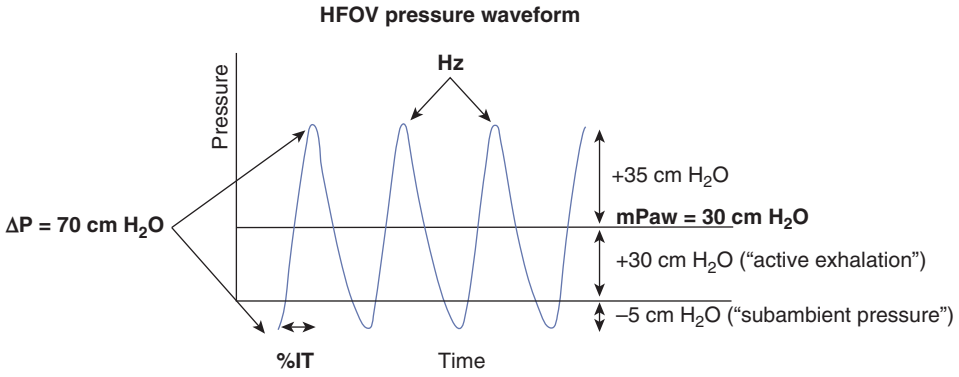


FIGURE 19-4 Waveform of high-frequency pressure oscillations in the circuit above the endotracheal tube. Both inspiratory and expiratory flows are actively driven by the oscillator diaphragm. Pressure cycles equally above and below the mean level. When the oscillatory pressure amplitude (ΔP) is more than twice the mean airway pressure (mPaw), subambient pressures may occur in the circuit without inducing air trapping or choke points in the lung.[37] The endotracheal tube filters the pressure swings, decreasing ΔP in the trachea and alveoli. Filtering is greater with smaller endotracheal tubes and higher frequencies.[71,84,96] (From Derdak S. High-frequency oscillatory ventilation for acute respiratory distress syndrome in adult patients. *Crit Care Med.* 2003;31:S317–S323. Reproduced with permission from Lippincott, Williams & Wilkins.)

Net transport occurs along the partial-pressure gradients for O_2 and CO_2, with CO_2 moving out of the lung along its partial-pressure gradient and O_2 moving inward to the alveolar–capillary interface. These flow oscillations cause symmetric oscillations of intrapulmonary pressure (ΔP) around a mean distending airway pressure (mPaw) (Fig. 19-4). Although subambient pressures can occur in the circuit, intrapulmonary air trapping or "choke points" are unlikely with appropriate mPaw settings.[36,37] One can view HFOV as a means of delivering "continuous positive airway pressure" with a built-in "shaker" to facilitate CO_2 elimination.

In contrast to current conventional approaches to supplying PEEP with additional inspiratory assist for CO_2 elimination, the mean distending pressure during HFOV is midway between the minimal and maximum values, introducing less risk of derecruitment during the expiratory phase for any given peak distending volume or pressure.[38] One attraction of HFOV has been the way in which it uncouples the regulation of oxygenation and CO_2 elimination into two separate control systems, unlike the situation with conventional ventilators, where it is often difficult to adjust one (i.e., the CO_2 level) without also affecting the other. Oxygenation is regulated by reversing atelectasis and then finding the mean distending pressure that maintains alveolar expansion. The FI_{O_2} then is set at a level that maintains appropriate arterial oxygenation goals. CO_2 elimination is relatively independent of mean airway pressure,[39] being regulated by frequency and stroke volume (i.e., power or ΔP) adjustments.[40,41]

Oxygenation

ACHIEVING ALVEOLAR AERATION

Although lung-volume optimization has become an accepted goal of HFOV, the "best way" to achieve this optimization remains controversial (Fig. 19-5). The small volume cycles of HFOV are simply not powerful enough to reopen atelectatic alveoli rapidly without some type of recruitment measure.

Ventilating on the "Deflation Limb". All initial animal studies and one early human trial used a brief recruitment maneuver to near total lung capacity, followed by reduction of mPaw to a maintenance level that prevented derecruitment.[42–46] This is termed getting the lung *onto the deflation limb* of its pressure–volume relationship. Recent investigations in both animal models and humans reinforce the value of ventilating on the deflation limb.[47–54] After a recruitment maneuver, oxygenation goals are achieved at substantially lower maintenance mPaw values (near the point of maximum curvature),[48,51,52] alveolar expansion becomes more homogeneous (which should reduce shear forces during ventilation and reduce volutrauma),[50,55] and the percentage transmission of HFOV pressure cycles into the lung is decreased relative to settings producing equal shunt reduction on the inflation limb.[49] Most studies in animals and humans have used one or more sustained inflation recruitment maneuvers to get the lung onto the deflation limb. A recent study in saline-lavaged pigs concluded that an escalating stepwise slow recruitment maneuver was more effective in opening the lung than brief sighs or a 20-second sustained inflation.[56] This study, however, is limited by the low pressures employed and the incomplete recruitment seen with all techniques tested.

Ventilating on the "Inflation Limb". Following the High-Frequency Intervention (HIFI) trial of the late 1980s,[57] fear of intraventricular hemorrhage in the fragile brain of the premature patient led most neonatologists to pursue stepwise increases in mPaw until either X-ray and blood-gas evidence of lung reexpansion was achieved or the mPaw level reached whatever level was deemed the "maximum allowable" level for a given institution.[58] Physiologically, this

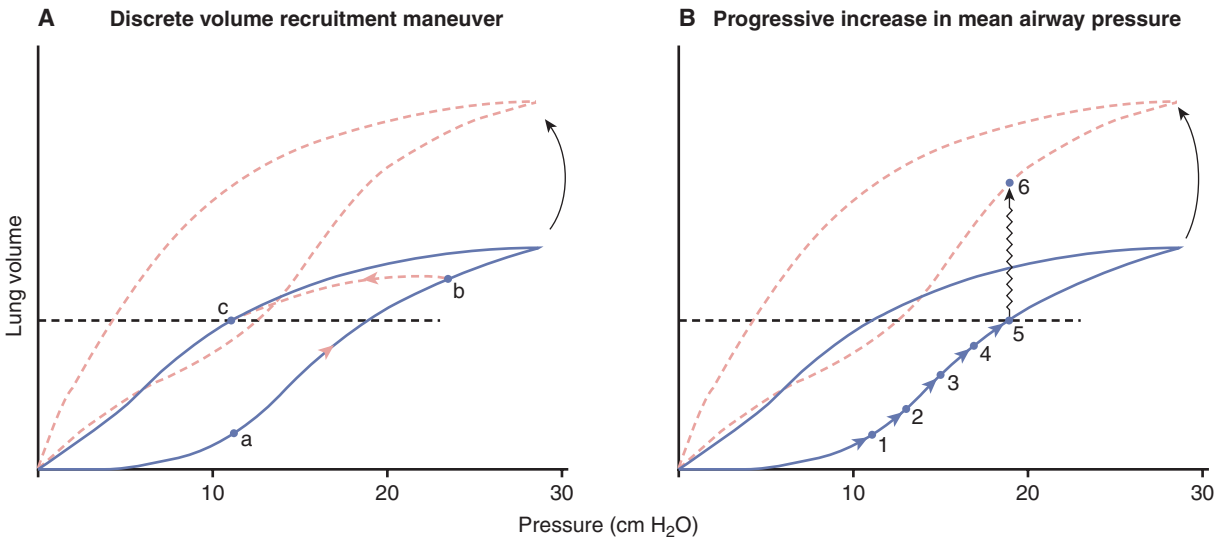


FIGURE 19-5 Schematic of two approaches to alveolar reexpansion during HFOV. The *horizontal dashed line* indicates the desired maintenance mean lung volume. The *solid line* is the pressure–volume relationship of a moderately diseased lung that still exhibits hysteresis. The *dashed line* indicates the pressure–volume relationship after some recovery has occurred. **A.** A brief sustained increase in mean airway pressure (mPaw) from *a* to *b* inflates the lung to near total lung capacity, putting it on the deflation limb of its pressure–volume curve. After this discrete recruitment maneuver, the target volume *c* is maintained at an mPaw of 11 cm H_2O. If the pressure–volume relationship happens to change (as with position, diuresis, etc.), the operational lung volume remains constant. This is the approach used in the Treatment with Oscillation and an Open Lung Strategy (TOOLS) trial.[54] **B.** A gradual march up the inflation limb of the pressure–volume relationship. Progressive increases in mPaw are used to achieve the target lung volume. An mPaw of 19 cm H_2O is now needed to maintain lung volume at *c*. Also, if the pressure–volume relationship of the respiratory system changes, overdistension of the lung could occur (i.e., movement from point 5 to point 6). This is the approach used in the majority of neonatal and adult trials of HFOV to date. When actual lung volumes are measured, settings thought to have optimized lung volume clinically by these stepwise increases in mPaw often prove to be inadequate.[61] (Froese AB. Neonatal and pediatric ventilation: Physiological and clinical perspectives. In: Marini JJ, Slutsky AS, eds. *Physiological Basis of Ventilatory Support.* 1998:1315–1357.)

can be described as "marching up the inflation limb" of the pressure–volume curve, as in Figure 19-5 *B.* Most post-HIFI trial neonatal/pediatric trials (including the largest recent randomized, controlled trials in 2002[59,60]) used stepwise increases in mPaw to "optimize" lung volume to oxygenation and chest X-ray targets. Unfortunately, when the actual lung volumes achieved by such clinical protocols are measured, many lungs prove to be suboptimally expanded.[61] It follows that many comparative trials of HFOV and lung-protective conventional ventilation over the last 25 years have not achieved optimal homogeneous alveolar aeration at the lowest effective mean airway pressure, thus missing some of the potentially protective features of HFOV. A recent analysis of neonatal trials identified many design problems and stressed the need for further well-designed and monitored comparisons of ventilator options in this population.[62] All early adult trials of HFOV started at mPaw levels of 3 to 5 cm H_2O above the mPaw on conventional ventilation and then increased mPaw incrementally—again marching up the inflation limb.[63–67]

A few human trials have used protocols that rapidly place the lung "on the deflation limb" of its pressure–volume relationship.[53,54] Although large comparative trials of the relative safety of these different recruitment protocols are not available, no evidence of risk from either barotrauma or intraventricular hemorrhage (IVH) has emerged using any of the neonatal or pediatric approaches since optimization of lung volume became an accepted goal of HFOV.[8,9] What we do know is that lung-volume optimization is essential for HFOV to be protective of the lung, and alveolar aeration is more homogeneous and achieved at a lower mPaw after a recruitment maneuver, with or without use of the prone position, has moved the lung onto the deflation limb of the pressure–volume relationship. In a recent human trial, the oxygenation improvements gained in the prone position were only sustained when patients were managed with HFOV after being placed supine again.[68] These observations suggest that the higher mPaw and small pressure and volume cycles of HFOV preserve alveolar reexpansion better than the current lung-protective tidal volumes of conventional ventilation.

Atelectrauma: The Costs of Inadequate Recruitment. The relationship between the pressure swings at the airway opening (ΔPao) and those applied to the airways and alveoli (ΔPtr/ΔPao) is multifactorial. Atelectasis markedly impacts the percentage pressure transmission.[69–72] Premature lambs,[69] lavaged pigs,[49] and lavaged rabbits[72] all demonstrate the high cost of failure to reverse atelectasis, as reflected in the percentage of ΔPao transmitted to the trachea, bronchi, and alveoli (Fig. 19-6). Pressure swings and the risk of overdistension of aerated lung reduce rapidly to normal values following lung recruitment. Failure to reverse atelectasis during HFOV exposes airways and alveoli unnecessarily to potentially damaging shear forces. When

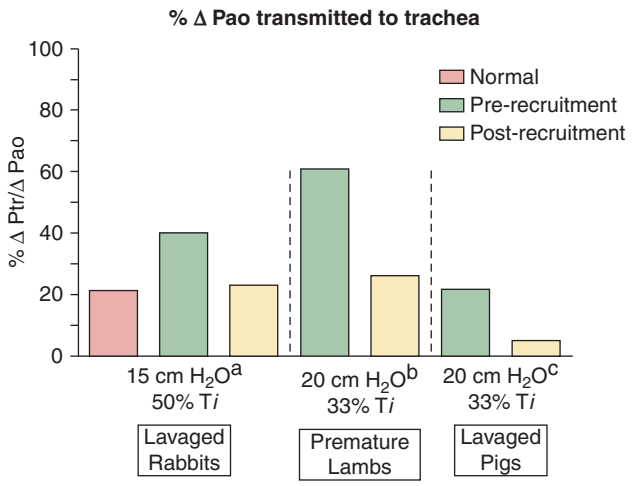


FIGURE 19-6 Effect of a recruitment maneuver (RM) on the transmission of ΔP from the oscillator circuit (ΔPao) to a tracheal sampling site (ΔPtr). Alveolar reexpansion from an RM substantially reduced the amplitude of the peak-to-trough pressure swing applied to the trachea in lavaged rabbits,[72] premature lambs,[69] and lavaged pigs.[49] Reversal of atelectasis protects lung tissue from potentially damaging shear forces. Note that ΔPmachine = ΔPcircuit = ΔPao in various sources.

van Genderingen et al[49] analyzed intrapulmonary pressure transmission in terms of the ratio of intratracheal and circuit (machine displayed) ΔP values, termed the *oscillatory pressure ratio,* pressure transmission into the lung increased substantially at low lung volume. In vivo, adequate alveolar reexpansion optimized oxygenation while also minimizing intrapulmonary pressure swings. For a given level of shunt reduction, both the oscillatory pressure ratio and the mPaw needed to achieve optimal gas exchange were substantially lower after a recruitment maneuver.

Inadequate alveolar recruitment also may trigger inappropriate increases in ΔP or decreases in frequency because of hypercapnia, when what was really needed was alveolar reexpansion. All high-frequency oscillators currently available are load-dependent and deliver less tidal volume at any given setting when the lung is stiffer, as with ongoing atelectasis.[73,74] If one's goal is to explore HFOV for the potential lung-protective effects of maintaining O_2 and CO_2 transport at the smallest possible intrapulmonary pressure and volume swings, then lung-volume optimization is essential.

Volutrauma: The Cost of Excessive Recruitment. In the presence of recruitable lung, it costs less to pursue lung recruitment vigorously than to accept ongoing atelectasis.[75] In late-phase disease with bronchiectasis, cysts, and progressive fibrosis, the opportunity for effective recruitment is past and should not be pursued. Similarly, in patients with milder acute lung injury (ratio of arterial partial pressure of oxygen to FI_{O_2} is 200 to 300) whose lungs are already reasonably well aerated, attempts at further lung recruitment will likely only result in overdistension of the already open lung.[76] All clinical trials done to date—from neonate to adult—that have mandated earlier lung-volume optimization have reported similar or decreased incidences of barotrauma, a transient need for inotropic support, and a decreased need for nitric oxide to reduce pulmonary vascular resistance despite using mean pressures in the thirties or forties when necessary to achieve oxygenation.[11,64,77–80] Recent computed tomography studies during HFOV in eight adult patients with acute respiratory distress syndrome documented substantial (approximately 800 mL) increases in normally aerated volume with only a minor increase in hyperinflated lung (<50 mL).[81] Overdistension certainly can occur, particularly if inappropriately high mPaw levels are maintained as the lung normalizes during treatment. Avoidance of this requires awareness and periodic reassessment of lung expansion.

Some algorithms warn against using mean distending pressures on HFOV higher than the plateau pressure limit of 30 cm H_2O currently advocated for conventional ventilation. This warning may produce inadequate volume optimization, particularly in extrapulmonary acute respiratory distress syndrome. The risk of a given "maximum pressure" will vary with the size of the lung and the size and rate of delivery of the tidal volume engendering that plateau pressure. If 60% or 70% of the lung is not participating in gas exchange, then a tidal volume of even 6 mL/kg may induce dangerous overdistension of the ventilated alveolar units, as well as exerting shear forces on any alveolar units reexpanded during the course of the breath. If, instead, 70% or 80% of the lung is kept expanded throughout the ventilatory cycle, then a mean distending pressure of 30 cm H_2O or more is safe, as proven in numerous clinical trials of HFOV,[65,77,78,82] presumably because that distending pressure is now accommodated within many more participating lung units, fewer units are sheared open during the course of a cycle,[38] and volume swings of only 1.5 to 2 mL/kg at high rates minimize peak distension. Conversely, if one fails to open the lung during HFOV and then keep it open, one will expose the lung to unwanted shear forces many more times per minute, particularly if forced to use lower rates and larger volume cycles because of inadequate recruitment.

MAINTENANCE MEAN AIRWAY PRESSURE

Numerous studies have tried to predict an optimal maintenance mPaw from some feature of the static pressure–volume curve of the respiratory system, such as the inflection point on the inflation limb.[51] These studies demonstrate a general property of the respiratory system, namely, that the mPaw needed to maintain a given level of oxygenation is substantially less after the lung has been inflated briefly to a pressure of 30 to 40 cm H_2O so that it is "operating on the deflation limb."[49] Because recruitment and derecruitment pressures vary markedly between lung regions[50,83] and between lung-injury models, generalizations to human ventilator management must be made cautiously. In clinical practice, a gradual deterioration in oxygenation over time that corrects with a recruitment maneuver indicates that the mPaw needs to be increased to keep alveoli/airways

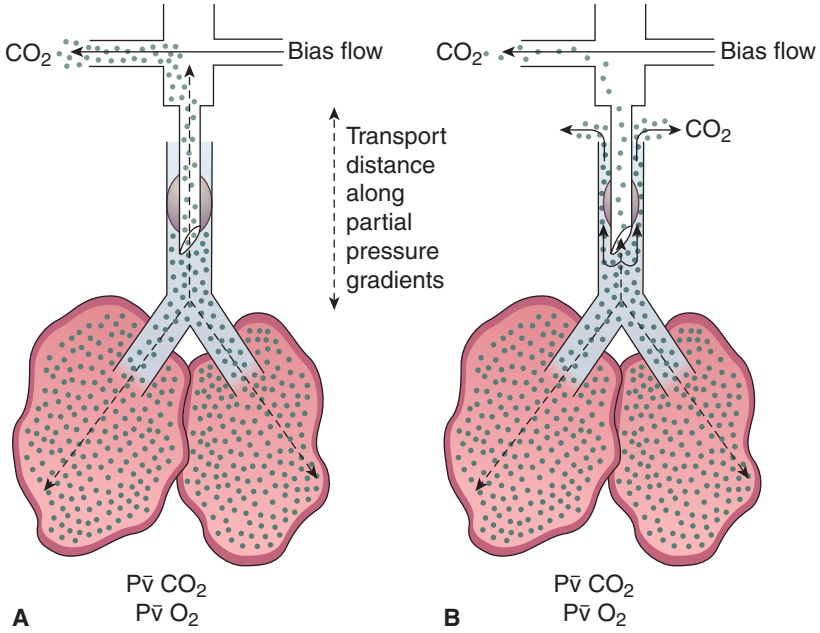


FIGURE 19-7 Schematic of the gas transport pathways during HFOV before and after establishment of a cuff leak. Transport distances are shown for CO_2. *On the left,* with the endotracheal tube (ETT) cuff occluding the trachea, the fresh-gas front for both CO_2 and O_2 is at the top of the ETT. Gas transport mechanisms must bring CO_2 from the alveoli to the top of the ETT before CO_2 is flushed away by the bias flow. *On the right,* with partial ETT cuff deflation, some of the bias flow passes down the ETT and flushes CO_2 molecules out beside the ETT, in effect reducing the transport distance substantially. The ETT represents 50% of the transport impedance during HFOV.[71,91] Introduction of a cuff leak reduces the tidal volume needed to support CO_2 elimination and decreases the intrapulmonary ΔP imposed on lung tissue.[84] A cuff leak also may increase tracheal contamination by oral secretions. The risk-to-benefit ratio of a cuff leak is not yet established.

above their closing pressures. Conversely, a rise in the partial pressure of arterial carbon dioxide (Pa_{CO_2}) at constant mPaw and power settings may indicate the lung is improving and is now overdistended, in which case a decrease in mPaw is needed.[84] Nothing can replace thoughtful reassessment of both patient and machine factors.[85] New bedside regional lung-volume monitoring techniques, such as electrical impedance tomography or respiratory inductance plethysmography, have the potential to clarify mPaw adjustments and may become more commonly used in the future.[48,86–88]

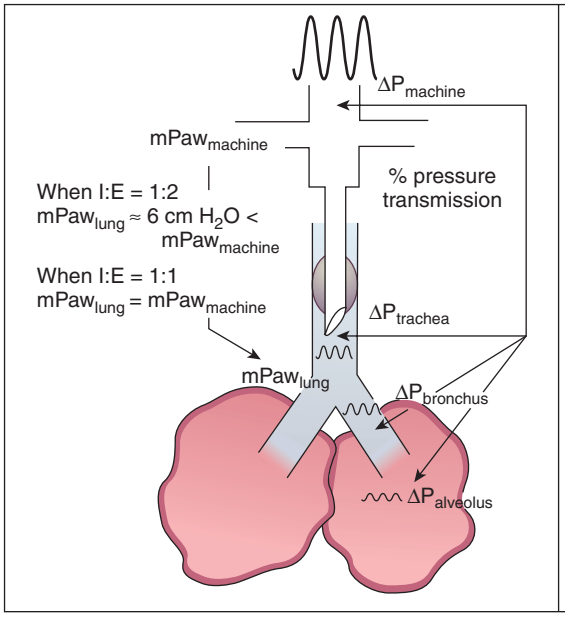
Carbon Dioxide Elimination

The basic transport studies of the 1980s were executed with accurate measurements of delivered stroke volumes over a wide range of frequencies using sinusoidal flow oscillations.[40,89,90] They established that the volume of CO_2 eliminated per minute ($\dot{V}_{CO_2}$) was proportional to the product of oscillatory frequency and the approximate square of the stroke volume ($\dot{V}_{CO_2} = V_T^{\sim 2} \cdot f$). The endotracheal tube contributes a substantial impedance to gas transport during HFOV.[91] If one uses an uncuffed endotracheal tube, or employs a partial cuff leak around a cuffed tube, such that the fresh-gas front moves to the bottom of the tube and CO_2 exits around rather than through the tube, the stroke volume needed to achieve normocapnia decreases by up to 50% (Fig. 19-7). The bias gas-flow rate also influences transport efficiency through its effect on gas tensions at the fresh-gas front.[92] Uncuffed tubes are used routinely in neonates and infants. Cuff leaks substantially assist CO_2 elimination in adults,[41,66] at the same time reducing intrapulmonary pressure swings.[84]

FREQUENCY SELECTION

Early HFOV trials in neonates used a frequency of 15 Hz and an inspiration-to-expiration (I:E) ratio of 1:1. Demonstration of small interregional mean pressure gradients at 15 Hz and 50% inspiratory period (T_I)[93] subsequently induced a shift to a lower operating frequency of 10 Hz and a 33% T_I in many centers. It is worth noting that although pressure gradients definitely occur in the lung during HFOV, their magnitudes are small (i.e., on the order of 1 to 3 cm H_2O from apex to base).[94] With a 33% inspiratory period, the mPaw measured in the circuit and displayed on the ventilator exceeds the mPaw within the lung by an amount that increases with tidal volume, frequency, and smaller endotracheal tube diameters, often in the range of 5 to 6 cm H_2O (Fig. 19-8).[95]

Frequency selection directly affects the pressure cycles applied to the lung. A smaller percentage of the circuit ΔP is transmitted down an endotracheal tube at higher frequencies.[71,96]



Factors affecting the percentage of the ΔP generated by the oscillator (machine ΔP) that is transmitted into the lungs

- ↓↓↓ with decreasing endotracheal tube diameter
- ↓↓ with increases in frequency (Hz)
- ↓ as lung compliance increases
- ↓ as aerated volume increases
- ↓ with introduction of a cuff leak
- ↓ with tracheal gas insufflation
- ↓ with increased length of ETT

Note: These factors can combine such that little or no ↑ in $\Delta P_{alveolar}$ may occur despite an ↑ in ΔP displayed on the oscillator. The converse can also occur.

FIGURE 19-8 Schematic of alterations in mPaw (*left side* of figure) between the oscillator circuit and lung using two different I:E ratios. Although mPaw values are relatively constant from the machine to the parenchyma with I:E = 1:1, mPaw decreases substantially along the endotracheal tube using an I:E = 1:2.[73,95] On the *right side* of the figure the peak-to-trough pressure amplitude (ΔP on the machine) is markedly dampened by passage through the endotracheal tube and airways to the alveoli. Oscillatory waveforms are drawn to scale using data from Sakai.[72] The associated table indicates multiple factors that reduce ΔP transmission into the lung.

Venegas and Fredberg[97] approached the question of optimizing frequency during conventional ventilation as a problem of providing adequate alveolar ventilation at minimal pressure cost in a variety of clinical scenarios. Their approach provided graphic depictions of the shifting boundary conditions for safe ventilator settings with varying lung pathology. Although the normal lung can be ventilated over a wide range of frequencies and PEEP levels without inducing dangerous overdistension, in the lung with poor compliance but relatively normal airways PEEP selection becomes critical during conventional ventilation, with penalties in terms of pressure cost and overdistension with either too low or too high a level of PEEP. At high frequencies, the zone of safe PEEP widens, making it easier to maintain more of the lung homogeneously aerated. In lungs with increased airways resistance, the optimal frequency moves to a lower rate. The relationship between frequency and the pressure cost of alveolar ventilation has been developed further by Pillow for HFOV.[70,71]

TIDAL VOLUME

Tidal volume delivery during HFOV is influenced by many factors (Table 19-1).[26,98] Adult HFOV initially used frequencies much lower than those used in infants and most animal experiments because machine power appeared inadequate to achieve CO_2 elimination at higher rates. Although the notion that HFOV delivers small tidal volumes has been challenged, newer data in adults suggest that very small tidal volumes can be delivered using adult HFOV, but at very low frequencies, tidal volumes may not be negligible.[96,99] For optimal lung protection, theoretically one should use the smallest tidal volume and highest frequency that achieves Pa_{CO_2} elimination targets. Fessler et al[100] studied thirty adult patients on HFOV after failing conventional lung-protective ventilation. CO_2 elimination was adequate in 83% of them using mean maximal frequencies of 9.9 ± 2.1 Hz. Introduction of a cuff leak is recommended before decreasing frequency below 7 Hz.[101] Even higher frequencies and small tidal volumes may prove preferable. The relative risk-to-benefit of early cuff leak versus lower frequencies requires further investigation.[85,102] Resonant amplification of the delivered volume has been demonstrated,[103,104] although at a median of 19 Hz in babies, well above rates used clinically.

TABLE 19-1: FACTORS DECREASING DELIVERED TIDAL VOLUME

- ↓ Endotracheal tube diameter (includes secretions, edema fluid)
- ↑ Endotracheal tube length
- ↑ Frequency (most HFOV devices)
- ↓ Power or amplitude
- ↓ Percent inspired time
- ↓ Respiratory system compliance

Although inability to eliminate CO_2 occurred in one of seventeen patients in the original report of Fort et al,[77] the incidence of ventilation failure (i.e., pH ≤7.15 with bicarbonate ≥19 mEq/L) was the same in both HFOV and conventional ventilation groups in the subsequent larger Multicenter Oscillatory Ventilation for Acute Respiratory Distress Syndrome Trial (MOAT)[82] and is rare if one follows current recommendations (see "Troubleshooting" below).

PHYSIOLOGIC EFFECTS OF HIGH-FREQUENCY OSCILLATORY VENTILATION

Cardiopulmonary Interactions

Much like high levels of PEEP on conventional ventilation, HFOV is a sensitive detector of intravascular hypovolemia. Patients need intravascular volume repletion before one initiates HFOV and optimizes lung volume. Fortunately, clinical experience and animal studies demonstrate that despite this need for an adequate volume status, treatment with HFOV does not induce "wet lungs."[105] Alveolar expansion has a powerful impact on pulmonary vascular resistance. Pulmonary vascular resistance goes up both in areas of atelectasis and overdistension. Therefore, the impact of HFOV on pulmonary artery pressure will be influenced strongly by the extent to which homogeneous alveolar expansion can be achieved. This varies with lung pathophysiology, decisions made about mPaw and recruitment techniques, and body position. In clinical experience, pulmonary hypertension secondary to the use of higher mPaw during HFOV has not been a problem. Rather, HFOV often has enhanced the responsiveness to inhaled nitric oxide in both infants and adults.[66,106–108] As with conventional lung-protective ventilator patterns, patients with preexisting right-ventricular failure need to be watched closely for the possible adverse effects of measures to optimize lung volume on right-ventricular output.

Cardiac output decreases as mPaw increases with any ventilator modality.[109] In early HFOV trials in the premature baboon, cardiac output was less during HFOV[45] unless mPaw was weaned as lung aeration improved.[110] Similar interactions of cardiac output and mPaw occur in infants.[111] Lesser hemodynamic impact can be expected when ventilating "on the deflation limb," where alveolar expansion can be maintained at a lower mPaw cost.[47,52] In adult clinical trials, such as the MOAT[82] and TOOLS[54] trials, there were no significant deleterious effects on mean arterial pressure, central venous pressure, pulmonary artery occlusion pressure, or cardiac output compared with conventional ventilation. Small (1 to 2 mm Hg), often transient increases in central venous pressure and pulmonary artery occlusion pressure were observed after transition to HFOV.[67] Echocardiography has proven useful to assess preload adequacy when clarification is needed.

Interaction with Spontaneous Breathing

Spontaneous breaths contribute forces that can help reexpand alveoli in dependent lung regions[112] and improve $\dot{V}_A/\dot{Q}$ distributions.[113–115] Forel et al,[116] however, reported a decreased proinflammatory response in patients given neuromuscular blocking agents for the first 48 hours. A subsequent larger trial found a 28-day mortality difference using lung-protective conventional ventilation with 48 hours of neuromuscular blockade.[117] With current HFOV circuit designs (i.e., the lack of an inspiratory demand flow), vigorous respiratory efforts in large patients may cause pressure swings that activate alarms, interrupt oscillations, and produce significant desaturations. For this reason, adults and large children need to have their respiratory efforts suppressed while on HFOV, and initial oscillator trials in adults recommended routine muscle paralysis. Current protocols attempt to balance the potential pros and cons of neuromuscular blockade in these patients by using paralysis when patients have extremely severe hypoxemia or are generating very large pressure swings despite adequate sedation.[41,85]

RATIONALE, ADVANTAGES, AND LIMITATIONS

If we accept that both overdistension and ongoing atelectasis damage lung tissue, then HFOV offers the ability to cycle the largest possible percentage of the total lung within that "safe" range of volume excursion. The key is to decipher exactly when small pressure and volume excursions will make a difference. All therapeutic advances in neonatal and pediatric ventilatory care over the past 30 years that have had a significant impacted on survival have exhibited one unifying feature: all have produced more homogeneous lung expansion (Table 19-2).

Advantages of High-Frequency Oscillatory Ventilation

It is much easier in theory than in practice to ventilate the lung within the safe zone of pressure and volumes in *all* lung regions.[118] Although much has been written about using

TABLE 19-2: PULMONARY THERAPIES DECREASING MORTALITY IN NEONATAL RESPIRATORY DISTRESS SYNDROME SINCE 1970

Early use of continuous positive airway pressure
Exogenous surfactant replacement therapy
HFOV/high-frequency jet ventilation with "optimized lung volume"
Conventional ventilation with "optimized lung volume" strategy

Note: All these produced more homogeneous lung aeration.

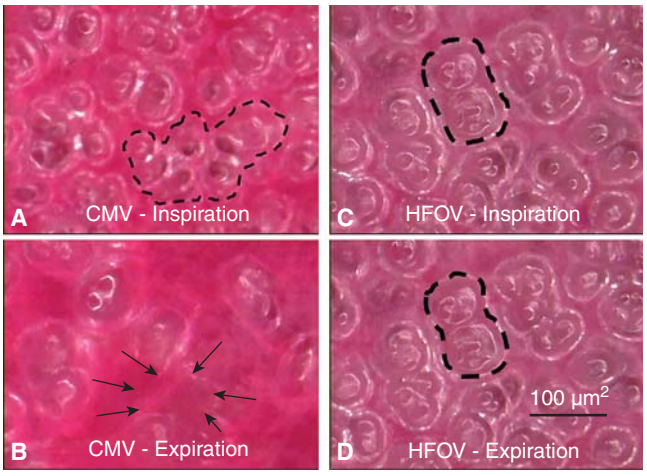


FIGURE 19-9 In vivo photomicrographs of subpleural alveoli of a rat after inducing lung injury by saline lavage. Animals were ventilated to equal oxygenation and targets using either conventional mechanical ventilation (*CMV*) or high-frequency oscillatory ventilation (*HFOV*). Alveoli in **A.** were inflated at end-inspiration during CMV to a peak pressure of 34 cm H_2O but collapsed during expiration **B.** with a PEEP of 9 cm H_2O (*arrows*). Alveoli were very stable during HFOV at a mean airway pressure of 19 cm H_2O. The same alveolus is seen at inspiration and expiration in panels **C** and **D** (*dots*). (Reproduced, with permission, from Lippincott Williams & Wilkins, Carney D, DiRocco J, Nieman G. Dynamic alveolar mechanics and ventilator-induced lung injury. *Crit Care Med.* 2005;33:S122–S128.)

the static pressure–volume curve of the respiratory system to guide ventilator settings, any single curve is only a crude composite of the family of pressure–volume curves occurring in different parts of the lungs. A safe peak or plateau pressure will be lower in nondependent and more normal lung regions; closing pressures will be higher in dependent, inflamed, or edematous regions than suggested by a single overall curve.[7,47,50,55,81] Studies in adults with acute lung injury and acute respiratory distress syndrome demonstrate that derecruitment often begins at PEEP levels substantially above the values recommended as protective of the lung.[7,119] As one raises PEEP, even acceptable degrees of permissive hypercapnia may be unattainable without exceeding safe peak and plateau pressures at conventional ventilator rates. In such patients, HFOV has the potential to keep that lung in the safe zone with a much larger margin of safety simply because of its ability to sustain gas transport with small volume cycles (Fig. 19-9).[38] This is particularly so at higher frequencies because of the impact of time-constant variability on alveolar filling.

A very old but elegant study demonstrated some fundamental features of lung reexpansion risk.[120] In essence, unless one exceeds airway/alveolar opening pressures, reexpansion will not occur. If one exceeds opening pressure with a long inspiratory period, atelectatic areas open, but normal areas become overdistended. Even very high pressures, however, will not overdistend normal lung if applied very briefly (<0.15 second in this study) because the time constant of highly compliant alveoli is long. Therefore, pressures high enough to exceed opening pressures are safer if applied as brief pulses, as with HFOV. As one turns down the frequency, this safety feature diminishes.

Lung-volume optimization and outcomes equivalent to HFOV have been achieved using recruitment maneuvers followed by rapid conventional ventilation with careful PEEP titration in saline-lavaged animal models.[121–123] Whether this equivalency extends to more established disease with greater inhomogeneity of opening and closing pressures has not been tested.

Limitations

Most of the perceived limitations of HFOV currently are really limitations of the machines available rather than the technique per se. Even minor modifications trigger expensive Food and Drug Administration (FDA) approval processes. Consequently, oscillator design in North America has been frozen for years.

INCREASED USE OF MUSCLE PARALYSIS

The adult-size oscillator currently available in North America does not support concurrent spontaneous ventilation. Infants and children are rarely paralyzed during HFOV. Paralysis of adults on HFOV can be minimized by titrating sedative agents, using higher bias flows to minimize air hunger, and reserving paralytic agents for as-needed bolus use rather than constant infusions.[41,85,124] Shallow breathing is tolerated in some adults without significant desaturation, particularly during the recovery phase of their disease. Currently, the lack of demand flow to augment spontaneous breaths requires adults to be transitioned to conventional ventilation for final weaning and extubation.[85]

INFECTION CONTROL

The lack of an expiratory filter initially limited the use of HFOV in patients with infections such as severe acute respiratory syndrome. A suitable filter on the expiratory limb of the circuit is now available (CareFusion, Yorba Linda, CA).

AEROSOL DELIVERY

Metered-dose inhalers are ineffective during HFOV. The Aeroneb nebulizer (Aeroneb Pro, Aerogen, Sunnyvale, CA) delivered the highest percentage of drug in test lung studies.[125]

TRANSPORT DURING HIGH-FREQUENCY OSCILLATORY VENTILATION

It is simplest to execute anticipated transports, such as for computed tomography scan, before starting HFOV, as there is no transport version of HFOV. Many patients receiving HFOV as rescue therapy may be too unstable to transport out of the intensive care unit unless absolutely indicated.

Cartotto et al[66] describe an effective protocol for transport during HFOV, such as to the operating room. It involves clamping the endotracheal tube while on HFOV, transitioning to a self-inflating bag with a 20 cm H_2O PEEP valve, unclamping of the endotracheal tube with vigorous manual ventilation during transport, and reversing these procedures once an oscillator has been set up at the destination. Recruitment maneuvers then are used as needed to reestablish oxygenation at the pretransport HFOV settings.

MONITORING

HFOVs have few ventilator alarms to alert one to a mainstem intubation, tension pneumothorax, or endotracheal tube obstruction. Patterns of possible changes in ventilator readouts with such events have been modeled.[85] This lack of monitoring on the ventilator makes it critical that clinicians pay attention to both the monitors and the general condition of the patient on HFOV (arterial oxyhemoglobin saturation, heart rate, blood pressure, and so on), and ensure that patients have symmetric chest movements with the oscillations. Absent chest wall movement suggests endotracheal tube obstruction or other ventilator malfunction, while asymmetry may indicate a pneumothorax or mainstem bronchus intubation; sudden increases in ΔP may be seen in both these situations. Also, ventilator noise necessitates brief piston interruption to auscultate heart or breath sounds.

UNFAMILIARITY OF PERSONNEL

A major limitation to the use of HFOV is the level of discomfort of personnel (i.e., physicians, respiratory therapists, and nurses) who encounter it rarely, often as a therapy of last resort.[126] If one does not understand that a mean pressure of 35 cm H_2O that is stenting 70% to 80% of a stiff lung open while supporting CO_2 elimination with small volume cycles may well induce less lung injury than a PEEP of 15 cm H_2O, plateau pressure of 30 cm H_2O, and larger tidal volumes being distributed to 30% to 40% of that lung, then HFOV "feels" dangerous. Only experience gained in less dire circumstances can produce a comfortable level of understanding of the interaction of ventilator decisions and lung pathophysiology. Then, and only then, can one really test the applicability of any high-frequency modality.[102]

PROTOCOL AND ALGORITHM LIMITATIONS

When protocols are generalized to patients outside the population on which the protocol was devised, HFOV may be used inappropriately. Several HFOV protocols specify maximum mean airway pressure limits that were derived in patients with primary pulmonary diffuse airspace disease. If these limits are applied to patients with major extrapulmonary factors, such as abdominal distension or chest wall burn eschar, adequate atelectasis reversal is unlikely because 30% to 70% of the applied mPaw will be lost to inflate the chest wall.[81]

INDICATIONS AND CONTRAINDICATIONS

Indications

Is HFOV still needed in the current era of "gentler" conventional ventilation? When HFOV first came into clinical use, large tidal volumes were considered safe during conventional ventilation as long as high peak pressures were avoided.[11] In this milieu, randomized, controlled trials in neonates demonstrated substantial outcome advantages from HFOV.[127] Conventional ventilator protocols then were modified to pursue the same lung protection.

In two recent randomized neonatal studies, significant differences between lung-volume optimizing HFOV and conventional ventilation protocols were seen only in the study in which just 40% of the infants meeting very-low-birth-weight criteria were randomized. These neonates required an FI_{O_2} of approximately 0.6 on an mPaw of 8 cm H_2O. In this trial, more neonates managed with HFOV (until extubation) survived without chronic lung disease and were extubated successfully 1 week earlier than were neonates receiving lung-protective ventilation at conventional frequencies.[60] When all very-low-birth-weight babies were randomized regardless of O_2 requirements, and on HFOV for only 72 hours, outcome with both ventilators was the same.[59] This neonatal experience reflects the predictions of the Venegas-Fredberg analysis.[97] If the lung is fairly normal, a wide range of tidal volumes, PEEP levels, and frequencies can be used without inducing atelectasis or overdistension. Ventilator choice becomes a matter of user preference. As the lung becomes more prone to atelectasis, the range of safe PEEP values shrinks, and injurious extremes of alveolar volume are avoided more reliably at higher frequencies. These are the lungs in which HFOV improves outcome.

NEONATAL AND PEDIATRIC PATIENTS

Current criteria for using HFOV vary among institutions. Experience in animal models, infants, and children has demonstrated the importance of instituting HFOV early in the lung at risk.[58,79,80,128,129] Increasingly, extremely low-birth-weight neonates are switched to HFOV as their first-intention ventilator in the presence of a rising FI_{O_2} requirement, Pa_{CO_2} greater than 60 mm Hg and/or falling aerated lung volume.[53,60,130,131] (Courtney SE, personal communication.) A postrecruitment FI_{O_2} of less than 0.30 is taken as evidence of adequate alveolar reexpansion following early institution of HFOV.[62,130]

Tissieres et al[131] found that 41.7% of neonates managed with early lung recruitment on HFOV achieved adequate oxygenation without exogenous surfactant, required shorter periods of ventilator support, and had a lower incidence of hemodynamically significant patent ductus. In pediatric patients, Duval et al[126] switched to HFOV at an oxygenation index greater than 13 or a pH less than 7.25 despite

a bicarbonate level of 20 mmol/L or greater and peak pressures of more than 30 cm H_2O. In older children, Doctor and Arnold[132] recommend institution of HFOV if an "open-lung strategy" using conventional ventilation generates a peak pressure of greater than 35 cm H_2O despite permissive hypercapnia or mPaw values approach 15 to 18 cm H_2O and the FI_{O_2} still exceeds 0.6.

Pulmonary hypertension occurs frequently in neonates. It can generally be reversed using HFOV (or high-frequency jet ventilation) to achieve better CO_2 elimination and normalize pH values. Randomized, prospective studies indicate that when inhaled nitric oxide is needed, therapeutic response is improved with concurrent institution of HFOV in both neonates and children.[108,133,134] All these guidelines represent an attempt to define the characteristics of a lung for which HFOV might be more protective than a conventional lung-protective strategy.

ADULT PATIENTS

Indications for HFOV are evolving in adult lung disease. These generally fall into two categories: first, use of HFOV when the patient is failing conventional therapy, either because of frank desaturations on high FI_{O_2} or the requirement of high airway pressures to achieve adequate gas exchange (Fig. 19-10). Second, use of HFOV for the primary prevention of ventilator-induced lung injury, in patients with severe acute respiratory distress syndrome. Although it may not be an independent predictor of mortality,[135] a consistent theme for both indications is that survival is better with early (<3 days) rather than late (>7 days) institution of HFOV.[65,77]

Clinicians typically turn to HFOV as a potential therapy[77,78,136] in the difficult-to-oxygenate patient when FI_{O_2} is above 0.8 despite a trial of high PEEP. In this setting, data from observational studies and randomized controlled trials suggest that HFOV is safe and effective in improving oxygenation.[85,101,102] Whether HFOV is more effective than lung-protective conventional ventilation at preventing ventilator-induced lung injury and reducing mortality remains a question for debate. The largest randomized controlled trial comparing HFOV with conventional ventilation in adults published to date (N = 148) found a trend toward improved mortality with HFOV (absolute risk difference: 0.15; $p = 0.1$).[82] The tidal volumes used in the control arm of this trial exceeded current recommendations. This may have contributed to excess mortality in the control arm.

Recently, all of the randomized controlled trials comparing HFOV to CV have been summarized in a metaanalysis (eight trials; $N = 419$).[15] Although none of the trials individually showed a mortality benefit, the combined results suggest a statistically significant reduction in mortality (relative risk [RR] 0.77; 95% confidence interval [CI] 0.61 to 0.98; $p = 0.03$). We view this as a hypothesis-generating result, given that it is a meta-analysis of several small trials, many with methodologic problems.

In experienced centers, a trial of HFOV may be considered when the FI_{O_2} requirements remain greater than 0.6, the plateau pressure approaches 30 cm H_2O, and PEEP is 10 to 15 cm H_2O.[85,101,102] The current challenge is to define the pulmonary characteristics that indicate that the lung is at risk of ventilator-induced lung injury using conventional ventilation and then to test whether HFOV is of benefit in

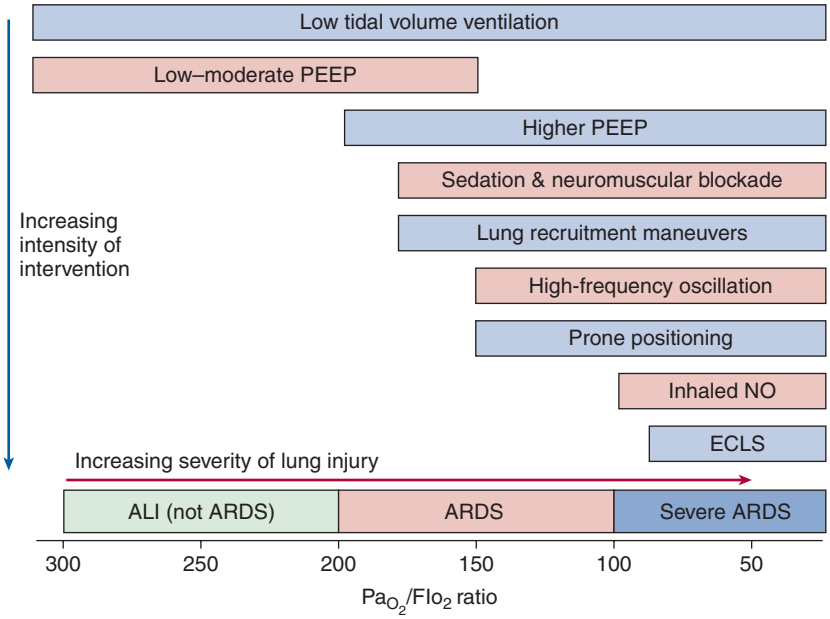


FIGURE 19-10 Schematic of various therapies for acute lung injury and acute respiratory distress syndrome and their applicability across the spectrum of disease severity. Some interventions (e.g., low tidal-volume ventilation) are broadly applicable, whereas others, such as extracorporeal life support (ECLS) and inhaled nitric oxide (iNO), should be reserved for the most severely hypoxemic patients.[16,17]

that population. The goal is to identify a group of patients with a significant inflammatory lung injury who may benefit from lung recruitment. Indicators such as PEEP responsiveness,[137] dead-space measurements,[138] and biomarkers[139] are being explored. Until additional information becomes available, indications are that it is patients with the most severe lung injury who are likely to be the most recruitable and most at risk for ongoing ventilator-induced lung injury with lung-protective conventional ventilation.[6,76] Indicators ideally would include an accurate bedside method to determine the extent of inhomogeneity of alveolar expansion across lung regions, both at end inspiration and at end expiration.[47,81,87]

Contraindications

Early literature advised against the use of HFOV in obstructive airway diseases, such as asthma, because of the theoretical risk of inadvertent gas trapping and hyperinflation. Recent reports demonstrate that HFOV can be used in such patients, even in patients demonstrating gas trapping on conventional settings. Case reports of patients with severe asthma and a series of infants with respiratory syncytial virus infection with severe bronchiolitis describe what is being termed the *open-airway strategy* for the management of such patients.[36,140] The goal in these patients is to find the narrow window of mean airway pressure that stents the diseased airways open enough to support high-frequency gas transport without inducing excessive lung distension with hemodynamic impairment. Extensive experience with HFOV is recommended before one pursues this application.[36] HFOV remains contraindicated in localized airway obstruction or bullous disease.

Before development of an expiratory gas filter, severe acute respiratory syndrome and other highly contagious airborne pathogens were a relative contraindication to HFOV.[141]

COMPARISON WITH OTHER MODES

Limited comparisons are available among various high-frequency modalities. When high-frequency jet ventilation was introduced into adult and neonatal use, the primary goal was to support gas exchange at the lowest possible peak and mean airway pressures to facilitate resolution of barotrauma. When HFOV was introduced in an early neonatal clinical trial, the primary goal was to optimize the volume of aerated lung. Both devices, in fact, can be used with either a low-pressure or open-lung strategy.[58] The strategy must be matched to the patient's pathophysiology. Only one study systematically compared three high-frequency options in an animal model of the atelectasis-prone lung.[142] Optimal outcome occurred with the mode (HFOV) in which the end-expiratory pressure was closest to the mean pressure level and the least time was spent at the end-expiratory level.

VARIATIONS IN DELIVERY

The performance of several commercially available devices for delivery of HFOV to neonates has been evaluated both in bench studies and in animal models. Substantial differences in performance have been demonstrated.[73,74,143] Any ventilator introduced into an intensive care unit should be thoroughly understood before clinical use. For example, all neonatal ventilators tested by Hatcher et al[73] and Pillow et al[74] showed a decrease in delivered volume with a decrease in lung compliance, but one ventilator (no longer available) exhibited the reverse phenomenon.[143] That outlier characteristic may explain puzzling episodes of hypercapnia during the weaning of infants with that ventilator. One ventilator failed to increase delivered volume at settings between 50% and 100% of its amplitude dial. It also was the only ventilator that markedly increased tidal volume as mean pressure increased.[73,143] Ventilators varied in the relationship of displayed mPaw and intrapulmonary mean pressure measured during endotracheal tube occlusion.[73] Threefold differences were documented in maximum tidal volume among ventilators tested at 15 Hz,[73,74] and frequency dependence of tidal volume varied substantially. It is amazing that HFOV has been used as safely and effectively as it has considering these major discrepancies in ventilator performance among the devices used.

At the time or writing, only one oscillator is approved in the United States and Canada (it is also available in Europe) for use in adults and large children (SensorMedics 3100B, CareFusion, Loma Linda, CA). Another device is approved in Europe and Japan, marketed as the Vision α (Novalung, Baden-Württemberg, Germany) or the R100 (Metran Corporation, Tokyo, Japan). In contrast to the 3100B, the Vision α also provides the ability to deliver several conventional modes of ventilation with the same circuit. The two devices also differ in how they generate and modulate the oscillatory waveforms during HFOV. We are not aware of any published studies comparing the technical or clinical performance of these two oscillators.

ADJUSTMENTS AT THE BEDSIDE

Preparation for Initiation of High-Frequency Oscillatory Ventilation

Table 19-3 lists suggested strategies for management of HFO in adults with recent-onset acute lung injury and acute respiratory distress syndrome.

Documentation of a patent endotracheal or tracheostomy tube is essential.[41] Partial obstructions impede gas transport much more during HFOV than with conventional modes. Tubes that allow passage of a suction catheter still may have a narrow lumen. If the patient has been intubated for more than 2 or 3 days, a preemptive bronchoscopy may be useful to verify tube patency as well

TABLE 19-3: SUGGESTED STRATEGIES FOR MANAGEMENT OF HIGH-FREQUENCY OSCILLATION IN ADULTS WITH RECENT-ONSET ACUTE LUNG INJURY AND ACUTE RESPIRATORY DISTRESS SYNDROME

	Titration Using a mPaw/FI_{O_2} Table	Alveolar Reexpansion Given Priority
Initial Settings	FI_{O_2} 1.0; mPaw 30 to 35 cm H_2O; I:E 33%; amplitude (ΔP) = 90 cm H_2O; frequency based on recent pH	
O_2 Management	• Initial RM (40 cm $H_2O \times 40$ s) ± repeat RM • Use mPaw/FI_{O_2} table to decrease both concurrently • Move up or down mPaw/FI_{O_2} table as needed according to SpO_2 • Repeat RM before increases in mPaw to >25 cm H_2O • Repeat RM for hypoxemia with disconnects etc.	• Initial RM (40 cm $H_2O \times 40$ s) ± repeat RM • Increase RM pressure and mPaw as needed to decrease required FI_{O_2} balancing pressure cost vs. recruitability • Hold mPaw that maintains oxygenation after RM • Wean FI_{O_2} until = 0.4 • Wean mPaw incrementally as long as FI_{O_2} stable • Repeat RM before any increases in mPaw • Repeat RM for hypoxemia with disconnects etc.
CO_2 Management	• Target pH 7.25 to 7.35 using highest frequency (*f*) possible; maintain ΔP = 90 cm H_2O • Consider a partial endotracheal tube cuff leak if $f \leq 6$ Hz	
Transition to CV	• Convert when $FI_{O_2} = 0.4$, mPaw = 20 to 24 cm H_2O and stable >12 hours • Initial settings: V_T 6 mL/kg PBW; FI_{O_2} 0.5; PEEP 16; RR 25	
Return to HFO	• Return to HFO if required $FI_{O_2} \geq 0.6$ to 0.7 on PEEP ≥14 • Return to HFO if pH <7.25 with V_T 6 mL/kg PBW and P_{PLAT} >30 cm H_2O	• Return to HFO if $FI_{O_2} \geq 0.5$ on above settings • Return to HFO if pH <7.25 on above settings

Abbreviations: CV, conventional ventilation; *ΔP,* oscillatory pressure amplitude; FI_{O_2}, fractional inspired oxygen concentration; *HFO,* high-frequency oscillation; *I:E,* inspiratory-to-expiratory ratio; *mPaw,* mean airway pressure; *PBW,* predicted body weight; *PEEP,* positive end-expiratory pressure; P_{PLAT}, inspiratory pressure plateau; *RM,* recruitment maneuver; SpO_2, oxygen saturation; V_T, tidal volume.

Note: This table outlines an overall approach while indicating areas in which different experts use somewhat different decision algorithms.

Source: Modified, with permission, from Fessler HE et al.[101]

as provide opportunity for removal of any mucus plugs. Hypovolemic patients will not tolerate the high mPaw used with HFOV; adequate volume status should be ensured before initiating HFOV.

Sedative and analgesic drugs should be titrated while the patient is still receiving conventional ventilation. Although muscle paralysis was used in most adult published trials, subsequent experience has found continuous paralytic infusions unnecessary in many cases when appropriate levels of sedation are established.[41,101] Small as-needed doses of muscle relaxants may facilitate the initial period of adjustment to HFOV and may be needed intermittently during periods of agitation to facilitate retitration of sedative and analgesic agents.[85,124] Preservation of some spontaneous respiratory effort is valuable, as with any type of prolonged ventilation, provided those efforts do not produce marked fluctuations in mPaw (>5 cm H_2O) or O_2 saturation (>3% to 5%). Careful observation for spontaneous breathing following transition to HFOV allows proper adjustment of high-pressure and low-pressure alarms. Patient comfort may be enhanced when bias flows of 40 to 60 L/min are used to achieve the target mPaw in adults.

Oxygenation

The approach used in most early algorithms and trials initiated HFOV with an FI_{O_2} of 1, an mPaw 5 cm H_2O higher than the mean pressure on conventional ventilation, and a 33% inspiratory time. Inability to reduce the FI_{O_2} below 0.6 was managed primarily with stepwise increases in mPaw, in essence gradually moving the respiratory system up the inflation limb of the pressure–volume relationship. More recent protocols apply one or more lung-recruitment maneuvers when HFOV is initiated, along with rapid upward titration of mPaw, with the goal of optimizing alveolar reexpansion to place the lung on the deflation limb.[54,101] Starting mPaw levels of 30 to 35 cm H_2O are now recommended in moderate to severe acute respiratory distress syndrome. Table 19-3 highlights two current approaches to optimizing oxygenation during HFOV.[101] Both utilize initial recruitment maneuver(s) but then differ on whether both mPaw and FI_{O_2} should be reduced in tandem (using a table) or whether measures to reduce FI_{O_2} should take priority over mPaw reduction (with FI_{O_2} being used as a surrogate measure of alveolar reexpansion).[101]

Recruitment maneuvers are performed by resetting the high-pressure alarm to a higher value (e.g. 50 cm H_2O), eliminating a cuff leak if present, turning off the piston, raising the mPaw slowly to 40 to 45 cm H_2O (maximum 50 cm H_2O) for 40 to 60 seconds, returning the mPaw to the original setting (or 3 cm H_2O higher), and then restarting the piston and restoring cuff leak and alarms to the original levels. Recruitment maneuvers should be considered if desaturation occurs after suctioning, bronchoscopy, circuit disconnects, or patient repositioning.

In the TOOLS trial, one to three recruitment maneuvers were performed immediately on initiating HFOV.[54] This methodology matches protocols used in many animal studies of lung protection using HFOV. With this protocol, an FI_{O_2} of less than 0.6 was achieved in 68% of patients by the end of the initial recruitment cycle, which delivered a mean of 2.4 recruitment maneuvers over 1.5 hours.

With both approaches, the accepted target has been projection of the diaphragm onto the eighth or ninth rib posteriorly on an anteroposterior film. An alternative reference in adults is visualization of the fifth rib above the diaphragm anteriorly or an apical diaphragm distance not greater than 25 cm.[144] Emerging techniques for the evaluation of regional expansion hopefully will soon replace these crude measures.[87] Information on the relative timing, efficacy in terms of achieving the most homogeneous lung expansion pattern, and complication rate of these two approaches is needed before it will be possible to define an "optimal" approach. The potential hazard of the first approach is too little recruitment too slowly. The potential hazard of the second approach is excessive lung distension at a rote value of 30 cm H_2O mPaw if that value is not reduced expeditiously enough in a lung that is very responsive to recruitment. What is becoming clear is the importance of ventilating "on the deflation limb," whether with conventional ventilation or with HFOV.[52,145]

It remains speculative whether the target FI_{O_2} for optimal lung protection should be 0.4 or 0.6. A substantial amount of ongoing atelectasis remains at an FI_{O_2} of 0.6. As one moves toward an earlier transition to HFOV—as in current neonatal and pediatric experience in many centers—lower FI_{O_2} targets become achievable at "reasonable" mean pressures. At high FI_{O_2} requirements, mPaw levels are reduced only when doing so does not increase FI_{O_2} requirement. When the FI_{O_2} is stable at 0.6, some protocols recommend reduction of mPaw before further FI_{O_2} decreases if the mPaw is greater than 35 cm H_2O. Whether this compromise between ongoing atelectasis and the risk of higher pressures is optimal will likely only be resolved when bedside methods of assessing areas of overdistension become available. One protocol that recommends this mPaw/FI_{O_2} compromise also recommends placing the patient in a prone position if the FI_{O_2} requirement remains 0.6 or more in order to potentiate alveolar recruitment in dorsal lung regions.[41]

Carbon Dioxide Elimination

The optimal approach to CO_2 elimination remains controversial. When should the transport advantages of an endotracheal tube cuff leak be introduced? Inasmuch as the lung-protective potential of HFOV lies in its small volume cycles, it would seem logical to introduce it at the time of initiating HFOV in a large patient. With a cuff leak of 5 to 8 cm H_2O, one can eliminate CO_2 at a higher frequency, deliver the smallest possible tidal volumes, and produce the lowest possible ratio of intratracheal to airway opening pressure swings.[84,96] With this approach, even very heavy patients generally can be ventilated at frequencies of 6 Hz or more. If reductions in frequency are required at any stage, the first response to a decrease in Pa_{CO_2} with recovery should be an increase in frequency. Whether the frequency target in adults should be 8 Hz or higher is presently unknown. Detailed protocols differing in their relative weighting of amplitude (ΔP) and frequency are available.[85,101,102]

An alternative approach is progressive reduction of frequency to 3 Hz as needed to achieve target CO_2 levels, with a cuff leak being added only when these much larger stroke volumes prove inadequate.

The advantage of instituting a cuff leak when initiating HFOV is the ability to use higher frequencies and smaller volume cycles. The disadvantages are a need for more nursing care to ensure removal of oral secretions and respiratory therapy involvement to remove and then reset the cuff leak whenever a recruitment maneuver is performed. Endotracheal tubes with infraglottic suction ports may prove useful in this context. In cases of severe upper airway swelling, a pharyngeal airway positioned just above the larynx can be used to provide an exit pathway for a cuff leak, as described by Cartotto et al[66] in a burn patient. Failure of mPaw to drop when instituting a cuff leak indicates swelling around the cuff or upper airway.

Protocols also differ in their approach to setting power or ΔP. Some advocate starting at maximal power so that one can use the highest frequency possible;[101] other algorithms manipulate both ΔP and frequency settings.[41,85] Current protocols favor targeting a relatively high and constant ΔP to enable one to use the highest possible frequency to deliver the lowest tidal volume and smallest intrapulmonary pressure swings that can achieve adequate CO_2 elimination. Transcutaneous P_{CO_2} sensors can provide useful trend information (not absolute values) to guide frequency adjustments during the initiation phase if rapid point-of-care blood-gas analysis is unavailable. Tighter Pa_{CO_2} targets are needed in patients with elevated intracranial pressure, as well as in neonates in whom the risk of retinopathy of prematurity may increase at high Pa_{CO_2}[8] while low Pa_{CO_2} levels produce neurodevelopmental deficits.[146,147]

Patient Positioning

Patients should be placed at 30 degrees head up unless hemodynamically unstable. The prone position also can be used during HFOV to optimize expansion of dorsal lung regions, with appropriate protocols for caring for the prone patient.[148] If the prone position is not feasible but hypoxemia remains severe, switching the patient from side to side in true lateral positions (i.e., 90 degrees to the mattress) may sometimes improve lung recruitability.

TABLE 19-4: Pa_{CO_2} PROBLEMS

Pa_{CO_2} Too Low	Pa_{CO_2} Too High	Acute Increase in Pa_{CO_2}
↑ *f* in increments of 1 to 2 Hz to 8[90] or 12 Hz[89]	↑ ΔP if not already at 90 cm H_2O in increments of 5 cm H_2O	Verify ETT is patent: • Pass suction catheter • Quick bronchoscopy • Can one ventilate adequately with manual bag/mask?
↓ ΔP in 5 cm H_2O increments	Institute a cuff leak if not present	Is there a pneumothorax? • Decreased vibrations unilaterally? • CXR
	Try RM(s) to reverse atelectasis Is a higher maintenance mPaw needed? (CXR or other measure of lung volume) ↓ *f* to a minimum of 3 Hz in 1 to 2 Hz decrements	Progressive Increase Pa_{CO_2} Is chest wall compliance decreasing? • Abdominal compartment syndrome • Burn eschar

Abbreviations: CXR, chest X-ray; *ΔP,* oscillatory pressure amplitude; *ETT,* endotracheal tube; *f,* respiratory frequency; *RM,* recruitment maneuver.

TROUBLESHOOTING

Partial Pressure of Arterial Carbon Dioxide Problems

It is particularly important to troubleshoot Pa_{CO_2} problems appropriately (Table 19-4).

DECREASED PARTIAL PRESSURE OF ARTERIAL CARBON DIOXIDE

As Pa_{CO_2} levels decrease during the course of lung recovery, the first response should be to increase frequency back up to the 8- to 10-Hz range (1- to 2-Hz increments) and then to decrease power (5 to 10 cm H_2O ΔP decrements) in order to minimize volume and pressure swings in the lung. A decrease in ΔP at a constant power setting may be an indicator that lung volume is increasing.

INCREASED PARTIAL PRESSURE OF ARTERIAL CARBON DIOXIDE

An abrupt substantial increase in Pa_{CO_2} in a previously stable patient may reflect plugging of the endotracheal tube, development of a pneumothorax, or atelectasis. One should ensure passage of a suction catheter, check one's ability to manually bag or mask ventilate, and perform a quick bronchoscopy while waiting for a chest X-ray to clarify the etiology. Before decreasing frequency or increasing power in response to a gradual increase in Pa_{CO_2}, one must ensure that the lung is expanded adequately. An abdominal compartment syndrome should be considered. Available oscillators all decrease delivered stroke volume when faced with a greater load.[73,74] Appropriate recruitment procedures often can resolve Pa_{CO_2} problems, while at the same time decreasing the phasic pressure swings within the airways and alveoli. A cuff leak should be considered before lowering frequency.

Oxygenation Problems

As discussed earlier, oxygenation depends on achieving and then maintaining end-expiratory lung volume. A gradual downward drift of O_2 saturation after a recruitment maneuver is indicative of too low a maintenance mPaw. Recruitment should be repeated with a return to an mPaw 2 to 3 cm H_2O higher than the previous level. If the FI_{O_2} requirement remains greater than 0.60 despite recruitment maneuvers, prone positioning should be considered.[16] Inhaled nitric oxide can be added, although whether this improves outcome as well as oxygenation remains unknown.[108] In the severely hypoxemic patient, HFOV is one of a number of recommended techniques (see Fig. 19-10).[16,17]

Air Leaks

Barotrauma occurs at similar frequencies during HFOV as with conventional ventilation, but may be more subtle in its manifestations. Displayed mPaw will remain stable even with a tension pneumothorax. The gradual development of hypotension and desaturation, with or without a unilateral decrease in chest wall motion, should trigger a portable chest X-ray. In an experimental model of pneumothorax during HFOV, air leak was minimized by the use of higher frequency, lower ΔP, lower mPaw, and shorter inspiratory period.[149] Excessive decreases in mPaw will promote atelectasis with a resulting increase in intrapulmonary pressure cost, delaying resolution of the air leak. In general, recruitment maneuvers are not advised in the presence of air leak, but this is not an absolute contraindication. In the presence of severe hypoxemia and unilateral air leak, recruitment

maneuvers performed with the patient in a full lateral position with the leak side down may achieve significant benefit by reexpansion of the nondependent lung.

Hemodynamic Compromise

Inability to tolerate the institution of HFOV or application of recruitment maneuvers may reflect an inadequate intravascular volume. Duval et al[140] reported a need for a transient increase in fluids and inotropic agents in some infants during transition to HFOV. Interpretation of filling pressures (central venous pressure, pulmonary artery occlusion pressure) may be difficult in the setting of high mPaw. A fluid challenge, cardiac echo study, or other assessment of cardiovascular status may be needed in ambiguous situations.[41]

IMPORTANT UNKNOWNS

HFOV protocols are under constant revision through animal experiments and clinical trials that evaluate both the gas exchange and ventilator-induced lung injury impact of ventilator setting decisions. We need criteria that indicate when any given ventilator pattern needs to be replaced by one with a greater potential for lung protection. This is a complex question considering that we do not even know when permissive hypercarbia becomes deleterious for patients.

The optimal frequency or frequencies for minimizing the intrapulmonary pressure and distension "cost" of HFOV in the adult lung with varying pathophysiologies remain unknown. Such information would clarify the risk-to-benefit ratio of early use of a cuff leak. Existing algorithms differ substantially in their management of frequency.[85,101]

Optimal methods of aerosol delivery during HFOV need further evaluation. Better bedside knowledge of which techniques (e.g., recruitment maneuvers, ventilator settings, position changes [prone/supine], and so on) produce the most homogeneous lung expansion across all lung regions would greatly aid decision making. Emerging technologies, such as electrical impedance tomography, show promise.

Neonates often are maintained on HFOV until extubation. Premature transition to conventional ventilation can negate the benefit of HFOV. Currently spontaneous breaths are not augmented during HFOV, so this approach is not feasible in large patients. This may change if demand flow is incorporated into new versions of this device.[150] The "optimal" timing of transition to conventional ventilation may be difficult to determine until this device limitation is resolved. It is well recognized that gross deterioration of oxygenation after transition to conventional ventilation should trigger an immediate reevaluation of the patient and possible return to HFOV.

FUTURE DIRECTIONS

Two large multicenter, randomized, controlled trials are currently underway comparing HFOV to conventional ventilation: OSCILLATE (ISRCTN87124254) and OSCAR (ISRCTN10416500). The OSCILLATE trial (target $N = 1200$) attempts to optimize lung volume "on the deflation limb" of the pressure–volume relationship and is recruiting patients from centers with significant experience with HFOV. The OSCAR trial (target $N = 1006$) employs a more traditional stepwise increase in mPaw (walking up the inflation limb of the pressure–volume curve), and is also assessing the applicability of HFOV as a novel technology in inexperienced centers. Currently, many centers use HFOV rarely and only for severe, refractory oxygenation failure or air-leak syndromes associated with end-stage lung disease. This is not the way to develop a cadre of physicians, nurses, and respiratory therapists who can skillfully troubleshoot interactions between the machinery and the patient's pathophysiology.

Redesigned Machines

Currently, high-frequency oscillators are still classified as class 3 devices by the FDA. This means that any redesign triggers expensive review costs, much in excess of that required for bringing a new conventional ventilator to market. Revision of this classification would greatly facilitate improvements in device design.

Clinical Lung-volume Monitoring

Developments in this area should take a lot of guesswork out of lung-volume optimization during both conventional and high-frequency ventilation. Hopefully, future guidelines for the initiation of HFOV will be able to include some measure of interregional inhomogeneity of alveolar expansion as one of the criteria, not just a plateau pressure, FI_{O_2}, or pH value.

SUMMARY AND CONCLUSION

High-frequency ventilators expand our ability to minimize both atelectrauma and overdistension injury in the vulnerable lung. Evidence of the benefits of early institution rather than late "rescue" use is growing. Optimal use requires constant attention to the interplay between the patient's pathophysiology and machine factors to keep the lung in its "safe zone." The full potential of HFOV will only be clarified when well-controlled randomized clinical trials are done that incorporate both early intervention and lung recruitment protocols that rapidly place the lung on the deflation limb of its pressure–volume relationship. Such trials need to compare HFOV to the lung-protective conventional ventilation protocol considered optimal at the time of study.

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EXTRACORPOREAL LIFE SUPPORT FOR CARDIOPULMONARY FAILURE

Heidi J. Dalton
Pamela C. Garcia-Filion

DEFINITION AND HISTORY

Extracorporeal life support (ECLS) is defined as total or partial diversion of a patient's circulating blood volume into a device that can act as a "lung," providing oxygenation and carbon dioxide removal, and a pump, which can act like a "heart," providing circulatory support, or a combination of both functions for patients suffering from both cardiac and pulmonary failure. Adapted from heart-lung machines used for cardiopulmonary bypass, this temporary form of support was termed extracorporeal membrane oxygenation (ECMO) in the past.[1–4] Because of vast changes in the circulatory devices now available and the patient populations being treated, however, the term ECMO is being replaced by ECLS as the designation for extracorporeal life support of a variety of indications and devices. Both are used interchangeably in the chapter. Figure 20-1 shows an example of an early cardiopulmonary bypass circuit.

ECLS was first developed to provide respiratory support in premature infants who had inadequate lung development to support gas exchange compatible with life. Difficulties with intracranial hemorrhage secondary to the heparinization required to prevent clotting of the artificial membrane lung and the circuit, however, caused ECLS to quickly fall out of favor in this population. Work continued, and following the development of the silicone-membrane oxygenator by Kolobow and others, ECLS was successfully applied to term newborns with respiratory failure.[5,6] One of the first of these patients was a newborn named Esperanza (which means hope) by the neonatal intensive care unit nursing staff who were caring for her at the University of California at Irvine in 1976. Esperanza had hypoxemia secondary to what we now would call persistent pulmonary circulation of the newborn. Dr. Robert Bartlett and colleagues were doing research on ECMO at the University of California at Irvine and were contacted for assistance with Esperanza. Their laboratory device was quickly approved by the institutional review board for emergency use, and adapted and applied in an attempt to save Esperanza. The procedure worked well and Esperanza is now a grown woman with children of her own. Following this event, other centers reported success in the use of ECLS in newborns with respiratory failure from diseases such as meconium aspiration syndrome, persistent pulmonary hypertension, and congenital diaphragmatic hernia.[7–10]

This initial success was met with some skepticism, and a randomized controlled trial of ECMO or ECLS versus conventional ventilation was undertaken in newborns with persistent pulmonary hypertension in the late 1980s. This was a two-phase project: if excessive mortality or

FIGURE 20-1 Early cardiopulmonary bypass circuit. (Courtesy of Heidi Dalton MD, with permission.)

benefit was noted in one group, the next twenty patients would be treated with the more successful therapy.[11] The safety monitoring board stopped Phase 1 of the study when four of the ten patients in the conventional arm died while all nine of the patients in the ECMO arm survived. Of the next twenty patients (all receiving ECMO), nineteen patients survived. Thus, 97% (twenty-eight of twenty-nine) of the ECMO patients and 60% (six of ten) of the conventional ventilator patients survived ($p < 0.05$). This trial aroused much controversy, especially regarding the randomization scheme and the fact that only families of patients randomized to ECMO were asked for consent.[12] Another randomized study from the United Kingdom also favored ECLS in neonatal respiratory failure.[13] Today, ECLS is an accepted therapy for neonates with refractory respiratory failure.[14]

At the same time, adults with respiratory failure were also receiving ECLS.[15,16] One of the first case reports, by Hill in 1972, involved a young man who suffered injuries, including a ruptured aorta, as the result of a motorcycle accident. Supported by a cumbersome ECMO circuit for 3 days, the man survived.[17] Further case reports and a historic meeting regarding ECLS held in Copenhagen in the late 1970s led to a National Institutes of Health-sponsored trial of ECMO versus conventional therapy in adult respiratory failure. Published in 1979 in the *Journal of the American Medical Association* (*JAMA*), the ECMO and conventional therapy groups had equivalently poor survival (<10%), and major complications of bleeding.[18] The study also took place during an epidemic of influenza, which may have skewed results. The study, in retrospect, was flawed given lack of consensus definitions of conventional treatment, maintenance of high levels of mechanical ventilator support in both groups with no attempt at lung-protective ventilation in the ECMO patients, and imprecise definitions of organ failure. Of a planned 300-patient enrollment, the study was stopped at ninety-two patients because of the high mortality rates in both groups.

These dismal results dampened enthusiasm for ECLS in the adult patient and it became poorly accepted among adult clinicians in the United States. Across the globe, however, investigators in Italy, Sweden, Germany, Japan, and elsewhere continued work on supporting adult respiratory failure with ECLS techniques.[19] Research by Gattinoni added to the understanding of the pathophysiology of adult respiratory failure, the detrimental impact of mechanical ventilation at high levels on the lung and the potential protective role of ECLS in lung recovery.[20] When Gattinoni published results of a low positive pressure ventilation scheme combined with ECLS, primarily for carbon dioxide removal, which achieved 49% survival in patients with similar entry criteria as the failed National Institutes of Health trial, interest in adult ECLS again began to arise. Further studies with similar results from other centers began to appear and culminated with a conference on ECLS in Marburg, Germany, in 1988.[21,22]

As a means of sharing information regarding patients receiving ECLS, an informal gathering of clinicians, bench researchers, industry representatives, technicians, and survivors was held in 1989. Titled the Extracorporeal Life Support Organization (ELSO), this volunteer consortium has established an international database that contains information on more than 45,000 patients from more than 100 centers. The annual symposium continues to provide dissemination of technology, networking, and discussions of advancements and areas of needed work in the field, and provides an important forum for interaction between clinicians, technicians, and industry and bench researchers.[23,24] ELSO has also established practice guidelines and standards of care for patients receiving ECLS. Membership in ELSO gives access to database information for research or center inquiry for specific patient populations. Quarterly reports on both individual and collective center outcomes, complications, equipment, and other parameters are provided. ELSO also provides small levels of grant support to advance the field of ECLS. Centers providing ECLS who do not report results to the ELSO group weaken the ability to track ECLS changes and outcomes globally. Currently undergoing some revision, to refine severity of illness parameters and other specifics, the ELSO registry continues to provide the most comprehensive information regarding trends in ECLS on an ongoing basis. Further information regarding this group can be found at www.ELSO.med.umich.edu.

As with other groups, use of ECLS in pediatric respiratory failure patients has been controversial. Attempts to establish mortality risks and outcome in pediatric respiratory failure were a prelude to a randomized trial of ECLS versus conventional care.[25] The earlier report of Timmons et al on 470 patients from forty-one pediatric intensive care units with respiratory failure (defined as a fractional inspired oxygen

concentration [$F_{I_{O_2}}$] ≥0.50 and positive end-expiratory pressure [PEEP] ≥6 cm H_2O for ≥12 hours) noted a mortality rate of 43%.[26] Using variables that included age, operative status, Pediatric Risk of Mortality (PRISM) score, $F_{I_{O_2}}$, respiratory rate, peak inspiratory pressure, PEEP, arterial oxygen tension (Pa_{O_2}), and arterial carbon dioxide tension (Pa_{CO_2}), a pediatric respiratory failure score was developed and validated against another patient subset.[27] This led to attempts to perform a randomized controlled trial of ECMO in pediatric respiratory failure patients using pediatric respiratory failure score guidelines. The trial was stopped early when interim analysis revealed a mortality of 18% in the control group (contrasted with a predicted mortality of 36% from earlier evaluations), and the likelihood of achieving statistical significance between ECMO and control groups was deemed futile. This trial was also likely impacted by changes that occurred in the management of respiratory failure: positive inspiratory pressure in the historical group (from which the pediatric respiratory failure score was developed) and peak inspiratory pressure in the control subjects in the randomized controlled trial were quite different (47 ± 15 vs. 34 ± 6 cm H_2O), as were the levels of Pa_{CO_2} (56 ± 17 vs. 66 ± 20 mm Hg). In addition, this trial occurred at the time of rising use of high-frequency ventilation (allowed in the control group), inhaled nitric oxide, prone positioning, and surfactant, and while another clinical trial with liquid ventilation was ongoing.[28–31] Because of the difficulties observed with this and other randomized trials of therapies in respiratory failure, especially with regards to consensus agreement on entry criteria, patient management techniques, and end points, enthusiasm for another randomized controlled trial of ECLS in pediatric respiratory failure has been dim. Despite the absence of any randomized controlled trial, ECLS continues to be used successfully in an ever-expanding population of children.

Perhaps the most successful randomized trial of ECLS is that recently reported from the UK regarding adult respiratory failure: CESAR (*C*onventional versus *E*CMO *S*upport in *A*dult *R*espiratory *F*ailure).[32] This trial involved adults who were randomized to conventional care or transfered to one adult ECMO center (Glenfield Hospital, Leicester, England) if appropriate inclusion criteria (based on a Murray score >3 or refractory hypercapnia with pH < 7.20) were met. Of 180 patients entered into the CESAR trial, equally divided between conventional and ECMO arms, survival at 6 months without disability was significantly higher in the ECMO arm than in the conventional arm (63% vs. 47%, $p = 0.03$); the estimated number to treat to achieve an additional life saved was six. The Data Safety and Monitoring Board stopped the trial for efficacy reasons after 180 patients had been entered. An economic analysis concluded that ECLS patients met "acceptable" cost-adjusted quality per life-year costs of £19,252, comparable to treatment of other conditions such as breast cancer.[33]

Despite the impressive results, the CESAR trial continues to generate controversy, especially regarding the fact that seventeen of the ninety patients randomized to the ECLS arm did not receive ECLS. These seventeen patients were treated at the ECLS center and fourteen survived. In the minds of many clinicians, the finding that patients with severe respiratory failure had improved survival in the ECLS center, whether or not they progressed to the need for ECLS, validated the fact that clinicians in such centers provide optimal care for these patients—and that having ECLS as a tool in the algorithm of care adds a survival benefit.[34–36] To others, this fact makes the trial results "invalid" because if the seventeen patients who did not receive ECLS are removed from the analysis, the survival benefit for ECLS is not significantly different from conventional care.

Another criticism of the CESAR trial is that patients managed in the "conventional" sites did not receive a specific algorithm of care, although use of low-tidal volume, pressure-limited ventilation was advocated. To many, the lack of mandated algorithmic care represents the "true" manner in which clinicians in non-ECLS sites provide care and makes the study even closer to what happens in "real life." To others, the lack of mandated algorithmic care only means that perhaps overall care in the ECLS center was "better," and the use of ECLS had nothing to do with the observed improved outcome. Also of interest (but without further analysis or explanation) is that patients in the ECLS center received corticosteroids more often than other patients. In summary, the CESAR trial provides important, current-era data and shows a positive benefit for use of ECLS in adult respiratory failure, but also raises questions for continued research and discussion.

On the heels of the publication of the CESAR trial came the H1N1 influenza epidemic of 2009–2010. Early reports of survival in patients with severe respiratory or multiple organ failure secondary to H1N1 from Australia and sites where the epidemic hit before moving west to North America revived interest among many clinicians for use of ECLS in adults. The finding that many patients succumbing to H1N1 were previously healthy young adults may also have impacted the willingness of clinicians to try something outside conventional mechanical ventilation.[37–39] Because there are only a few centers in the United States that provide adult ECMO, many ECMO centers were overwhelmed with requests for patient transfer. An H1N1 website developed by the ELSO organization and a U.S. "bed board" map that listed open centers with contact numbers were quickly established to track patients and provide clinicians with needed expertise and assistance. To date, 263 patients have been entered into the ELSO H1N1 database with 63% survival. Two-thirds of patients are older than the age of 18 years.[40]

The use of extracorporeal techniques today continues to rise in every patient age group. New equipment, better understanding of pathophysiology, improved patient management, and increased interest in ECLS in a wider variety of patients makes it an exciting time in this field.

The following focuses on the use of ECLS in, predominantly, the venoarterial mode, because the use of venovenous techniques is discussed in Chapter 21.

CRITERIA FOR EXTRACORPOREAL LIFE SUPPORT

The ability to determine selective criteria for respiratory failure that will separate those patients who will survive with conventional care from those who will not, and thus are most in need of alternative techniques such as ECLS, is a pursuit somewhat similar to the Holy Grail. Despite the creation of multiple severity indices and subsequent evaluation of their efficacy in determining risk of death or morbidity, none have proven sustainable over time or universally correct in predicting outcome.[41–46] Nonetheless, the most commonly used criteria for determination of respiratory failure and candidacy for ECLS are the following:

1. Alveolar-to-arterial oxygen difference ($AaDO_2$), which is calculated using the alveolar gas equation:

$$AaDO_2 = [FI_{O_2} \times (P_B - P_{H_2O}) - Pa_{CO_2}/RQ] - Pa_{O_2}$$

   where P_B represents barometric pressure (760 mm Hg at sea level), P_{H_2O} represents pressure of water vapor (47 mm Hg), and RQ is assumed to be 1. $AaDO_2$ has been historically used in neonatal respiratory failure. An $AaDO_2$ of greater than 610 over 8 hours correlated to 80% mortality in neonatal respiratory failure in historical controls. Among pediatric patients, an $AaDO_2$ of greater than 470 was noted by Timmons to be 81% predictive of death, based on data published in 1991.
2. Oxygenation index (OI), which is calculated as follows:

$$OI = \frac{FI_{O_2} \times \text{mean airway pressure (cm } H_2O) \times 100}{Pa_{O_2} \text{ (mm Hg)}}$$

   An OI greater than 40 predicted mortality of greater than 80% (historically). An OI of 25 to 40 predicted mortality of 50% to 80% (historically). An OI greater than 40 or remaining greater than 25 over several hours continues to be associated with high mortality in neonates, pediatric patients, and adults (especially in those following lung transplantation). In pediatric respiratory failure, high OI even at seemingly short duration of mechanical ventilation of less than 24 hours, is associated with high mortality, as shown in Figure 20-2.[46]
3. Compliance (C), calculated as C = Δvolume/Δpressure, or C = tidal volume/(peak inspiratory pressure* PEEP), although it is preferable to use plateau pressure rather than peak inspiratory pressure. Compliance values of less than 0.5 mL/cm H_2O have been used in the selection of adult patients for ECLS.

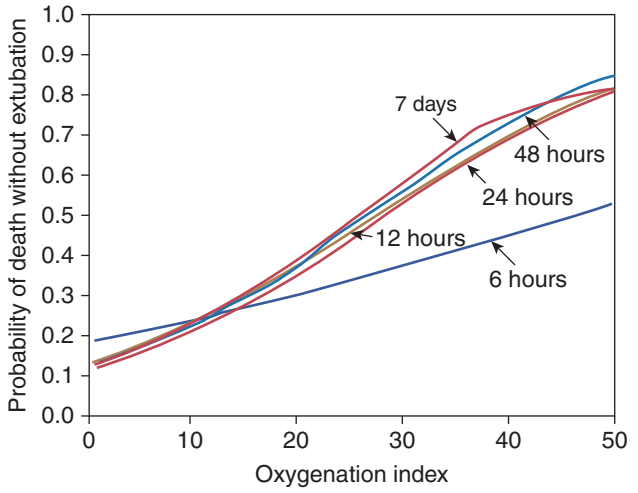

FIGURE 20-2 Oxygenation index and mortality. The presence of a high oxygenation index at any time during mechanical ventilation was associated with increased risk of death without extubation. (Adapted, with permission, from Trachsel et al.[46])

4. Intrapulmonary shunt greater than 30% to 50% on FI_{O_2} greater than 0.6. Shunt has been predominantly used as a selection criterion in adult ECLS.
5. Murray score greater than 3. The score is based on Pa_{O_2}/FI_{O_2}, PEEP, compliance, and number of quadrants exhibiting disease on chest radiograph. The score ranges from 0 to 4, is used in adult ECLS, and was an entry criterion in the CESAR trial.
6. Ventilatory failure. Hypercarbia with persistent pH less than 7 on high ventilator support, such as peak inspiratory pressure greater than 40 cm H_2O.
7. Pa_{O_2}/FI_{O_2}. Calculation is illustrated by the following example: for Pa_{O_2} 50 torr, and FI_{O_2} 100% (1.0), Pa_{O_2}/FI_{O_2} is 50/1, or 50. Pa_{O_2}/FI_{O_2} values of 50 to 100 torr have been described in adult ECLS.

CRITERIA FOR CARDIOPULMONARY FAILURE

If it is difficult to define criteria for respiratory failure, it is equally so when ECLS is considered for cardiac or multiple organ dysfunction. Although no specific criteria have been identified and universally accepted, the following are suggestions from the literature and clinical experts:[47–50]

1. Plasma lactate persistently greater than 5 mM/L.
2. Mixed venous oxygen saturation ($S\bar{V}O_2$) less than 55% at an estimated cardiac index of at least 2 L/min.
3. Severe ventricular dysfunction.
4. Intractable arrhythmia with hemodynamic compromise.
5. Cardiac arrest.
6. Inotrope score greater than 50 for 1 hour or greater than 45 for 8 hours,[50,51] calculated as

Dopamine (mcg/kg/min) + Dobutamine (mcg/kg/min) + 100 × Epinephrine (mcg/kg/min).

A modified inotrope/vasoactive score, calculated as Dopamine (μg/kg/min) + Dobutamine (μg/kg/min) + 100 × Epinephrine (μg/kg/min) + 100 × Norepinephrine (μg/kg/min) + Milrinone (μg/kg/min) × 10 (15 is also used by some clinicians) + 10,000 × vasopressin dose (μg/kg/min).

7. Failure to wean from cardiopulmonary bypass.

VENOARTERIAL CANNULATION MODES

Venoarterial ECLS has been the predominant mode of support in infants and children for many years secondary to lack of adequately sized venous vessels to obtain the amount of blood flow needed to support the patient. Figure 20-3 is an example of a typical venoarterial ECLS circuit with cervical cannulation, a roller head pump, and silicone membrane

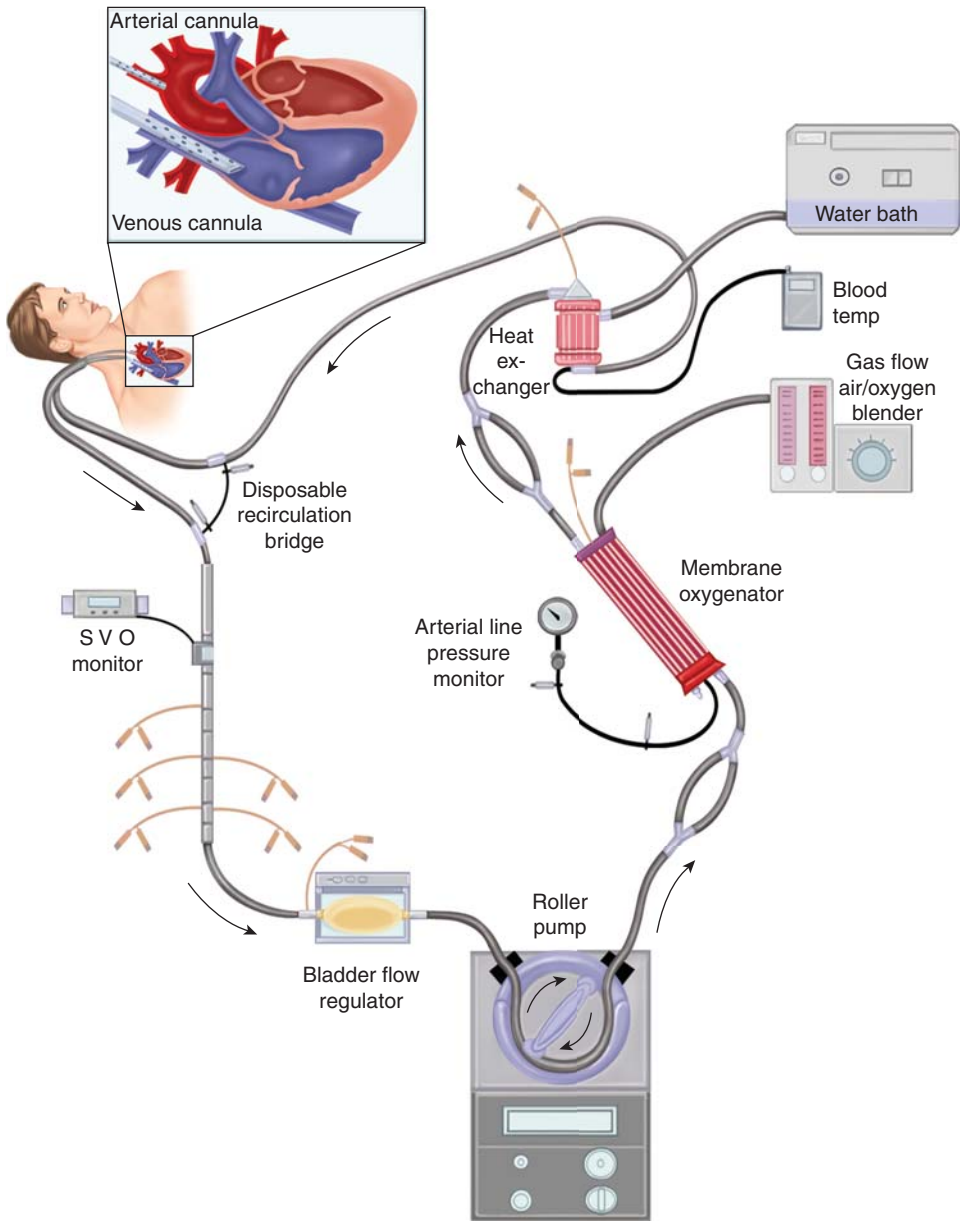

FIGURE 20-3 Venoarterial ECLS circuit with roller-head pump and silicone membrane oxygenator. Note venous saturation device on drainage limb; bladder reservoir device is before pump head. Silicone membrane oxygenator has now been almost totally replaced by new hollow-fiber devices. Heat exchanger device rewarms or cools blood before its return to patient.

FIGURE 20-4 Centrifugal pump and hollow-fiber oxygenator system. These systems often have lower priming volumes, are easier and faster to set up, and do not require gravity drainage. Note that the oxygenator and pump head should be below the level of the patient.

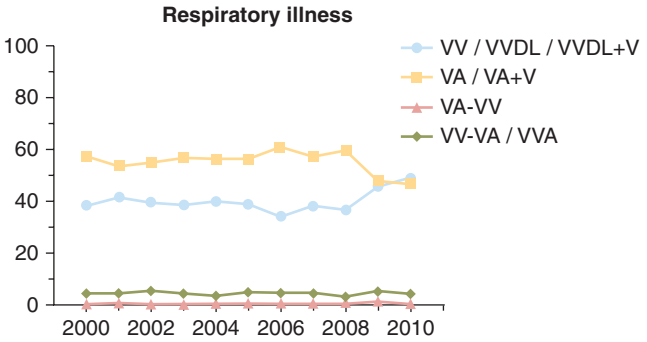

FIGURE 20-5 Cannulation mode for patients with respiratory failure (all ages). *VA*, venoarterial; *VA+V*, additional venous cannula added; *VA-VV*, venoarterial cannulation changed to venovenous during ECLS course; *VV*, venovenous; *VVDL*, venovenous double lumen; *VV-VA*, venovenous cannulation changed to venoarterial during ECLS course.

lung. Figure 20-4 depicts more current equipment with centrifugal pump and hollow-fiber oxygenator. With the advent of double-lumen, single cannulas, and improvements in flow characteristics of available cannulas, venovenous support is now becoming more popular and feasible even among neonates.[51,52] Gone are the days when modifications of thoracostomy or endotracheal tubes provided the "cannulas" for ECLS support; wire-reinforced, thin-walled cannulas now permit excellent flows at smaller internal and external diameters.[53] Venoarterial support, however, remains a mainstay of support in patients with combined cardiopulmonary dysfunction or in those with primary cardiac failure. Figures 20-5 and 20-6 show the changes in mode of cannulation by category and diagnostic group.

Cervical Cannulation

In neonates, use of the internal jugular vein and right common carotid artery is the predominant venoarterial cannulation technique. Figure 20-7 is an example of cannulation through the internal jugular vein and carotid artery for venoarterial extracorporeal support with monitoring parameters that can be used for patient management. While centers may vary somewhat in cervical cannulation technique, most use an open approach to vessel access.[54] Repair of the carotid artery at decannulation is controversial, practiced routinely in some centers and avoided in others.[55–58]

Follow-up studies of repaired vessels has noted patency in 80% to 100% of repaired vessels, but stenosis in repaired vessels also has been noted in several studies, as has the development of aneurysms or pseudoaneurysms of the vessel with need for emergent surgical intervention. In one follow-up report of neurodevelopmental outcome from pediatric patients receiving support for cardiac dysfunction, use of the carotid artery for vascular access was not associated with neurologic dysfunction. Similarly, small comparative studies of neonates, with or without carotid repair at decannulation, did not find neurodevelopmental changes at follow-up between groups and noted good collateral flow in patients where the carotid had been ligated. Despite the lack of evidence in favor of repair of the carotid artery, there is increasing interest, especially in older patients, in avoiding the carotid artery for cannulation because the potential risk for stroke seems higher (anecdotally) despite no proven evidence of this concern. Only long-term outcome studies, up to the ages when stroke becomes more common, will be able to definitely answer whether carotid artery ligation or repair following ECLS is an associated risk factor.

Internal jugular cannulation can be performed with a semi-Seldinger technique or via direct venotomy and insertion of the cannula. Some centers also insert a small retrograde venous drainage cannula to the level of the jugular bulb to obtain more venous drainage from the cerebral circuit and/or to monitor cerebral venous saturation as an indication of adequacy of perfusion to the brain and oxygen delivery and extraction (this is presumably even more important in venovenous support).[59,60] Some clinicians report having been able to increase venous drainage by up to 30% in neonates with this technique, although others have noted clotting difficulties in the retrograde cannula and have abandoned this technique. The effects of ligation of the internal jugular vein on cerebral venous drainage and risk for intracranial hemorrhage from venous stasis or hypertension

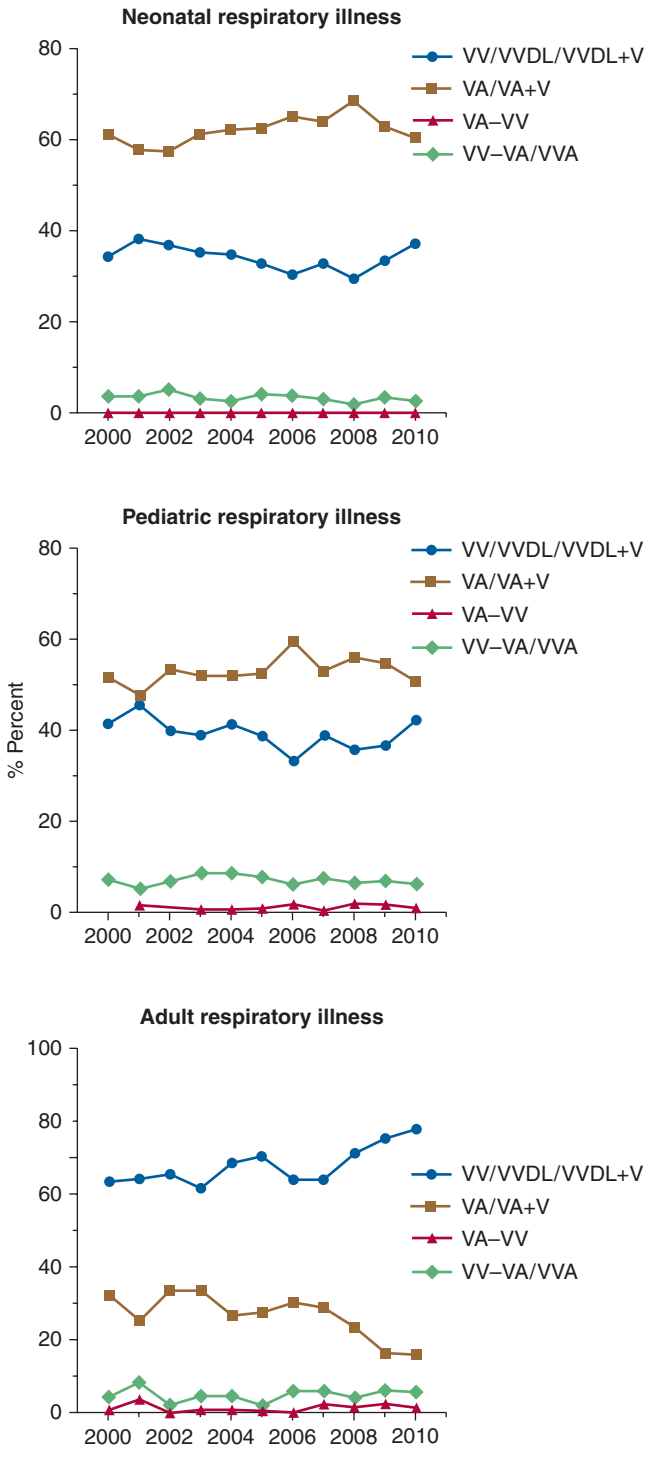

FIGURE 20-6 Cannulation mode by age. Note increase in venovenous support over past several years. *VA*, venoarterial; *VA+V*, additional venous cannula added; *VA-VV*, venoarterial cannulation changed to venovenous during ECLS course; *VV*, venovenous; *VVDL*, venovenous double lumen; *VV-VA*, venovenous cannulation changed to venoarterial during ECLS course.

has not been completely defined. Repair of the vein at decannulation is not practiced routinely, although patency has been described. For cardiac patients in whom future surgeries may involve use of the superior venous system, such as single ventricle patients, judicious use of the internal jugular vein for ECLS and consideration for repair if cannulation occurs should be discussed.

Central Cannulation

ECLS can also be provided through direct insertion of large-bore cannulas into the right atrium and into the aortic arch. This method of cannulation allows the largest volume of blood to be obtained for support. This technique is used predominantly in patients transitioned to ECLS directly from cardiopulmonary bypass or following acute deterioration (including arrest) in the early postoperative period when the sternum can be easily reopened.[61,62] It has also recently been identified as a potential factor in successful support of patients with septic shock and multiple organ failure, who may require high levels of flow to obtain adequate oxygen delivery. In the most cited report, children in septic shock who received central cannulation were unexpectedly found to have improved survival as compared to those in whom other cannulation strategies were used (73% vs. 38% survival, $p = 0.05$, $n = 11$).[63] These patients required sternotomy for cannula insertion after peripheral cannulation proved inadequate for support or vascular access could not be obtained. The major differentiating feature between the groups was the higher flow rates obtained with the central cannulation mode. The authors speculated that this improved flow provided better oxygen delivery and resolution of organ failure with resultant improved survival. A follow-up report of twenty-three children with septic shock supported with ECLS over a 9-year period using central cannulation noted 74% survival to discharge.[64] Although central cannulation in patients without a prior sternotomy is not routine in most centers, the aforementioned reports have led it to be considered in non–cardiac-surgery patients and we have used it successfully in septic patients in whom peripheral cannulation was ineffective. Bleeding from the mediastinal site continues to be a major complication.

Femoral Cannulation

In children older than the age of 2 years or roughly weighing more than 15 kg, femoral vessels may be adequate for venoarterial ECLS. Concern with use of the carotid artery in older patients has already been discussed. Thus, in larger patients (especially adults), femoral cannulation is often preferred. Figure 20-8 is a typical example of femoral/arterial cannulation. Venous cannulation can be performed percutaneously or with open venotomy.[65–67] Optimally, a long, large-bore cannula is passed up the femoral vein to the junction

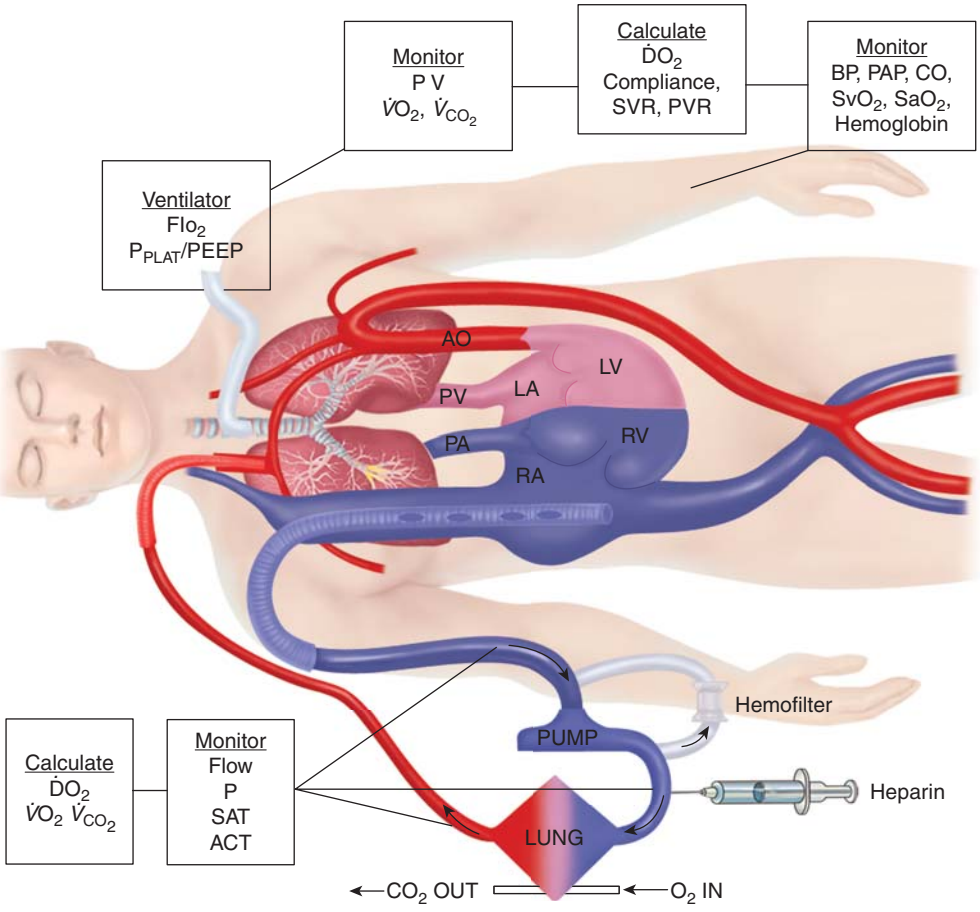

FIGURE 20-7 Venoarterial cannulation. Boxes represent calculations and parameters that can be measured by monitoring site. *ACT*, activated clotting time; *BP*, arterial blood pressure; *CO*, cardiac output (estimated); DO_2, oxygen delivery; *P*, pressure; *PAP*, pulmonary artery pressure (only in patients with a pulmonary artery catheter in place); *PEEP*, positive end-expiratory pressure; P_{PLAT}, plateau pressure; *PVR*, pulmonary vascular resistance; SaO_2, arterial oxygen saturation; *Sat*, saturation of blood; $S\bar{V}O_2$, venous oxygen saturation; *SVR*, systemic vascular resistance; *V*, volume; $\dot{V}_{CO_2}$, carbon dioxide; $\dot{V}O_2$ oxygen consumption. (Courtesy of Robert Bartlett, MD, with permission.)

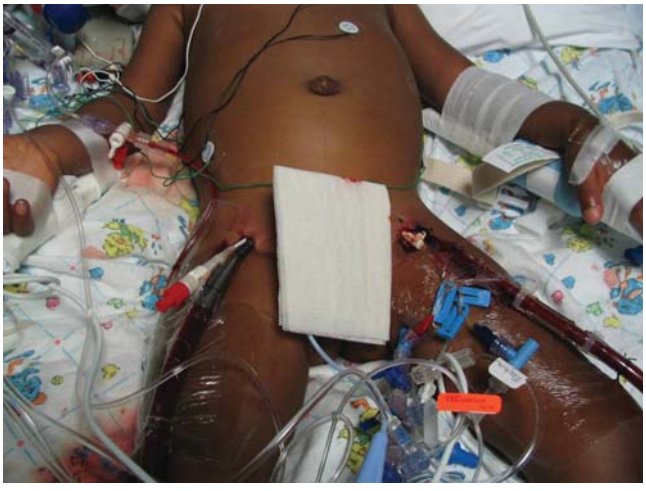

FIGURE 20-8 Modified femoral venoarterial ECMO: For patients usually >15 kg, adequate support can be obtained from femoral venous and femoral arterial cannulation. In this depiction, the patient also has sheaths for cardiac catheterization in the right groin. (Courtesy of Heidi Dalton MD, with permission.)

of the inferior vena cava-right atrium. Figure 20-9 depicts a typical femoral venoarterial cannulation. It should be noted that as the flow characteristics of a cannula are dependent on internal diameter and length, longer cannulas will have higher resistance to flow; however, achieving access near the right atrium allows for the largest pool of venous blood to be obtained, and, thus, short femoral cannulas (while having less resistance) will frequently not result in adequate venous drainage for ECLS support, especially in small patients. Femoral arterial access can be performed by percutaneous or open cannulation. Typically, a short (18 to 25 cm) cannula is used for ECLS return. In access via the femoral vessels, integrity of distal perfusion or venous drainage of the limb is at risk. Measuring vessel size with bedside ultrasound and picking a cannula with an internal diameter slightly less than the vessel can help allow flow around the cannula and prevent blood flow inadequacies to the distal limb.

Placement of small drainage cannulas (for venous engorgement) or distal perfusion cannulas (for distal arterial ischemia) have both been described and used efficiently

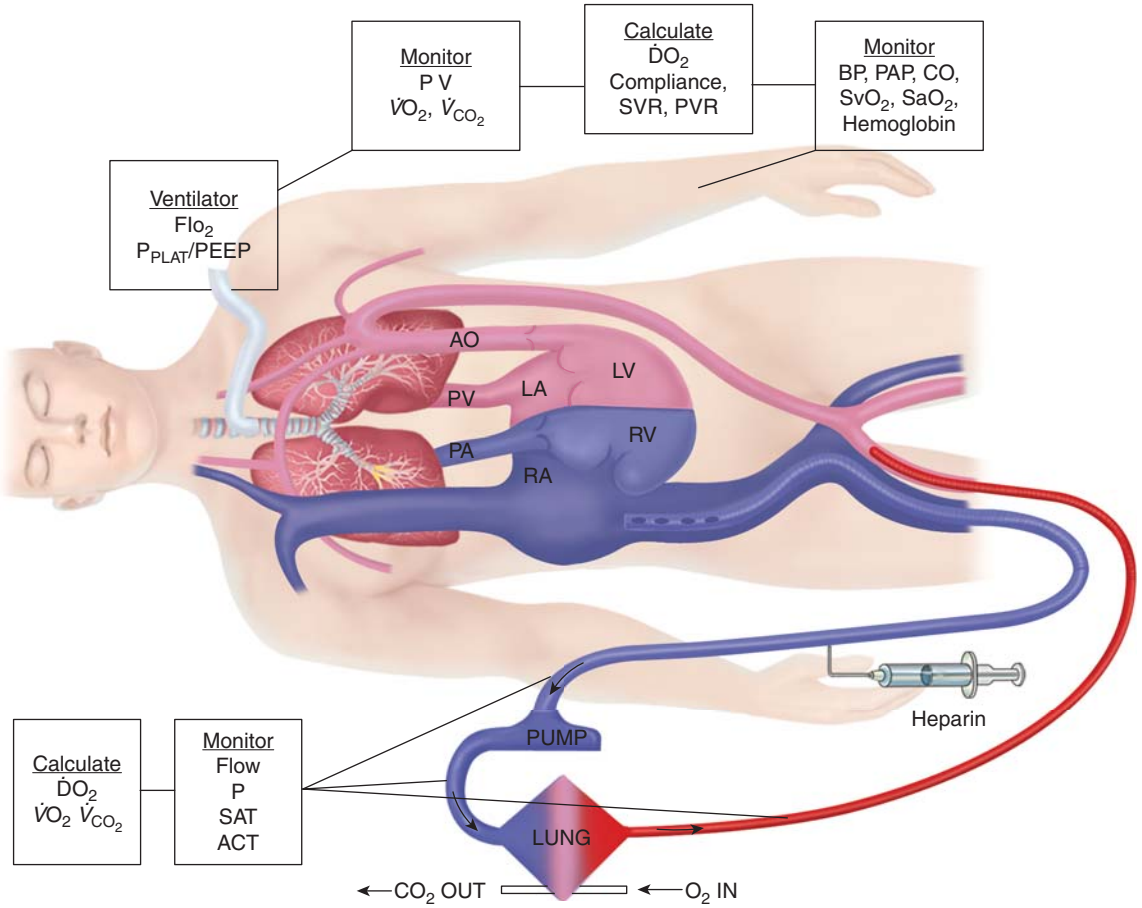

FIGURE 20-9 Femoral venoarterial cannulation. Long femoral drainage cannula to right atrium and short arterial return cannula in femoral artery. Boxes represent calculations and parameters that can be measured by monitoring site. *ACT*, activated clotting time; *BP*, arterial blood pressure; *CO*, cardiac output (estimated); DO_2, oxygen delivery; *P*, pressure; *PAP*, pulmonary artery pressure (only in patients with a pulmonary artery catheter in place); *PEEP*, positive end-expiratory pressure; P_{PLAT}, plateau pressure; *PVR*, pulmonary vascular resistance; SaO_2, arterial oxygen saturation; *Sat*, saturation of blood; $S\bar{V}O_2$, venous oxygen saturation; *SVR*, systemic vascular resistance; *V*, volume; $\dot{V}_{CO_2}$, carbon dioxide; $\dot{V}O_2$, oxygen consumption. (Courtesy of Robert Bartlett, MD, with permission.)

to prevent compartment syndrome or limb loss.[68] Despite these maneuvers, however, limb injury to the extent of amputation has been described several times following femoral access. Thus, close neurovascular monitoring is required.

As venous flow obtained from the femoral route is usually less than that obtained from the internal jugular or central venous sites, the amount of support provided in this mode of venoarterial ECLS is often less than can be obtained with other cannulation techniques. This results in a lower arterial oxygen saturation (SaO_2) secondary to increased mixing of desaturated blood from the patient (assuming the patient has severe respiratory failure and impaired gas exchange) than with other forms of venoarterial cannulation. Oxygen saturation often will be 80% instead of 90% to 100% and will mimic that seen with venovenous support. Another important factor with femoral venoarterial support is that the oxygenated arterial return from the ECLS circuit runs retrograde up the aorta to flow coming out of the native heart. How far up the aorta the oxygenated ECLS blood extends is a product of the amount of bypass performed and the amount being ejected from the left ventricle. One concern with femoral venoarterial bypass is that with severe respiratory failure, blood from the left ventricle will be about the same saturation as that in the right atrium, and this relatively desaturated blood will be what is perfusing the upper body, especially the head and heart. This can result in a "blue upper body and red lower body" phenomenon. Whether this is harmful depends on the extent of desaturation and patient-specific factors. For a patient with evidence of myocardial ischemia, having desaturated blood flowing into the coronary vessels may not be optimal. Similarly, if the patient is exhibiting signs of inadequate cerebral oxygenation (by clinical exam or near-infrared spectroscopy monitoring or some other parameter), then this may be an indication that oxygenation is inadequate. If upper-body oxygen delivery is deemed to be significantly impaired, one technique is to place a venous cannula into the right internal jugular vein or in the femoral vein and direct some of the oxygenated ECLS return into this cannula by means of a Y connector on the return limb of the

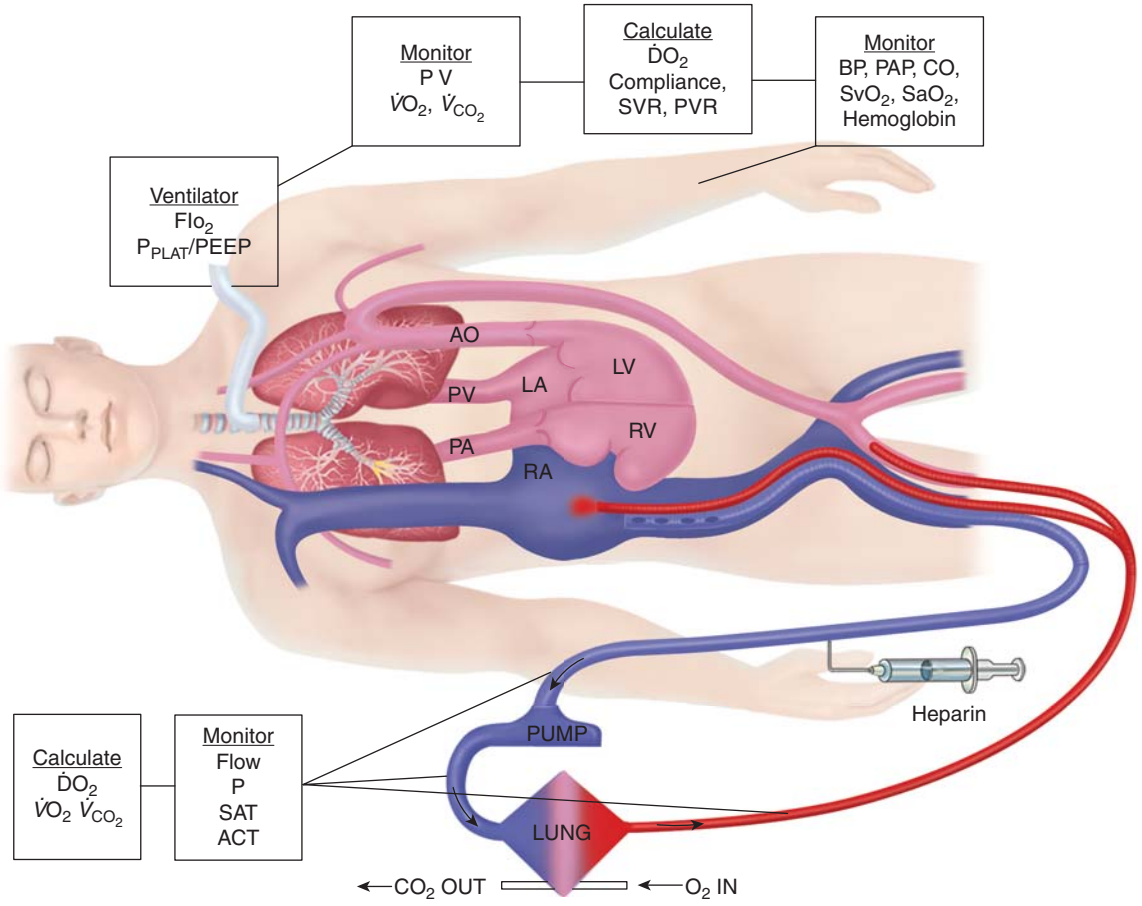

FIGURE 20-10 Hybrid femoral venoarterial cannulation with additional femoral cannula for additional oxygenation to venous circulation. Although the depiction shows additional cannula in same site as venous drainage cannula, it is more common to place additional cannula in the opposite femoral vein or internal jugular vein. Boxes represent calculations and parameters that can be measured by monitoring site. *ACT*, activated clotting time; *BP*, arterial blood pressure; *CO*, cardiac output (estimated); DO_2, oxygen delivery; *P*, pressure; *PAP*, pulmonary artery pressure (only in patients with a pulmonary artery catheter in place); *PEEP*, positive end-expiratory pressure; P_{PLAT}, plateau pressure; *PVR*, pulmonary vascular resistance; SaO_2, arterial oxygen saturation; *Sat*, saturation of blood; $S\bar{V}O_2$, venous oxygen saturation; *SVR*, systemic vascular resistance; *V*, volume; $\dot{V}_{CO_2}$, carbon dioxide; $\dot{V}O_2$, oxygen consumption. (Courtesy of Robert Bartlett, MD, with permission.)

circuit. Figure 20-10 illustrates this method of hybrid femoral venoarterial cannulation with an additional venous cannula providing some oxygenated return. Although the figure depicts two cannulas in one femoral vein, this approach is not common; most clinicians either will place the additional venous cannula in the right internal jugular vein or in the opposite femoral vein. This increases the venous saturation of blood in the right atrium and thus the saturation of blood being ejected out the left ventricle. Careful monitoring of flow in both the venous cannula and the femoral arterial cannula should be performed to prevent one cannula from receiving inadequate flow (as blood will always take the path of least resistance) and clotting. Manipulation of flows to multiple cannulas "Y-ed" into the circuit can be done with a simple screw clamp or other devices. The need for increased venous drainage in femoral venoarterial ECLS can also be achieved by adding another venous cannula (usually in the right internal jugular) and "Y-ing" it into the venous drainage side of the circuit.

Although other vessels, such as the axillary and subclavian, have been used as access for venoarterial ECLS, reports of their use are infrequent. Improved cannula designs with better flow rates and characteristics, may allow improved access to other vessels, even to the point of using umbilical vessels for premature infant support, in the future. Careful attention to neurovascular monitoring is paramount when vessels, especially outside the norm, are cannulated.[69]

PHYSIOLOGY OF VENOARTERIAL EXTRACORPOREAL LIFE SUPPORT

Venoarterial ECLS allows for drainage from the right side of the heart, thus reducing blood flow through the native cardiopulmonary circuit. In patients with impaired pulmonary gas exchange, diversion of venous blood into the ECLS circuit, where it undergoes oxygenation and removal of carbon dioxide, and direct return of oxygenated blood

into the arterial system allows for increased systemic oxygenation. The more blood diverted into the ECLS circuit, the more bypass is performed and the higher the systemic oxygen delivery provided by ECLS. Increasing ECLS flow will decrease the proportion of blood flowing through the diseased lungs, which is ejected out the left ventricle to mix with the oxygenated return from the ECLS circuit. Thus, at higher ECLS flows, systemic oxygen delivery and SaO_2 will increase. This has led to the adage, "If the O's are low, turn up the flow." Similarly, at a constant ECLS flow without manipulations in oxygenation of blood within the membrane oxygenator, a simple herald of improving native respiratory function is an increase in SaO_2, as the patient's lungs become more efficient at gas exchange and the arterial oxygen content (CaO_2) of ejected left-ventricular blood increases. Just as in normal care of a critically ill patient, understanding the role of CaO_2 and oxygen delivery in ECLS is important. As a reminder, CaO_2 is calculated as: (hemoglobin g/dL × % SaO_2 × 1.36 mL/g) + (0.003 mL/dL × Pa_{O_2}) × 10. Thus, the major contributors to CaO_2 are hemoglobin concentration and SaO_2. Pa_{O_2} is of little impact on CaO_2 unless severe anemia exists. Figure 20-7 shows a typical venoarterial circuit with parameters that can be followed or calculated.

To determine the overall oxygen delivered to the patient during ECLS, both the CaO_2 and flow must be considered. The following example illustrates the principles involved:

Assume that perfusate blood is 100% saturated with a Pa_{O_2} of 500 torr, as might be seen with 100% FI_{O_2} applied to the membrane lung. If native respiratory failure is so severe that no oxygenation occurs in the pulmonary circuit, blood returning from the native lungs and being ejected out the left ventricle will have the same saturation as right-atrial venous blood. With normal oxygen delivery and extraction, right-atrial venous saturation is 75% and the partial pressure of oxygen (P_{O_2}) 35 torr. At a hemoglobin of 15 g/dL, the perfusate oxygen content is 22 mL/dL and the right- and left-atrial ventricular oxygen content is 15 mL/dL. If 50% of the native blood flow is diverted into the ECLS circuit and 50% flows through the native cardiopulmonary circuit, the measured systemic oxygen content in the patient will be a combination of these amounts and will result in an oxygen content of 18.5 mL/dL, which corresponds to an SaO_2 of 90% and a Pa_{O_2} of 55 torr. These are the values that will be obtained from the patient's arterial blood, assuming that the blood is being measured past the site where the ECLS return enters the patient so that mixing with native output has occurred.

Thus, an improvement in oxygenation during venoarterial ECLS indicates either (a) improving lung function, (b) decreasing native cardiac output (at constant ECLS flow), or (c) increasing ECLS flow (if native cardiac output is constant). The amount of oxygenation that occurs in the membrane lung, is dependent on gas exchange properties, thickness of the blood film, hemoglobin concentration, the residence time of red blood cells within the membrane lung, and the gradient between inlet venous blood and the oxygen content in the ventilating gas flow.[70,71] Assume that the mixed venous oxygen tension (PvO_2) reaching the membrane lung is 35 to 40 torr and even with room air, the P_{O_2} of ventilating gas is around 100 torr with a saturation of 100%, oxygen will flow into the venous blood and saturation at the outlet of the oxygenator will be optimally 100%. Increasing the FI_{O_2} of the sweep gas may increase the P_{O_2} in outlet blood but will not increase oxygen saturation to greater than 100%; thus, the increase in oxygen content at higher sweep gas FI_{O_2} will be minor unless the patient is severely anemic. If the patient requires more oxygen delivery and blood exiting the membrane lung is 100% saturated, then increasing ECLS flow is needed. For many oxygenators, adequate saturation can be achieved with only room air in the sweep gas. As membrane lung efficiency may decrease over time, an increase in FI_{O_2} of the sweep gas may be required to achieve 100% outlet saturation. Each oxygenator is rated for optimal blood flow (defined as the rate of venous blood flow which results in an increase in SaO_2 from 75% to 95% as blood travels through the device from inlet to outlet). Increasing blood flow rates above the "rated flow" impairs optimal oxygen delivery by the device.

CO_2 removal with venoarterial ECLS is extremely efficient and is dependent on membrane lung surface area, material, geometry, and membrane lung ventilating gas flow (usually termed the "sweep gas flow"), as well as P_{CO_2} content in the patient's blood. Normally, sweep gas flow contains no CO_2 so the gradient for CO_2 exchange across the membrane lung is dependent on the difference between the venous blood reaching the oxygenator and the sweep gas flow. At high sweep gas flows, or with larger membrane surface areas, more CO_2 is removed from the blood, similar to increasing minute ventilation as a means of increasing CO_2 elimination in a normal state. In small patients, CO_2 elimination can be so efficient that the P_{CO_2} returning to the patient is very low and respiratory alkalosis severe. For patients cannulated via the cervical or central arterial route into the arch of the aorta, the ECLS return often reaches the left carotid artery (and thus the brain) first. Because a very low P_{CO_2} in this blood may adversely affect cerebral vascular blood flow, maintaining normal Pa_{CO_2} in the blood returning to the patient is recommended. Some centers regulate P_{CO_2} returning to the patient by manipulating sweep gas flow as a lower sweep will decrease CO_2 removal. Others blend CO_2 gas into the sweep gas mixture to decrease the gradient across the membrane lung between native blood and sweep gas. It should be remembered that CO_2 elimination is better than oxygen uptake across both the silicone membrane and microporous/hollow-fiber oxygenator devices.[72–75]

One important note with venoarterial support is that arterial flow coming from the ECLS circuit *increases* afterload to the left ventricle. This is of paramount importance in situations of left-ventricular dysfunction, because this increase in afterload may result in sudden and complete failure of the left heart. The majority of coronary artery perfusion during venoarterial ECLS has been shown to result from native left-ventricular ejection.[76] Given that venoarterial ECLS never provides complete bypass, because flow from bronchial and thebesian vessels will continue to the left heart,

inability of the left heart to eject can result in impairment of left-ventricular myocardial flow from elevated intracardiac pressure, left-atrial hypertension, pulmonary venous hypertension, and pulmonary hemorrhage. Although a short period of cessation of left-ventricular function can often be tolerated, attempts at afterload reduction with medications such as milrinone or nitroprusside can also be helpful. In patients with prolonged left-ventricular failure, poor aortic ejection, evidence of pulmonary congestion (such as pulmonary edema or hemorrhage), an atrial septostomy can be performed to allow left-atrial blood to be drained via the right-atrial cannula in order to decrease left-atrial pressure.[77,78] In patients with sternotomy, a left-atrial vent can also be placed and "Y-ed" into the venous side of the ECLS circuit to offload the left heart. If the patient's cardiopulmonary function is being "tested" while clamped off ECLS before complete removal of the cannula's to see if adequate recovery has occurred (this process is called "trialing off ECLS"), the left-atrial cannula must be removed or clamped during this process to allow normal filling of the left heart. Echocardiography can be invaluable to follow the extent of left-ventricular dysfunction, overall cardiac function and recovery, adequacy and optimal placement of ECLS cannulas, and assessment for pericardial effusion during ECLS.

Unlike cardiopulmonary bypass, ECLS is intended to provide partial (not *total*) bypass, as animal studies show that complete bypass of the pulmonary circuit is associated with ischemia.[79] The "total" bypass used during cardiac surgery is also thought to be a factor in the reperfusion injury noted in the lung, cytokine generation, and the inflammatory response observed in the post-bypass period. Thus, goals for venous saturation, arterial oxygenation, and hemodynamic support are set for each patient (usually on a daily basis) and ECLS flow adjusted to maintain set parameters. For patients with severely impaired gas exchange, the level of bypass support is set at providing adequate oxygen delivery to support tissue function. In general terms, this often equates to a starting ECLS flow of 100 to 150 mL/kg in neonates, 80 to 100 mL/kg in children, and 50 to 60 mL/kg in adults. The adequacy of support is monitored by establishing normal venous oxygen saturations (>65% to 70%), normalization of lactate levels and base deficit as well as adjunct measures such as clinical exam, vital signs such as blood pressure, neurologic alertness, urine output, near-infrared spectroscopy monitoring, and other measures used by clinicians to identify appropriate organ perfusion.[80] Flow returning from the ECLS circuit is mainly nonpulsatile. One indication of the amount of bypass being performed in a patient with adequate cardiac function is merely following the pulse pressure and systolic pulse contour on the arterial waveform. More bypass will decrease the systolic upswing and give a more narrow pulse pressure.

Several practical points regarding ECLS use in patients with predominant cardiac failure are to maintain intracardiac filling pressures at low levels so as to promote endocardial blood flow and myocardial perfusion. Thus, close attention to central venous pressure and left-atrial pressure (if available) is required. Use of echocardiography to assess cardiac function (how "full" or "empty" the heart is) and aortic outflow is very helpful during ECLS, especially in the cardiac patient and during weaning.[81]

PATIENT POPULATIONS TREATED WITH VENOARTERIAL EXTRACORPOREAL LIFE SUPPORT

Table 20-1 reviews the ELSO registry for patient populations in neonatal (<30 days), pediatric (31 days to 18 years), and adult (>18 years) age groups in terms of major diagnostic categories and outcome. Table 20-2 outlines major diagnostic groups within categories and outcome in the most recent time period of 2000 to 2010. Figures 20-11 and 20-12 show the changes in ventilator settings and blood-gas parameters in age groups and respiratory failure patients. Note that pH has declined and Pa_{CO_2} has increased over time, perhaps indicating adoption of the "permissive hypercapnia" approach to mechanical ventilation. This has not been accompanied, however, by a large change in OI over time, as might be expected if "gentler ventilation" with lower mean airway pressures was occurring. Potential explanations for the lack of change in OI is that mean airway pressure with the high frequency oscillator is often higher (at least initially) than with conventional mechanical ventilation or that clinicians are accepting greater levels of hypoxia as part of "gentler ventilation."

Neonatal

The use of ECLS in neonates has declined over the past 10 years as improved perinatal care and management techniques have advanced.[82,83] Infantile respiratory distress syndrome has largely disappeared with the advent of surfactant and better lung-protective ventilation strategies, as well as changes in ventilator technology, such as the high-frequency oscillator. Meconium aspiration syndrome is also not as prevalent as in the past, and group B streptococcal infection has also declined. These diseases have been replaced with other infections and more complex infant illnesses. Congenital diaphragmatic hernia remains a large group for neonatal ECLS and survival in these patients remains only approximately 50% despite the many different management algorithms and approaches for surgical repair that have been introduced over time.[84–89] The overall survival in neonatal ECLS patients is 69% over the past 10 years, with about 1000 infants receiving ECLS per year.[90] Based on ventilator setting and blood-gas data, there has been little change in severity over time based on oxygenation index (average: 45 to 50) or Pa_{O_2}/FI_{O_2} ratio (average: 50–60 torr) for neonates, although a steady decline in pH and concomitant increase in Pa_{CO_2} have been observed. A recent evaluation of the ELSO registry from 2000 to 2010 revealed a 2.5% decline in survival per year ($p < 0.01$).[91]

TABLE 20-1: PATIENT POPULATIONS TREATED WITH EXTRACORPOREAL LIFE SUPPORT AND OUTCOME

ECLS Registry Report
International Summary
July, 2011

Extracorporeal Life Support Organization
2800 Plymouth Road
Building 300, Room 303
Ann Arbor, MI 48109

Overall outcomes

	Total Patients	*Survived ECLS*		*Survived to DC or Transfer*	
Neonatal					
Respiratory	24,770	20,951	85%	18,558	75%
Cardiac	4,375	2,649	61%	1,723	39%
ECPR	694	438	63%	270	39%
Pediatric					
Respiratory	5,009	3,251	65%	2,785	56%
Cardiac	5,423	3,468	64%	2,609	48%
ECPR	1,347	720	53%	539	40%
Adult					
Respiratory	2,620	1,655	63%	1,428	55%
Cardiac	1,680	894	53%	660	39%
ECPR	591	225	38%	173	29%
Total	46,509	34,251	74%	28,745	62%

DC, hospital discharge; *ECLS*, extracorporeal life support; *ECPR*, extracorporeal life support during cardiopulmonary resuscitation.
Survival is off ECLS and then to hospital discharge.
From the International Registry of the Extracorporeal Life Support Organization, Ann Arbor, MI, with permission.

Although venoarterial access has been the mainstay in neonates, the fact that many infants with respiratory failure have good cardiac function makes them good candidates for venovenous support. Improved double-lumen, single-site cannulas that can be placed in the internal jugular vein have been developed, which allows for venovenous ECLS to be used in almost half of neonatal respiratory failure patients. Figure 20-13 shows a typical venovenous cannula that is currently widely used in larger children and adults. Figure 20-14 depicts a typical venovenous circuit. One problem that has been encountered with double-lumen cannulas has been difficulty with collapse of the drainage lumen if a high amount of venous "suction" is generated. This is potentially more of an issue with centrifugal pumps than with the older style semiocclusive, rollerhead devices.[92] Development of wire-reinforced double-lumen, single cannulas has been spurred by the many centers that are changing to centrifugal equipment for its ease of use and ability to use shorter circuits with less priming volume. Although these cannulas have been very successful in larger patients, smaller sizes have encountered some difficulty with accurate placement, and clinical reports of unexplained tamponade occurring days after placement without well-identified myocardial perforations have surfaced. Newer models are expected in clinical trials soon. Current management is to try venovenous ECLS support in almost any neonate without known complete cardiac collapse before implementing cardiac cannulation for venoarterial support. Successful use of venovenous support even in infants with primary respiratory failure and pre-ECLS need for vasoactive support has been well described.[93]

Pediatric

As experience with ECLS has grown, the expansion to patient populations avoided in the past is nowhere as clearly seen as with pediatric patients. The "old days" when a healthy child would contract overwhelming pneumonia and be rescued with ECLS support are now a memory, as most pediatric ECLS patients today have underlying comorbidities in addition to their acute critical illness.[94–101] The latest review of pediatric respiratory failure patients entered into the ELSO database was recently published.[102] This report compared patients who received ECMO from 1993 to 2007. Survivors were noted to have a lower median body weight (9 vs. 9.9 kg), with a similar median age in survivors and nonsurvivors. Older children (ages 10 to 18 years) had lower survival (50%) compared to infants (57%), toddlers (61%), and children (55%). Although there was little change in survival over time, patients with comorbidities increased from 19% in 1993 to 47% in 2007. Renal failure, chronic lung disease, and congenital heart disease (two ventricles) formed the bulk of underlying comorbid conditions. Other conditions, which represent the changes in exclusion criteria

TABLE 20-2: OUTCOME ACCORDING TO MAJOR DIAGNOSTIC GROUP (2000 TO 2010)

Primary Diagnosis	n (%)	Survival
Neonatal	9086	68.6
MAS	2239 (24.6)	92.9
RDS	203 (2.2)	85.2
PPHN/PFC	1820 (20.0)	75.9
Air leak syndrome	16 (0.2)	75.0
Sepsis	252 (2.8)	70.2
Other	1785 (19.7)	65.5
CDH	2767 (30.5)	46.7
Pneumonia	4 (0.04)	25.0
Pediatric	2992	55.7
Aspiration	13 (0.43)	69.2
Bacterial	134 (4.48)	62.7
ARDS, post-op/trauma	80 (2.7)	60.0
Acute respiratory failure, not ARDS	306 (10.2)	56.5
Pneumocystitis	16 (0.53)	56.3
Other	2246 (75.1)	55.1
ARDS, not post-op/trauma	185 (6.2)	54.1
Viral	12 (0.4)	50.0
Adult	1921	56.0
Viral	35 (1.8)	74.3
Aspiration	7 (0.4)	71.4
Bacterial	156 (8.1)	62.8
ARDS, post-op/trauma	143 (7.4)	60.1
Acute respiratory failure, non-ARDS	102 (5.3)	57.8
Other	1266 (65.9)	55.4
ARDS, not post-op	212 (11.0)	47.2

ARDS, acute respiratory distress syndrome; *CDH*, congenital diaphragmatic hernia; *MAS*, meconium aspiration syndrome; *post-op*, postoperative; *PPHN/PFC*, persistent pulmonary hypertension of the newborn, or persistent fetal circulation; *RDS*, respiratory distress syndrome.

Data analyzed from ELSO registry years 2000 to 2010. Survival is to hospital discharge. (Unpublished data, Dalton HJ and Garcia-Filion P, with permission.)

over time, note that patients with cancer, solid-organ transplantation, immunodeficiencies, and even stem cell transplantation patients have received ECLS and survived. All these conditions would have been excluded as candidates for ECLS in the past. Nonetheless, children with no comorbidities have experienced improved survival with ECLS over time: 57% in 1993 to 72% in 2007. Another important factor in this summary of more than 3000 pediatric ECLS patients is that a significant decline in survival was not noted until patients reached a ventilator duration of longer than 14 days before ECMO. This is a large change from prior reports, which found that a ventilator duration of longer than 7 days was associated with worsening outcome. The use of high-frequency ventilation did not change over the period 1993 to 2007, and survival was not different between modes of ventilation. Patients who received high-frequency oscillation, however, did have a longer period of ventilation before ECMO than did those who received conventional mechanical ventilation (4.6 vs. 3 days). Nonsurvivors had a higher oxygenation index (48 vs. 42) and lower pH (7.27 vs. 7.31). Of note, pre-ECMO pH was progressively lower in both survivors and nonsurvivors as the years progressed. A trend in increased use of venovenous ECMO over years was also observed, and venovenous ECMO was associated with improved outcome. As the ELSO registry gives little detail on severity of illness before ECMO, however, interpretations of outcome comparisons between venoarterial and venovenous ECMO can be difficult.

Table 20-2 shows the major categories of pediatric respiratory failure who have received ECLS. One difficulty in interpreting ELSO data is that many patients who are currently receiving ECLS have a combination of respiratory and cardiac failure, making assigning them to one of the three major groups in the ELSO registry (respiratory, cardiac, or emergency cardiopulmonary resuscitation) difficult. This skews the ability to accurately report results and is one major area where the ELSO registry is being renovated. Without data on severity of illness beyond the respiratory indices previously discussed, identifying risk factors for outcome or complications is difficult. A growing population where this is easily represented is patients in septic shock: these patients often have both respiratory and cardiac dysfunction, as well as injury to other organs.[103] Outcome of patients in septic shock is believed to be lower than in patients with single-organ failure, although good comparisons on a large scale have not been conducted. Better refinement of organ failure and severity of illness by the ELSO registry may allow more sophisticated analyses of these complex patients in the future. Debate (without resolution) continues as to the efficacy of ECLS in high-output failure versus low-cardiac output states, where it seems more intuitive that the additional oxygen delivery provided by ECLS may be of greater benefit to tissue oxygenation. In the Australian series of children with sepsis, central cannulation achieved significantly greater flow rates than did peripheral cannulation.[63] This observation requires confirmation in a larger series. As with neonates, lower pH and higher Pa_{CO_2} values have been observed over time, with oxygenation index and Pa_{O_2}/FI_{O_2} remaining fairly constant (see Fig. 20-4). Despite the push for more venovenous support and better cannula availability, there does not seem to have been much of a change in the mode of ECLS support for respiratory failure patients. Although not statistically significant, an overview of data from the ELSO registry between 2000 and 2010 noted a slight increase in survival, 1.9% per year, despite the complexity of patients receiving ECLS.[104]

Adult

An increase in the use of ECLS in adults is occurring with the advent of new technology, the CESAR trial, the H1N1 epidemic, and reports of successful use around the globe.[15,105] Although most adult patients with respiratory support may be appropriate candidates for venovenous support, about one-third are managed with venoarterial cannulation. There has been an increase in venovenous support, however, over the past 2 years probably as a consequence of improved double-lumen cannulas and simpler, easier-to-use pumps

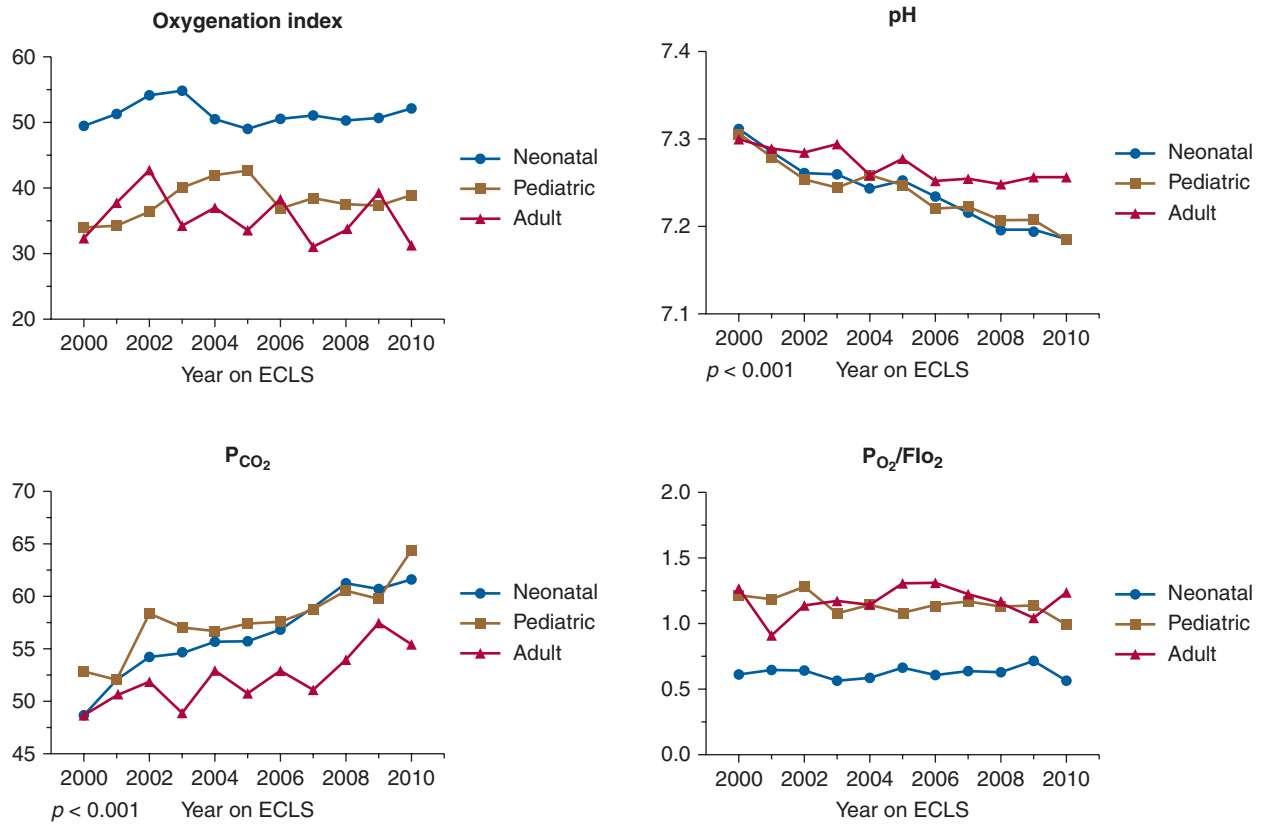

FIGURE 20-11 Severity indices and blood-gas parameters over time by age group (2000 to 2010). Oxygenation index and P_{O_2}/FI_{O_2} have decreased slightly in adults over time; pH has decreased and Pa_{CO_2} has increased, possibly reflecting greater use of "lung-protective" ventilation. Increased use of high-frequency oscillation ventilation (HFOV) in neonates and pediatric patients versus adults may influence the oxygenation index because mean airway pressure is often higher with HFOV.

and oxygenators.[106,107] Over the past year, three-quarters of adult patients received venovenous ECLS via multiple sites or use of a double-lumen cannula. Chapter 21 discusses the use of venovenous support and the various devices that focus on gas exchange. Within the ELSO registry, overall survival in adult respiratory failure is similar to that in pediatric patients at 56%. One difficulty with both pediatric and adult patients is that the largest category reported to ELSO is "other," which is obviously ill-defined and makes it difficult to identify exactly what type of disease these patients have. Similar to pediatric ECLS patients, adult survival between 2000 and 2010 has noted a slight (nonsignificant) increase in survival of 2.5% per year.

Cardiac

Although not the focus of this chapter, most patients requiring venoarterial support have cardiac failure, as a result of congenital heart defects, myocarditis, cardiomyopathy, cardiogenic shock, or before or after heart transplantation.[77,106–120] Patients who receive ECLS emergently as a rescue mode of resuscitation from cardiac arrest (external cardiopulmonary resuscitation [ECPR]) are now an increasing population within the ELSO registry. Up to July 2011, 694 neonatal ECPR patients were reported, with 39% surviving to discharge; 1347 pediatric EPCR patients, with 40% survival; and 591 adult ECPR patients, with 29% surviving to discharge. The acceptance of advanced cardiac life support as a resuscitative tool is highlighted by recent statements from groups such as the American Heart Association: "To consider extracorporeal cardiopulmonary resuscitation [cardiopulmonary resuscitation] for in-hospital cardiac arrest refractory to initial resuscitation attempts if the condition leading to cardiac arrest is reversible or amenable to heart transplantation, if excellent conventional cardiopulmonary resuscitation has been performed after no more than several minutes of no-flow cardiac arrest, and if the institution is able to rapidly perform extracorporeal membrane oxygenation."[121–123]

PATIENT MANAGEMENT DURING VENOARTERIAL EXTRACORPOREAL LIFE SUPPORT

Supporting patients who are receiving ECLS involves a mixture of providing adequate gas exchange, hemodynamic support, and minimizing risks of major complications such as

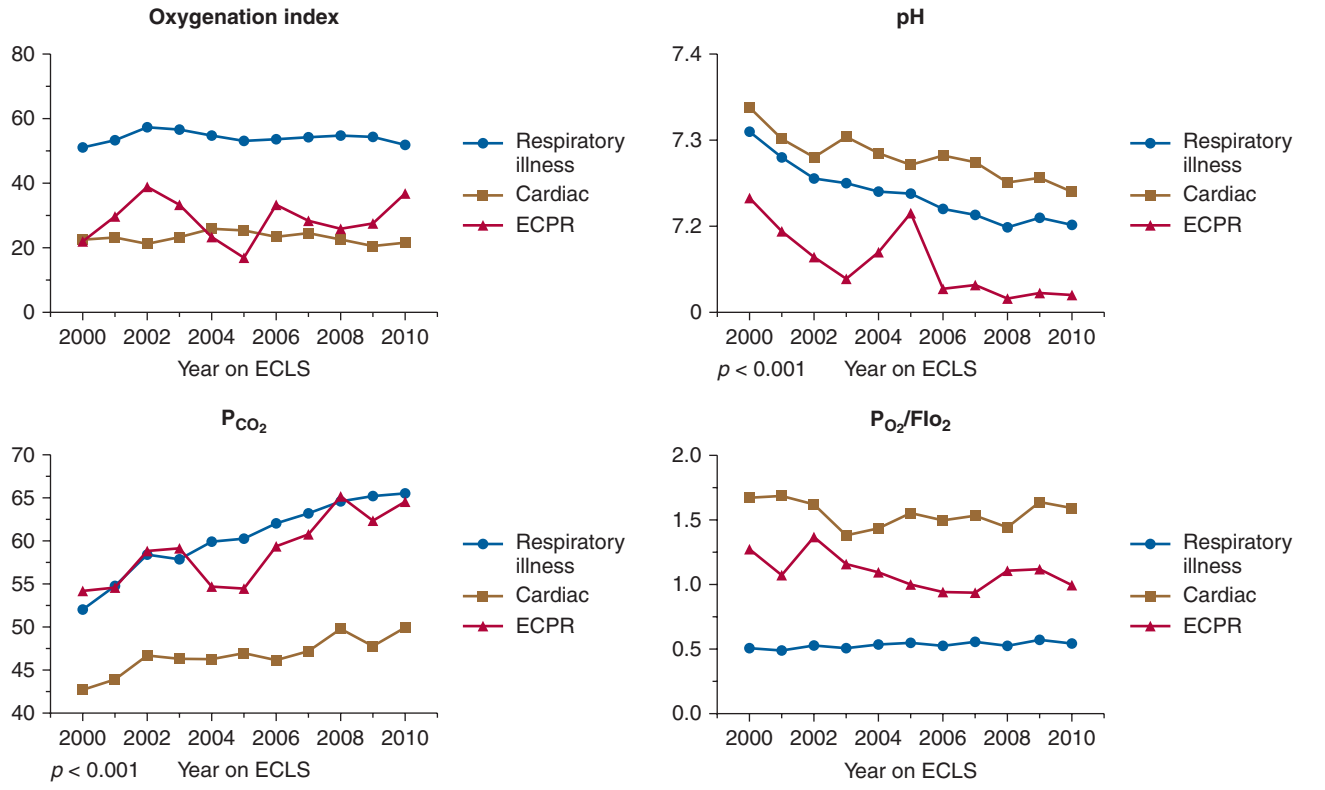

FIGURE 20-12 Severity indices and blood-gas parameters over time by diagnostic category (2000 to 2010). Oxygenation index and P_{O_2}/FI_{O_2} have decreased slightly in adults over time; pH has decreased and Pa_{CO_2} has increased, possibly reflecting greater use of "lung protective" ventilation. Increased use of high-frequency oscillation ventilation (HFOV) in neonates and pediatric patients versus adults may influence oxygenation index because mean airway pressure is often higher with HFOV.

bleeding and infection. As already discussed, gas exchange is controlled by a combination of blood flow to the oxygenator, surface area of the oxygenator, and sweep gas mixture. Oxygenation is predominantly influenced by the amount of blood flow to the oxygenator and carbon dioxide by the amount of sweep gas and surface area provided by the membrane in relation to the blood flow through the oxygenator. The measured oxygen saturation and carbon dioxide in the patient is a combination of the blood returning from the oxygenator and that being ejected by the patient's left ventricle. The extent of hemodynamic support is provided by the amount of blood returning from the oxygenator to the patient, as well as the systemic vascular resistance, oxygen delivery, and extraction rates in the patient. Patients with poor cardiac function require more support from the ECLS circuit, and oxygen delivery can also be increased by provision of well-oxygenated blood returning from the ECLS as compared to that poorly oxygenated blood ejected from the left ventricle in patients with severe respiratory failure. Careful monitoring of the adequacy of ECLS support over time is important, because failure to reverse lactic or metabolic acidosis in the first 24 hours after ECLS is associated with poor outcome.[124,125] As centrifugal pump systems are becoming more widely used in ECLS, it is important to recognize that these systems are especially reliant on adequate preload in the patient for venous drainage and sensitive to afterload for arterial return. When a patient's systemic vascular resistance (SVR) increases, flow from the centrifugal circuit to the patient can be reduced unless the revolutions per minute are increased to maintain forward flow and overcome the added resistance being generated in the patient. Thus, an unexpected decrease in flow in the ECLS circuit may be the result of agitation, temperature decrease, or other factors that can increase SVR. Afterload reduction or other measures that reduce SVR may augment forward flow from the circuit. Likewise, reduction in SVR, as in sepsis, may indicate a need for increased flow to provide adequate oxygen delivery. There are some patients in whom tissue oxygenation is inadequate no matter what the flow provided; these patients are the most difficult to treat and have high mortality.

To maintain consistent patient support, most centers set daily goals for bedside personnel to follow with regards to the levels of oxygen, carbon dioxide, blood pressure, hemoglobin, and anticoagulation to be maintained.

Exposure to the ECLS circuit causes destruction of red blood cells and adherence of platelets, necessitating intermittent administration of blood products.[126] The underlying illness may also affect blood product production or increased consumption. It is conventional wisdom to maintain hemoglobin close to 15 g/dL to optimize oxygen content, although no studies have definitively shown that maintaining a high hematocrit enhances survival.[127–129] The current debate regarding the risks and benefits of blood

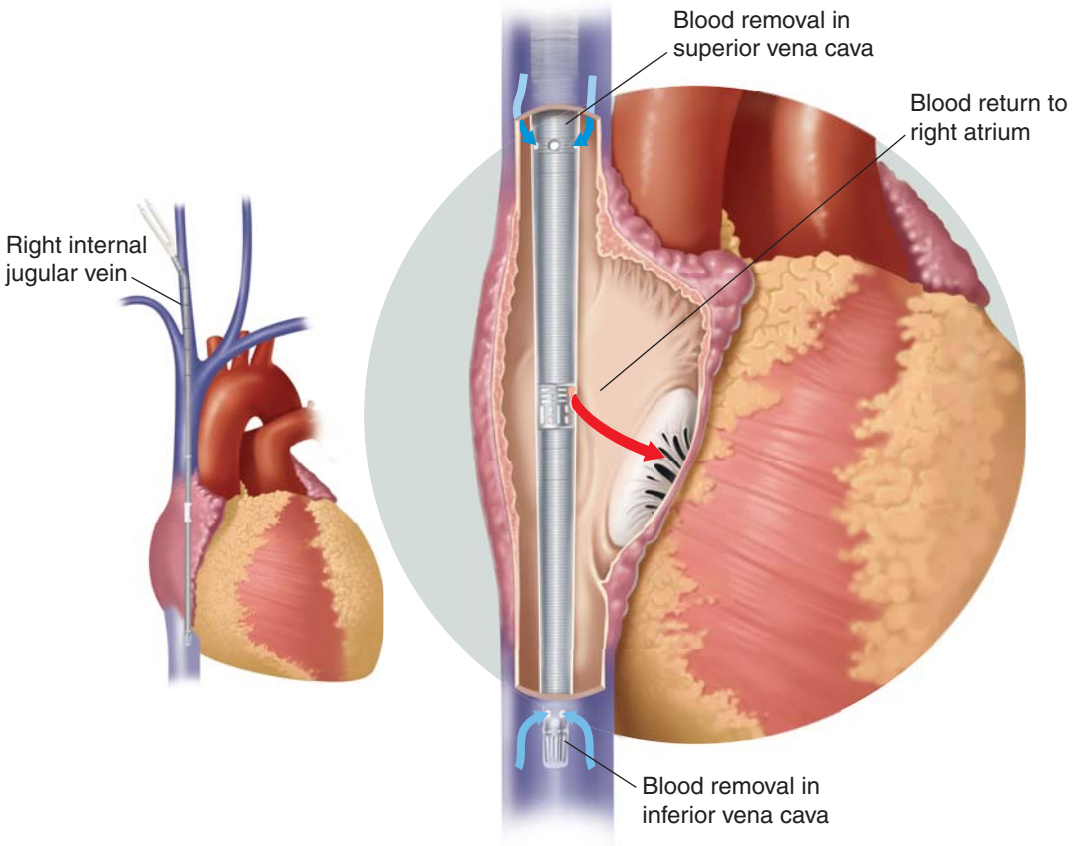

FIGURE 20-13 Venovenous double-lumen cannula. To be properly positioned, the distal drainage port must sit in the inferior vena cava at the right-atrial junction and proximal drainage port in the superior vena cava/right-atrial junction. The inflow port will be directed at the tricuspid valve. (Photo courtesy of Avalon Laboratories, LLC, Rancho Dominguez CA.)

transfusion in critically ill patients holds true for ECLS: some clinicians limit blood exposure by maintaining hematocrit levels closer to 30%, whereas others maintain levels greater than 40%.[130,131] The rheology of blood flowing through newly available cannulas, tubings, and oxygenators make this question a needed focus for future research to determine what is the "best" hematocrit during ECLS.

In a similar fashion, platelets levels have traditionally been maintained at more than 100,000, although there are numerous reports where patients have platelet levels of 20,000 or less without excessive bleeding. When bleeding does occur, attempts to increase platelet levels is a common practice, although, again, no definitive study shows that this step improves outcome.[132] Other coagulation indices (prothrombin time, partial thromboplastin time, fibrinogen) are followed, and corrected with administration of replacement factors with plasma or cryoprecipitate.

As anticoagulation with heparin is standard practice to avoid clotting of the extracorporeal circuit, maintaining adequate heparinization while avoiding bleeding is a delicate balance. The activated clotting time, determined by a bedside test, is the standard measurement used for adjusting heparin dosage with ECLS.[133] Usually maintained at levels of 180 to 220 seconds, recent studies show that this test correlates poorly with measured heparin levels and indices of anticoagulation measured by other means. There is a continued need to develop more effective methods to assess how the level of anticoagulation relates to observed bleeding. The best method to reverse bleeding that is poorly controlled by simple administration of blood products or surgical intervention to establish hemostasis remains the most perplexing problem with ECLS today. Use of factor concentrates, such as VIIa and antithrombin, as well as monitoring of antithrombin, factor Xa, and thromboelastograph data are the current methods used by clinicians in an attempt to address bleeding and anticoagulation concerns.[134–140] Bleeding remains one of the most common complications during ECLS. Lowering the heparin dose, even to the point of stopping heparin for 12 to 24 hours, has been successfully reported.[141] Heparin-induced thrombocytopenia is another problem, leading to use of alternative agents such as argatroban or lepirudin.[142] Bleeding has also been treated with agents that help stabilize clot, such as aminocaproic acid or aprotinin (which is no longer available in the United States).[143]

Maintaining adequate fluid balance is another goal during ECLS. While diuretics remain the mainstay of fluid removal, many patients have renal insufficiency requiring hemofiltration or dialysis.[144–148] The association between renal insufficiency and outcome has produced both reduced survival and unchanged outcomes in various reports.

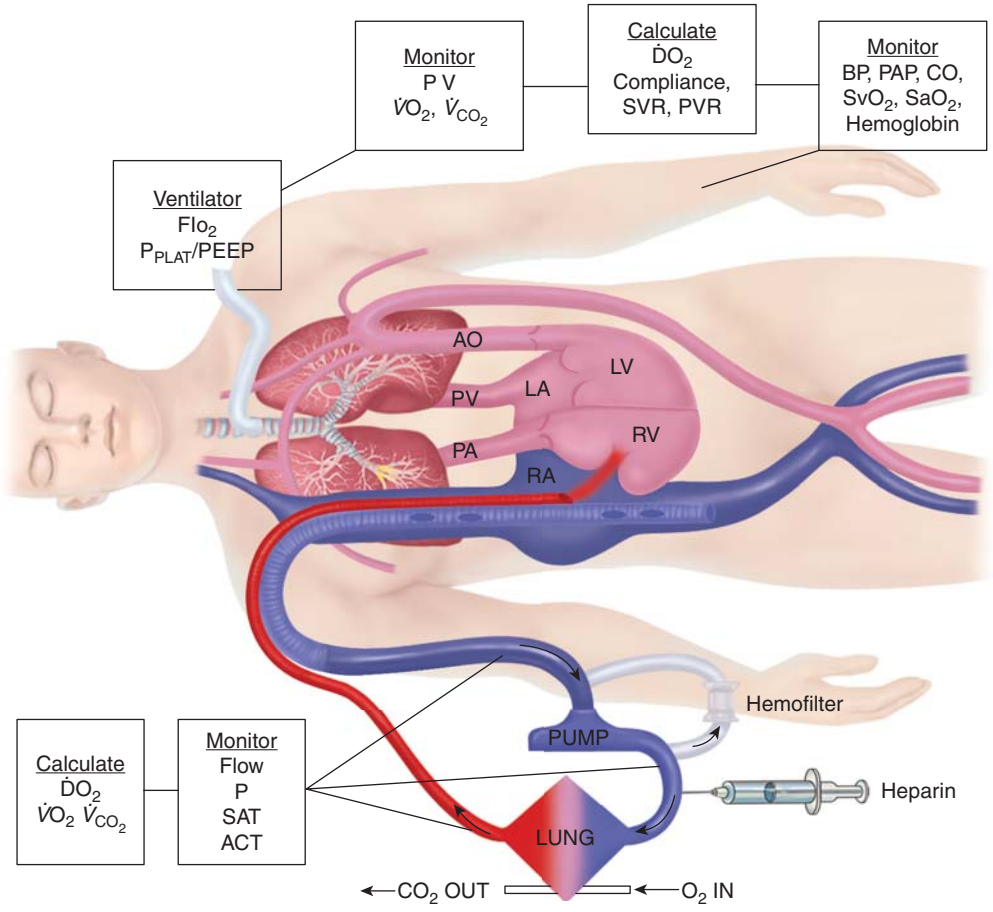

FIGURE 20-14 Venovenous ECLS circuit. Boxes represent calculations and parameters that can be measured by monitoring site. *ACT*, activated clotting time; *BP*, arterial blood pressure; *CO*, cardiac output (estimated); DO_2, oxygen delivery; *P*, pressure; *PAP*, pulmonary artery pressure (only in patients with a pulmonary artery catheter in place); *PEEP*, positive end-expiratory pressure; P_{PLAT}, plateau pressure; *PVR*, pulmonary vascular resistance; SaO_2, arterial oxygen saturation; *Sat*, saturation of blood; $S\bar{V}O_2$, venous oxygen saturation; *SVR*, systemic vascular resistance; *V*, volume; $\dot{V}_{CO_2}$, carbon dioxide; $\dot{V}O_2$, oxygen consumption. (Courtesy of Robert Bartlett, MD, with permission.)

Patients on ECLS are at risk for infection from changes in leukocyte function, nosocomial contamination of indwelling cannulas, and underlying critical illness.[149–151] Although infection during ECLS has been reported, and may be associated with worsened survival, the early practice of "prophylactic" antibiotics has been fairly well abandoned. Periodic monitoring and treatment of documented infection is important, and successful recovery, even after nosocomial infection with organisms such as fungus, has been reported.

Satisfactory nutrition is important to promote healing during ECLS. Enteral nutrition is preferred, although parenteral support may be required if a patient cannot tolerate full enteral calories.[152,153] The ability to tolerate feedings can be adversely affected by medications that reduce gut motility. Chief among these are narcotics.

One major difference in patient management between centers is the use of sedation.[154,155] The growing movement to lessen sedation and keep patients more awake on ECLS produces benefit beyond the ability to monitor neurologic function. It also promotes the ability to adequately feed the patient, and maintain normal body movement to reduce peripheral edema and promote skin integrity. Minimizing sedation decreases the inherent risks of using increasing doses of sedative and analgesic agents secondary to toxicity or withdrawal. The new, more miniaturized circuits and improved cannulas are one reason that more patients are being maintained wide-awake on ECLS, riding exercise bikes, or reading or eating ice cream (Fig. 20-15). Hopefully, this trend will continue.

The optimal ventilator management during ECLS is debatable, although all agree that minimizing ventilator-induced lung injury is a goal.[156–158] For the patient who is awake on venoarterial ECLS, because most gas exchange needs can be performed by the oxygenator, ventilator weaning to the point of extubation or minimal settings is a possibility. Some patients exhibit air-hunger or distress despite adequate oxygenation and ventilation provided by ECLS, and may require some pressure support or breathing assistance. Use of PEEP to maintain lung expansion may prevent atelectasis. Keeping inspiratory pressure of less than 30 cm H_2O is recommended. Promoting spontaneous breathing is important and recommended. Although use of high frequency ventilation is

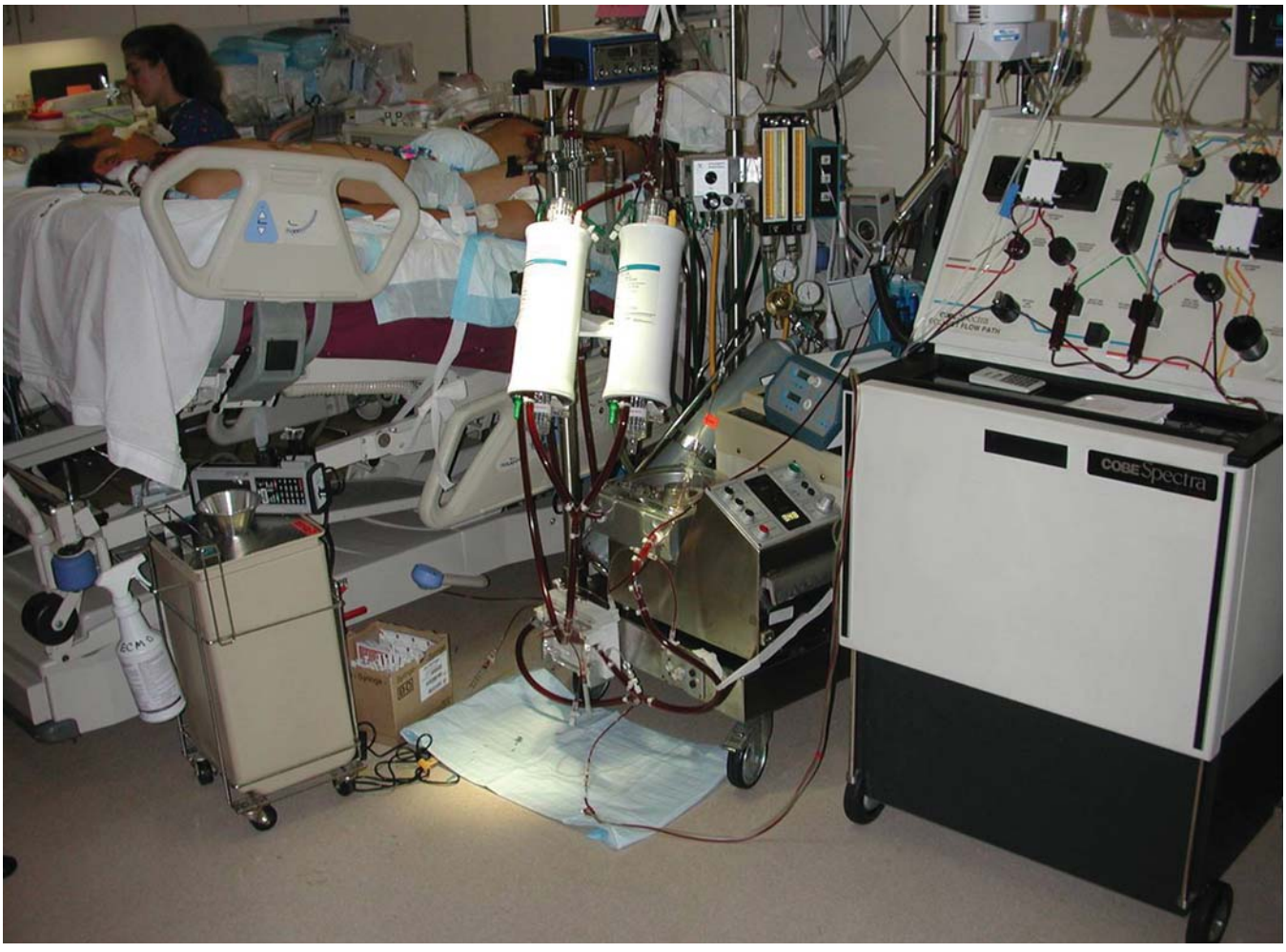

FIGURE 20-15 Ambulatory ECLS is becoming more common. (Photo courtesy of Ira Cheifetz MD, with permission.)

also described, this mode makes it difficult to keep patients awake and interpret actual tidal volumes. It is not commonly used unless attempts are being made to "push" the patient off ECLS secondary to complications.

Determining when a patient is ready for weaning is relatively simple during venoarterial ECLS. For patients with respiratory failure, improving oxygenation, clearing of the chest radiograph and improved tidal volumes at low pressure ventilation often herald recovery.[156–158] For patients with hemodynamic compromise, the ability to maintain adequate blood pressure and tissue perfusion on lowered flows of ECLS may indicate time to wean.[159] Use of low-dose vasoactive agents may be needed to assist cardiac function and facilitate weaning. To truly assess the ability to wean off venoarterial support, most centers clamp the patient off support and observe gas exchange and hemodynamics with the patient separated from ECLS support. Echocardiography to evaluate cardiac performance may also be useful during this period.[160] If weaning is not tolerated, the cannulas can be unclamped and the patient continued on ECLS. During clamping, it is important to remember that a patient needs to remain heparinized and the cannulas "flashed" by releasing the clamps every few minutes to prevent clotting. Patience is required while awaiting organ recovery. A recent report noted no difference in survival for patients who required ECLS for less than 10 days compared to those maintained for more than 21 days. The impact of ventilation days before ECLS has also shown that survival can be obtained with durations thought "too long" in the past.[161,162]

OUTCOME

Tables 20-1 and 20-2 list the overall survival for different patient groups. The greatest need is for long-term studies to assess neurodevelopmental outcome. Although short-term reports have found reasonable outcome, the impact of ECLS on school performance, risk for stroke later in life, and quality of life is not well known.[163,164] Older children and adults seem to have global neurologic function that matches that observed when they are discharged. The most in-depth reports of outcome have been in neonates with respiratory or

cardiac failure.[165–168] In the ELSO registry, neonates placed on ECLS for respiratory failure have an incidence of seizures of approximately 10%, although there is poor correlation with seizures noted during ECLS and overall neurologic outcome. Approximately 7% of neonates with respiratory failure are noted to have abnormal imaging studies (either hemorrhage or stroke). Two-thirds of neonatal respiratory failure survivors appear to have a normal neurodevelopmental outcome. Severe chronic respiratory disease in patients treated with ECMO is uncommon. Most authors report an incidence of bronchopulmonary dysplasia (defined as the need for oxygen beyond the first month of life) of 4% to 27%.[169] Most cases occurred in patients who had required extreme ventilator settings for more than 7 days before ECMO rescue. A follow-up report of neonates treated with ECMO and evaluated at 10 to 15 years post-ECMO found that although the ECMO patients had some impairment on pulmonary function testing, they had similar aerobic capacity and were able to reach similar anaerobic exercise goals as age-matched healthy controls.[170]

Of 5000 pediatric respiratory ECMO patients listed in the Registry through July 2011, 9% had intracranial infarct or hemorrhage on computed tomography examination. Brain death occurred in 6% of the patients and another 6% had seizures. Long-term neurologic outcome data are sorely missing in the pediatric population. In one review of fifteen pediatric and four adult patients, 58% survived to discharge. Patients were evaluated by use of the pediatric cerebral performance category, which measures cognitive impairment, and the pediatric overall performance category, which measures functional morbidity. Overall, 64% of survivors had normal pediatric cerebral performance category scores, 27% had mild disabilities, and 9% had moderate cognitive disability. Functional morbidity was normal in 27%, while 45% had mild disability, 18% moderate disability, and 9% were severely disabled.[171] In another small series of twenty-six patients followed 1 to 3 years after ECMO, 38% of pre–school-age children were described as normal and 31% exhibited abnormalities. Four patients (31%) who had prior neurologic dysfunction remained at baseline following ECMO. Among school-age children, 77% were described as normal by parental report. More specific neurologic follow-up in the pediatric age groups is needed.[172,173]

Neurologic complications in cardiac patients who receive ECMO parallel that of respiratory failure patients: 49% developed brain death, 3% had intracranial infarct, and 6% had intracranial hemorrhage. Because many cardiac patients are in a state of prolonged low cardiac output or sudden cardiac arrest before ECMO, the ability to assess neurologic function once ECMO is instituted is vitally important. Paralysis and sedation should be minimized until neurologic examination can be performed. This information is especially important in patients who are being listed for transplantation, so as to avoid transplanting a viable organ into an inappropriate recipient. Among neonatal patients placed on ECLS for cardiac dysfunction, most have congenital heart disease. Outcome of survivors reveals that approximately 50% have normal neurodevelopmental outcome. New reports of neurodevelopmental outcome in patients with congenital heart disease reveal abnormalities, which were previously unsuspected. How many of the post-ECLS abnormalities are the result of the underlying condition, pre-ECLS events, or the result of ECLS itself, cannot be ascertained.[172] In a recent 2-year follow-up study of ECLS performed in patients younger than 5 years of age, 46% survived to discharge and 41% were alive at the 2-year assessment.[174] Neurodevelopmental concerns were identified in most survivors, with a mean mental score of 73 ± 16, mental delay in 50% of survivors, and motor or sensory disability in 12%.

In an evaluation of patients who had undergone ECLS for resuscitation during cardiopulmonary resuscitation, 22% of patients had acute neurologic injury, defined as brain death, brain infarction, or intracranial hemorrhage identified by ultrasound or computerized tomography imaging. Brain death occurred in 11%, cerebral infarction in 7%, and intracranial hemorrhage in 7%. The in-hospital mortality rate in patients with acute neurologic injury was 89%. During ECMO, neurologic injury was associated with ECMO complications such as pulmonary hemorrhage, dialysis use, and cardiopulmonary resuscitation. Pre-ECMO factors, including cardiac disease and pH greater than 6.8, were associated with decreased odds of neurologic injuries. In a review of adults resuscitated from cardiac arrest with ECLS, overall survival was 27%, with brain death occurring in 28% of nonsurvivors. Pre-ECLS factors, such as higher Pa_{O_2}, lower Pa_{CO_2}, ECLS finding of pH less than 7.2, need for renal replacement therapy, and development of hyperbilirubinemia or central nervous system injury on ECLS, were associated with poor outcome.[175,176]

Among adult patients who received venovenous ECLS for respiratory compromise, a follow-up study of twenty-one patients noted that pulmonary function was at least 80% of normal. Quality-of-life measurements revealed that patients were adversely affected as compared to normal, although most had returned to work. Several other studies also note good recovery after ECLS survival.[177] Follow-up studies of patients from the CESAR trial will add much in terms of neurodevelopmental function in adult ECLS survivors.

Longer-term evaluation of patients surviving ECLS and comparison to patients with similar disease severity and diagnosis is imperative to adequately interpret neurologic outcome.[178–183]

THE FUTURE

The current extension of ECLS systems to older pediatric and adult patients in various clinical settings highlights the changes that have occurred in this environment. Progress in renal replacement, liver support, and plasmapheresis, and the development of new cardiac support devices applicable to pediatrics, may further expand the use of ECLS

techniques. Additionally, the development of small, portable systems for cardiopulmonary resuscitation may herald a new age of ECLS and make interhospital transport easier, safer, and more available.[184–186] Single-site, double-lumen catheters for venovenous ECMO may obviate the risks of arterial cannulation and offer the benefit of requiring only one surgical site for venous access. Heparin-bonded circuits may decrease the need for systemic anticoagulation and the risk of hemorrhagic complications.[92,184,187] Given the myriad adverse events associated with mechanical ventilation, the thought that extracorporeal gas exchange may obviate the need for intubation in respiratory failure has been suggested. Until the day when medical science may make the need for ECLS obsolete, research into ways to make it safer and more efficient should continue.[188]

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EXTRACORPOREAL CARBON DIOXIDE REMOVAL

Antonio Pesenti
Luciano Gattinoni
Michela Bombino

ARTIFICIAL ORGANS FOR RESPIRATORY FAILURE

Extracorporeal carbon dioxide removal ($ECCO_2R$) refers to a technique of life support focused on the removal of CO_2 from blood rather than improving blood oxygenation.[1] This chapter introduces the concept of $ECCO_2R$ and discusses some of the experience and future on this exciting topic. $ECCO_2R$ has been developed mainly with a view to applying it in patients with the most severe form of acute respiratory distress (ARDS).[2] We will try, however, to widen the perspective to cover also the possible role of $ECCO_2R$ in the prevention of hyaline membrane disease[3] and in the treatment of severe asthma,[4–8] multiple bronchopleural fistulas,[9–10] and severe chronic obstructive pulmonary disease.[11]

The mainstay of supportive treatment in ARDS is mechanical ventilation, a lifesaving procedure introduced in the management of patients with bulbar polio in the great epidemic that struck Copenhagen in 1952. These patients, paralyzed by polio, required long-term artificial ventilation;[12] they became the first critical care patients. The use of mechanical ventilators later was extended to all patients with severe acute respiratory failure, whose main problem often was altered gas exchange and not respiratory muscle weakness or paralysis. The critical care profession witnessed both the pros and cons of optimizing gas exchange through use of the ventilator: The focus shifted from high to low tidal volumes, from high to low airway pressures, and from high to lower inspired oxygen fractions (FI_{O_2}). It is provocative to consider how we support the failing lung. In ARDS, we use an artificial organ (the ventilator), which is designed to substitute for the respiratory muscles rather than to act as a gas exchanger. Technology has been the limiting factor for a widespread application of artificial gas exchange,[13] but research and development continues at a promising pace.

Membrane Oxygenators, Membrane Gas Exchange, and Membrane Lungs

Extracorporeal oxygenation was first provided as a heart–lung machine to render major cardiovascular surgery feasible and safe.[14] The first oxygenators were based on bubbling of oxygen through the blood or filming of blood in an oxygen atmosphere. To avoid the problems caused by the direct contact between blood and gas,[15,16] Kolff designed a membrane oxygenator,[17] which Clowes[18] and Kolobow[19] developed further into clinically applicable membrane gas exchangers.[20–22] Attention was focused on extracorporeal oxygenation, and the term *extracorporeal membrane oxygenation* (ECMO) was coined. Very little attention was paid to concurrent CO_2 removal: Hypocapnia was recognized as a common annoyance to be prevented by adding CO_2 to the gas ventilating the oxygenator.

Pioneers

In 1967, Ashbaugh et al[23] described ARDS. Soon this became a very common diagnosis in critical care, and mechanical ventilation moved to center stage as the main supportive therapy.[24] To optimize oxygenation, tidal volumes of 10 to 15 mL/kg were recommended, levels of positive end-expiratory pressure (PEEP) ranged from 5 to 60 cm H_2O.[25,26] With these ventilator settings, patients with ARDS experienced high inspiratory pressures and gross disruption of lung parenchyma. Barotrauma was common.[27–29] In 1972, Hill et al[30] published the first successful ECMO application in a patient with ARDS. Over the next few years, 217 patients with acute respiratory failure were supported with ECMO.[31] In 1973, a group of pioneers initiated a National Institutes of Health (NIH)-sponsored randomized trial of ECMO in severe ARDS. The entry criteria (Table 21-1) were intended to enroll a population with a 70% mortality rate. In fact, final mortality was 90% in both the control and ECMO groups.[32] The NIH-ECMO study proved that long-term extracorporeal life support was feasible, but it did not show any benefit on survival. Consequently, adult ECMO almost stopped,[33] with the exception of a few centers, such as the one where Bartlett conducted innovative studies on extracorporeal life support in infants and adults.

Meanwhile, astute observers pondered the question: Why did the NIH-ECMO study fail?[34]

Why Did the National Institutes of Health Extracorporeal Membrane Oxygenation Study Fail?

ECMO was aimed at buying time for the lung to rest and heal.[35] This could not be achieved under the persisting damage caused by high tidal volumes and pressures, however. Lung management in the ECMO group was not much different from that in the control group; this fact could explain the similarities in survival.[34] The choice of a venoarterial bypass, aimed in part at lowering pulmonary blood flow and pulmonary artery pressure, might have contributed to severe

TABLE 21-1: EXTRACORPOREAL MEMBRANE OXYGENATION ENTRY CRITERIA: $Pa_{O_2} \leq 50$ mm Hg (REPEATED THREE TIMES)

Study Entry Speed	Entry Testing Period (hours)	FI_{O_2}	PEEP, cm H_2O	Qs/Qt	Pa_{CO_2} mm Hg	ICU Care Duration Before Entry Testing (hours)
Rapid	2	1.0	≥5	—	30 to 45	—
Slow	12	≥0.6	≥5	≥0.3	30 to 45	≥48

ECMO EXCLUSIONS

Contraindication to anticoagulation (e.g., gastrointestinal bleeding, recent cerebrovascular accident, chronic bleeding disorder)
Pulmonary artery wedge pressure >25 mm Hg
Mechanical ventilation >21 days
Severe chronic systemic disease or another clinical condition that in itself greatly limits survival, for example,
- Irreversible central nervous system disease
- Severe chronic pulmonary disease (FEV_1 < 1 L, FEV_1/FVC < 30% of predicted, chronic Pa_{CO_2} > 45 mm Hg, chest X-ray evidence of overinflation or interstitial infiltration, previous hospitalization for chronic respiratory insufficiency)
- Total body surface burns >40%
- Rapidly fatal malignancy
- Chronic left-ventricular failure
- Chronic renal failure
- Chronic liver failure

FEV_1, forced expiratory volume in 1 s; *FVC*, forced vital capacity; *Qs/Qt*, right-to-left shunt fraction.

Source: Data from Zapol et al[32] and the National Heart, Lung, and Blood Institute.[85]

maldistribution of pulmonary blood flow. In turn, this might have deprived the lungs of enough blood flow to defend against the damage of high-tidal-volume, high-pressure ventilation.[36]

THE CONCEPT OF EXTRACORPOREAL CARBON DIOXIDE REMOVAL

In 1976, Kolobow et al[1] noted that membrane oxygenators more appropriately constituted membrane lungs than just oxygenators. They observed that a membrane lung can exchange CO_2 much more easily than it can oxygenate blood. They explored the potential of $ECCO_2R$ in a series of innovative experiments.

DISSOCIATING RESPIRATORY FUNCTIONS

Blood oxygenation and CO_2 removal take place through different mechanisms.[37] When normal venous blood reaches the lungs, its mixed venous oxygen tension (Pv_{O_2}) is typically 47 mm Hg, and mixed venous carbon dioxide tension (Pv_{CO_2}) is 43 mm Hg (Fig. 21-1). Let us assume that oxygen consumption and CO_2 production amount to 250 and 200 mL/min, respectively. The hemoglobin carried in venous blood (150 g/L) is normally 70% to 85% saturated; the lungs therefore can add just 40 to 60 mL of oxygen per liter of venous blood. Thus, to fulfill the requirements for oxygenation, we need a blood flow of at least 4 to 7 L/min. Note that ventilation is not required to oxygenate blood, whereas what is strictly needed is enough oxygen to compensate for its consumption and maintain a constant alveolar concentration. In summary, oxygenation requires a high blood flow (4 to 7 L/min) and a small supply of oxygen (250 mL/min). The opposite applies to CO_2 removal. Pv_{CO_2} content is at least double the maximum O_2 content (Fig. 21-2). Consequently, the normal CO_2 production per minute can be removed easily from less than 1 L of blood, provided that ventilation is high enough.

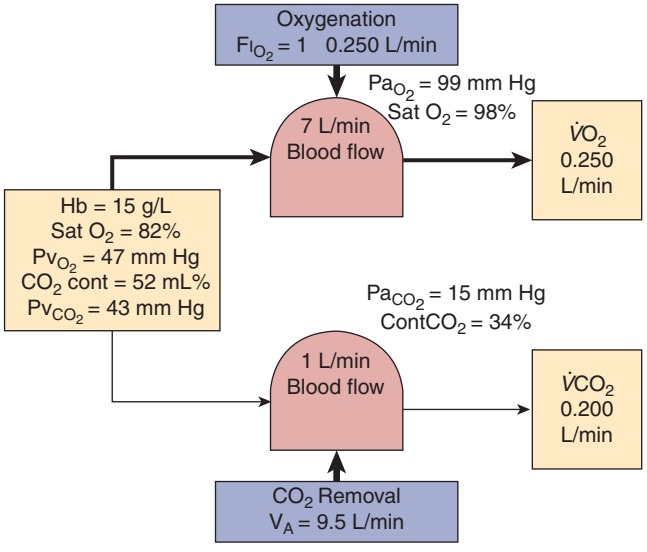

FIGURE 21-1 Dissociation of oxygenation and CO_2 removal. For normal mixed venous blood (v), oxygenation requires normal pulmonary blood flow and a continuous O_2 supply equal to O_2 consumption (250 mL/min in this example) without any ventilation. Removal of CO_2 can be accomplished by a reduced pulmonary blood flow if this is matched by a sufficiently high alveolar ventilation. (Reproduced, with permission, from Gattinoni L, Pesenti A, Kolobow T, Damia G. A new look at therapy of the adult respiratory distress syndrome: motionless lungs. *Int Anesthesiol Clin.* 1983;21:97–117.)

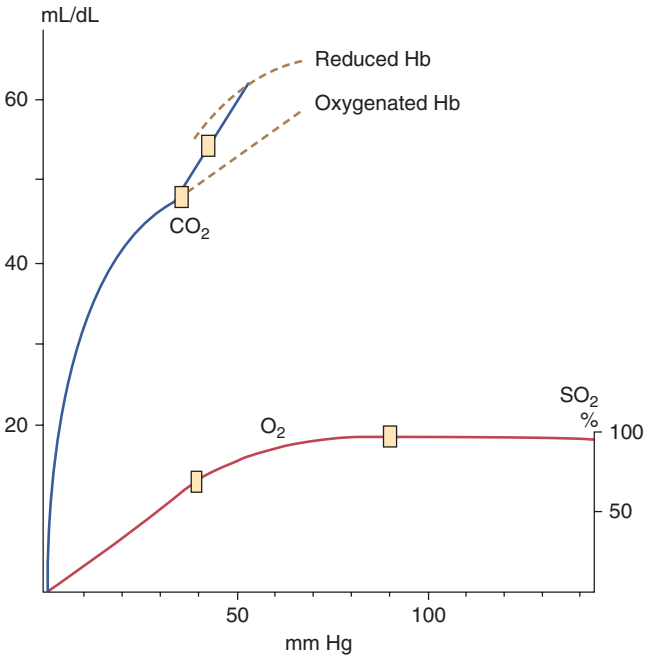

FIGURE 21-2 Gas dissociation curves for O_2 and CO_2 in blood. The *solid rectangles* represent arterial and mixed venous blood points. The line connecting the CO_2 dissociation curves for reduced and oxygenated hemoglobin (*Hb*) represents the nominal in vivo CO_2 dissociation curve as mixed venous blood becomes oxygenated in the lung (Haldane effect).

In conclusion, oxygenation requires a high blood flow, whereas CO_2 removal can be achieved at low blood flows. Kolobow et al[38] exploited the concept that if CO_2 is removed by a membrane lung through a low-flow, high-ventilation venovenous bypass, then oxygenation can be maintained by the natural lung without any ventilatory constraint. Physicians now had an opportunity to adjust the ventilator settings free of the constraints of tidal ventilation.

EXTRACORPOREAL CARBON DIOXIDE REMOVAL AND THE CONTROL OF SPONTANEOUS BREATHING

When CO_2 was removed by the membrane lung, unsedated lambs decreased their spontaneous ventilation, reducing both respiratory frequency and tidal volume.[39] Changes in

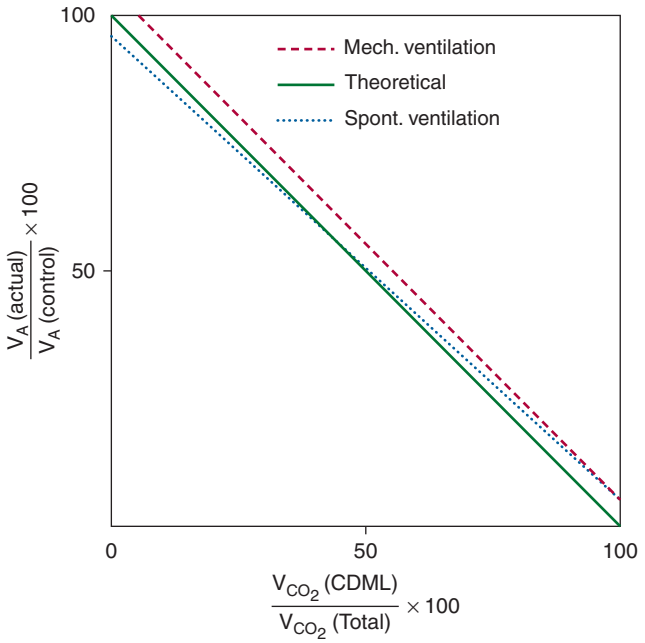

FIGURE 21-3 Alveolar ventilation (percent of control values) as a function of extracorporeal CO_2 removal (percent of total CO_2 production, i.e., V_{CO_2} of carbon dioxide membrane lung [CDML] plus natural lung). The theoretical values are computed assuming that Pa_{CO_2} and total V_{CO_2} are constant throughout the procedure. (Reproduced, with permission, from Gattinoni L, Pesenti A, Kolobow T, Damia G. A new look at therapy of the adult respiratory distress syndrome: motionless lungs. *Int Anesthesiol Clin.* 1983;21:97–117.)

alveolar ventilation were highly predictable, targeted toward a constant pH and Pa_{CO_2}. The greater the removal of CO_2 by the membrane lung, the greater was the decrease in alveolar ventilation (Fig. 21-3). The amount of CO_2 excreted by the natural lung decreased to maintain the total CO_2 removal (sum of membrane lung plus natural lung) constant and equal to the rate of CO_2 production by the body.

We can postulate that the control of spontaneous breathing in chronic obstructive pulmonary disease patients, while resetting the CO_2 balance with extracorporeal removal. Could be easy to achieve and predictable. We have experience about the control of respiratory drive in patients with ARDS during their recovery phase, when extracorporeal CO_2 removal can be titrated to the needs of the patient until weaning is completed.[40] Unfortunately, very little is known about the impact of $ECCO_2R$ upon the respiratory drive in the acute phase of ARDS.

Apneic Oxygenation

When CO_2 production is entirely removed by a membrane lung, then ventilation is no longer needed. The lung can be kept motionless, provided the alveolar oxygen concentration is kept constant by continuously supplying oxygen to match the body's O_2 consumption.[38] This process, known as *apneic oxygenation,*[41] is otherwise normally limited by the CO_2 rise. In this case, the membrane lung avoids an increase in CO_2. Apneic oxygenation therefore can be maintained at will by $ECCO_2R$: The lung can be kept completely motionless, the ultimate goal being lung rest and recovery.

Low-Frequency Positive-Pressure Ventilation

A decrease in respiratory compliance and functional residual capacity was noticed during apneic oxygenation. This led to the introduction of low-frequency positive-pressure ventilation (LFPPV). LFPPV with $ECCO_2R$[42] is simply apneic oxygenation to which a few (deep) breaths (sighs) per minute are added. With LFPPV-$ECCO_2R$, respiratory compliance and functional residual capacity can be maintained at baseline for days or weeks.

Alveolar Partial Pressure of Oxygen Control during $ECCO_2R$

During $ECCO_2R$, the respiratory quotient (R), that is, the ratio of CO_2 removal from the natural lung to oxygen uptake, changes according to the amount of CO_2 removed by the membrane lung. If baseline R equals 1, when we remove 50% of the body's CO_2 production by $ECCO_2R$, the new R of the natural lung will be 0.5. This affects alveolar oxygen tension (PA_{O_2}), which follows Riley's alveolar gas equation: At any given FI_{O_2}, when R decreases, PA_{O_2} decreases. Figure 21-4 shows the changes in FI_{O_2} required to maintain a constant PA_{O_2} at varying R values. Note that Pa_{CO_2} is held constant through the effect of $ECCO_2R$.[37]

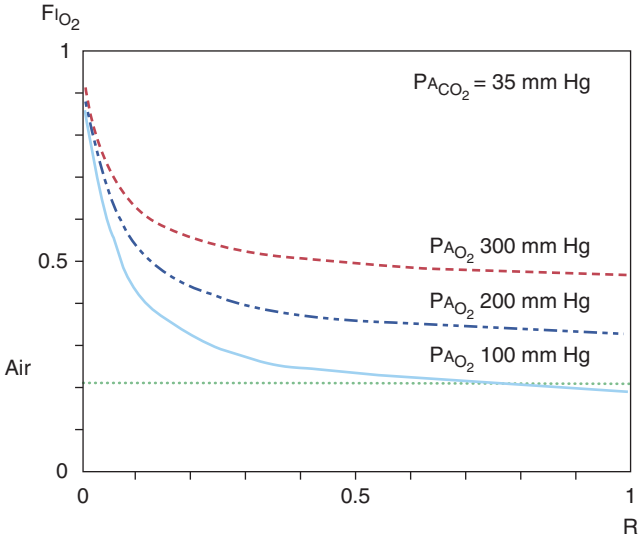

FIGURE 21-4 FI_{O_2} required to maintain a PA_{O_2} of 100, 200, and 300 mm Hg at constant Pa_{CO_2} as function of pulmonary respiratory quotient (R) according to Riley's alveolar air equation. (Reproduced, with permission, from Gattinoni L, Pesenti A, Kolobow T, Damia G. A new look at therapy of the adult respiratory distress syndrome: motionless lungs. *Int Anesthesiol Clin.* 1983;21:97–117.)

When $ECCO_2R$ equals 100% of the CO_2 produced by the body, then alveolar ventilation is nil, and FI_{O_2} must be raised to 1 to compensate for oxygen consumption. This does not at all mean that the alveolar oxygen concentration must be 100%. At this extreme of physiology, the gas mixture ventilating the membrane lung is of the utmost importance. At a steady state and during apneic oxygenation, the only gas exchange taking place in the lung is oxygen consumption. No nitrogen, CO_2, or water exits or enters the alveolar gas. If the gas ventilating the membrane lung is 100% humidified oxygen, then alveolar gas will be 100% oxygen minus CO_2 and water. If nitrogen (N_2) is added to the gas ventilating the membrane lung, then mixed venous blood P_{N_2} will equilibrate with P_{N_2} of the gas in the membrane lung, causing a corresponding change in PA_{O_2}.[38] During apneic oxygenation, despite the need to keep FI_{O_2} at 1, PA_{O_2} will be determined by the P_{N_2} of gas in the membrane lung. The role of membrane lung P_{N_2} in preventing reabsorption atelectasis during $ECCO_2R$ is entirely speculative but based on accepted physiology.[43]

Because of the Haldane effect, Pa_{CO_2} (and Pa_{CO_2}) will be higher than Pv_{CO_2} secondary to changes in the CO_2 dissociation curve related to the oxygenation of hemoglobin. During $LFPPV\text{-}ECCO_2R$, PA_{O_2} is mostly regulated by FI_{O_2}. If a continuous oxygen flow is added to compensate for oxygen consumption taking place between breaths, then many factors come into play. Experimental data exemplify the complexity of these mechanisms.[44]

RATIONALE FOR EXTRACORPOREAL CARBON DIOXIDE REMOVAL USE IN ACUTE RESPIRATORY DISTRESS SYNDROME

The goals of $ECCO_2R$ are different from those of the 1974 to 1977 ECMO trial[32] (Table 21-2). The reasons for these differences are rooted in ARDS pathophysiology. As already outlined, mechanical ventilation was developed by many workers[45–52] who pointed out how positive pressure and tidal volume interact in optimizing oxygenation. At the same time, however, the dangers and drawbacks of mechanical ventilation became apparent.[27] This was no surprise. Teplitz, a U.S. Army pathologist during the Vietnam War, described ARDS as "an end-stage pathologic picture which ... is not a new disease process ... but a result of iatrogenic modification of the pathology of noncardiogenic pulmonary edema." This view underlined the interaction between the original insult and the evolution and damages caused by treatment.[53]

Pontoppidan[50] suggested a tidal volume of 12 to 15 mL/kg as ideal for patients with ARDS. He also issued warnings[27–29] about the side effects of continuous positive-pressure ventilation and the appearance of lung damage related to high FI_{O_2}, high pressure, and high volumes.

In the late 1970s and early 1980s, the deleterious effects of mechanical ventilation were elucidated, and the concept of barotrauma evolved to that of volutrauma.[54,55] A third mechanism of damage was proposed later: the release of inflammatory mediators from the ventilated lung, leading eventually to multiple-organ failure and possibly death.[56–60] The term *ventilator-induced lung injury* became popular. In the meantime, a revolutionary idea was gathering momentum: Why strive to maintain a normal Pa_{CO_2} in patients with ARDS? Trying to achieve this goal can damage the lung severely, whereas accepting a higher than normal Pa_{CO_2} may induce only minor side effects. In 1990, Hickling et al[61] reported a better outcome by lowering tidal ventilation and tolerating high Pa_{CO_2} levels. They proposed the term *permissive hypercapnia,* indicating the price to be paid for limiting barotrauma. The targets of gas exchange in ARDS changed quickly.[62] A similar approach had been suggested previously for severe asthma.[63]

Several studies were performed to investigate the effects of lung-protective (low-pressure, low-tidal-volume) ventilation.[64–69] Only two studies[64,66] demonstrated benefit, but their effect has been striking. For the first time, the mode of ventilation was shown to affect outcome. One limitation with lung-protective ventilation, however, is hypercapnia. In selected patients, low-flow $ECCO_2R$ offers a very powerful tool for overcoming these limitations while offering total lung rest.

Hypoxemia, however, is the main characteristic of ARDS. Supportive therapy in ARDS is directed to its relief because hypoxemia is a major determinant of organ dysfunction and even may be the direct cause of death. Mechanical ventilation can be tailored to correct hypoxemia primarily by increasing FI_{O_2} and airway pressures.[70] Use of high airway pressure, however, is limited by several factors mainly related to hemodynamics and barotrauma. The solution is often to decrease tidal volume and increase frequency; this solution culminates in the use of high-frequency ventilation or oscillation.

TABLE 21-2: NATURAL (PATIENT) LUNG TREATMENT AND GOALS: ECMO VERSUS $LFPPV\text{-}ECCO_2R$

	ECMO[32]	$LFPPV\text{-}ECCO_2R$
GOALS		
Ventilation	Minimize FI_{O_2}, TRADITIONAL V_T	Minimize FI_{O_2}, LUNG REST
Extracorporeal circulation	Arterial Oxygenation	CO_2 removal (to rest the lung)
TREATMENT		
Lung ventilation	$V_T = 0.6$ L $P_{PEAK} = 50$ cm H_2O PEEP = 10 cm H_2O VR = 15/min	V_T low $P_{PEAK} = 35$ to 40 cm H_2O PEEP = 17 cm H_2O VR = 2 to 4/min
Lung perfusion	Low (0.1 Q_t)	High (all Q_t)

P_{PEAK}, peak airway pressure; Q_t, cardiac output; *VR*, ventilator rate; V_T, tidal volume.

With high-frequency oscillation, the mean airway pressure is in principle much higher than during positive-pressure ventilation. High-frequency ventilation has proven safe and effective in the treatment of adult patients with ARDS.[71–73] Use of high airway pressures, however, combined with inspiratory pressure limitation may lead to insufficient carbon dioxide removal.

In summary, the major aims of $ECCO_2R$ are to prevent ventilator-induced lung injury and barotrauma by limiting the ventilation in a nonhomogeneous lung, to put the lung to rest, and to foster healing while maintaining a selected Pa_{CO_2}. In addition, $ECCO_2R$ enables the application of a constant mean airway pressure targeted to optimal oxygenation and free of the constraints dictated by tidal ventilation.

CLINICAL APPLICATIONS: VENOVENOUS BYPASS

To the present time, the main indication for $ECCO_2R$ is severe ARDS secondary to a potentially reversible cause.[74,75] Generally accepted contraindications to extracorporeal life support and $ECCO_2R$ include the presence of significant bleeding, surgery in the preceding 72 hours, severe brain damage, uncontrolled severe sepsis, unresolved malignancies, severe chronic systemic disease, and ARDS of a known irreversible origin.

Bypass Technique

In 1979, Gattinoni et al[2] reported the use of LFPPV-$ECCO_2R$ in an adult patient with ARDS. The technique involved venovenous bypass: The common femoral and jugular veins were cannulated both distally and centrally through surgical cutdowns. The wounds and the multiple cannulation involved continuous oozing of blood and limitations in nursing care and patient mobility.[76] Subsequently, we developed a double-lumen cannulation of the femoral vein that allowed a single cutdown.[77] With saphenosaphenous bypass,[78] surgery became very superficial and distal drainage was unnecessary. The number of cannulas therefore was reduced to two. The most significant improvement in cannulation, however, came with the springwire-reinforced percutaneous cannulas,[9,79] which are placed by a modified Seldinger technique,[80] with a shorter procedure time, practically no bleeding, a reduced risk of cannulation-site infection, and very simple decannulation.

Blood flow is normally kept at 15% to 30% of the patient's cardiac output. The system must have a capability of running at 50 to 60 mL/kg/min should we need to substitute for the natural lung oxygenation (Fig. 21-5).

Our current standard includes the use of two springwire-reinforced percutaneous femoral cannulas (20F to 28F), a centrifugal pump, and a plasma tight hollow-fiber polymethylpentene oxygenator. The entire circuit is surface heparinized to minimize the need for systemic anticoagulation.[81–83]

Anticoagulation

Following an initial 50 to 100 IU/kg intravenous heparin bolus at the time of cannulation, heparin infusion is started, aiming at the selected activated clotting time (150 to 200 seconds in the case of Jostra Bioline surfaces). Surface-heparinized circuits can even be run without any systemic anticoagulation[84] for at least 12 to 48 hours as needed to stop or prevent incidental bleeding. Antithrombin III activity is maintained around 100% to promote surface-bonded and intravenous heparin function. Platelets are transfused when lower than 50,000/μL. When heparinized surfaces are not in use, activated clotting time and/or partial thromboplastin times of 1.5 to 2 times normal must be maintained at all times.

Clinical Management

$ECCO_2R$ normally is started in a sedated, paralyzed patient. After the initial adjustments (which normally take 1 to 2 hours), the ventilator is set to provide a low-frequency sigh over a baseline constant PEEP (e.g., using intermittent mandatory ventilation or biphasic positive airway pressure). PEEP is adjusted to maintain mean airway pressure at the prebypass level and to prevent acute worsening of lung edema. A catheter inserted into the inspiratory line provides a constant oxygen supply and constant PEEP during the long expiratory pause. As soon as possible, attempts are made to reestablish spontaneous respiratory activity, most often in the form of pressure supported breathing with an intermittent sigh (e.g., biphasic positive airway pressure plus assisted breathing or intermittent mandatory ventilation plus pressure support).

Hemodynamics are not affected by the venovenous bypass. Changes in lung function can be followed with venous admixture measurements. Very high values of mixed venous saturation and arterial O_2 saturation suggest decreased cardiac output with an increased proportion of extracorporeal blood flow/total cardiac output. When lung function improves, weaning is attempted by decreasing FI_{O_2} and PEEP and by decreasing the CO_2 removal from the membrane lung.[40] When necessary, the extracorporeal circuit setup allows low-flow venovenous $ECCO_2R$ to be converted into high-flow venovenous ECMO, and management then is focused on achieving a viable oxygenation despite an extremely reduced or even absent natural-lung oxygen transfer.

Complications of Venovenous $ECCO_2R$

We have never stopped $ECCO_2R$ because of a technical accident. From day to day, however, various changes of circuit elements may be required, mainly involving the membrane lung and/or the centrifugal pump(s).

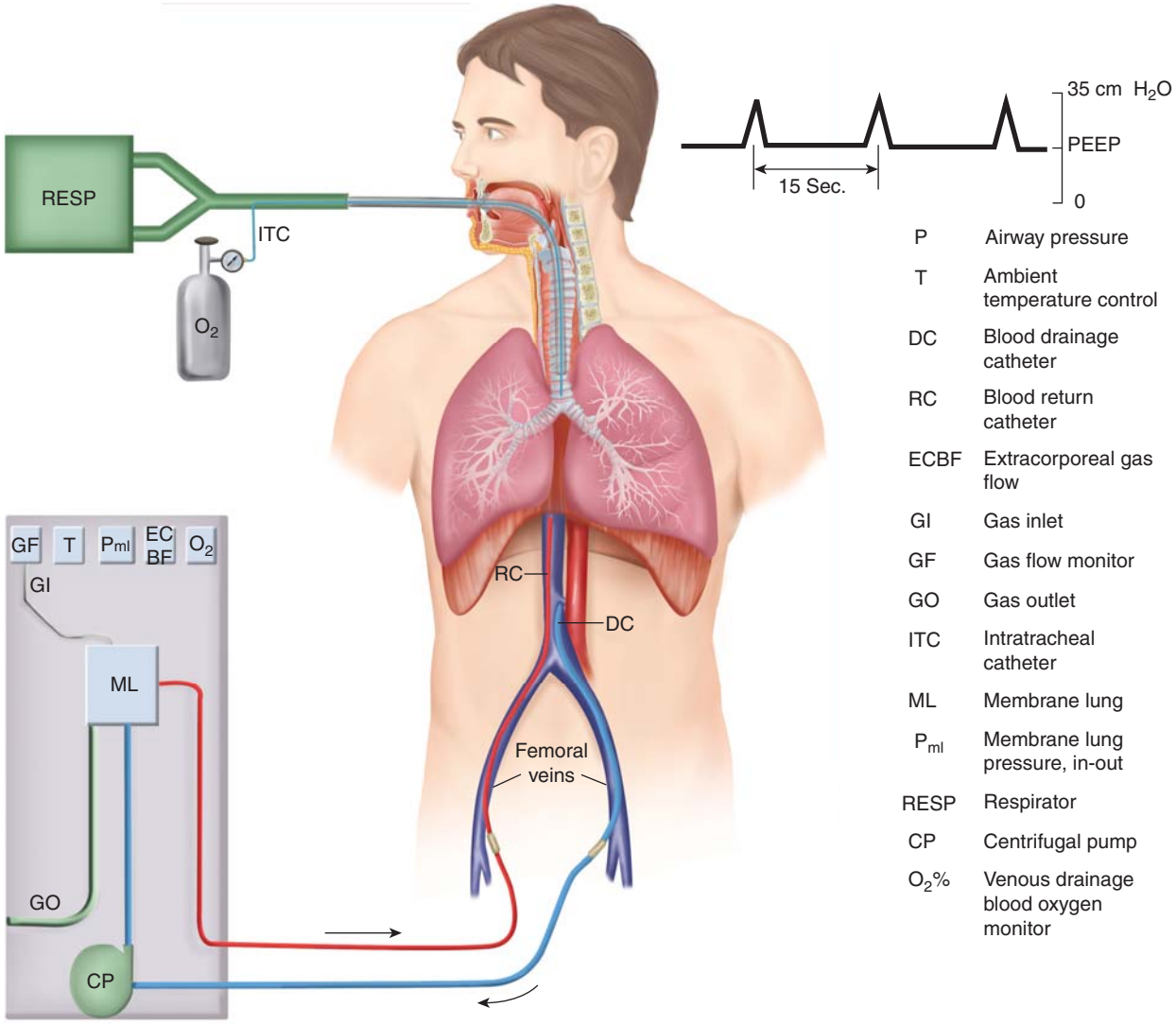

FIGURE 21-5 LFPPV-ECCO$_2$R circuit. (Reproduced, with permission, from Gattinoni, et al. *JAMA*. 1986;256:881–886,. Copyright © 1986 American Medical Association. All rights reserved.)

Bleeding always has been the major complication with extracorporeal life-support techniques. The NIH-ECMO study reported an average blood-product transfusion of 3575 mL/day.[85] In 1986, we reported[86] an average blood-product requirement of 1.8 L/day in our first forty-three patients. The use of percutaneous cannulation coupled with heparinized surfaces decreased the packed-red-cell requirement to 200 to 300 mL/day.[75] Bleeding from the chest drainage tubes is a major complication that often demands a surgical approach.[87] The major threat posed by extracorporeal support remains intracranial hemorrhage. We reported that a prebypass Pa_{CO_2} of greater than 75 mm Hg, disseminated intravascular coagulation, or a positive brain computed tomographic scan before bypass increase the risk of fatal intracranial hemorrhage during bypass.[75]

Clinical Results in Acute Respiratory Distress Syndrome Patients

It is difficult to isolate from the literature the experience with venovenous ECCO$_2$R because of undefined boundaries between venovenous ECCO$_2$R, venovenous ECMO, and partial extracorporeal CO_2 removal (PECO$_2$R).[40] ECCO$_2$R refers more to a way of managing the diseased lung rather than to technical details, and the flexible handling of the circuitry is one of the advantages of ECCO$_2$R. The technique can shuttle back and forth between venovenous ECCO$_2$R, venovenous ECMO, and PECO$_2$R in the same patient.

Table 21-3 is an attempt to collect the available experience on ECCO$_2$R, defined as such by authors, including our own data (see also Table 21-4). At the time of writing, patients

TABLE 21-3: VENOVENOUS $ECCO_2R$ FOR ARDS: INTERNATIONAL EXPERIENCE

Author (Ref.)	Year	Center	No. Patients	Survivors	% Survival
Wagner (87)	1990	Marburg (Germany)	76	38	50%
Bindslev (82)	1991	Stockolm (Sweden)	14	6	43%
Brunet (121)	1993	Paris (France)	23	12	52%
Morris (88)	1994	Salt Lake City (USA)	21	7	33%
Guinard (122)	1997	Paris (France)	10	4	40%
Gattinoni, Pesenti	2008	Milan, Monza (Italy)	124	49	40%
Total			268	116	43%

with severe ARDS are still starting on $ECCO_2R$ later and later in their illness. Whether this is wise, we have our doubts. Moreover, the time spent on bypass gets increasingly longer (139 days for our longest survival run), probably indicating increases in unmeasured elements of disease severity at the time of connection. Despite these considerations, many patients with ARDS suffer from complications related to ventilator-induced lung injury and are doomed to an unfavorable outcome. ARDS carries a substantial mortality, 31% to 39.8% in the ARDS Network studies.[66]

Only one controlled, randomized trial has been conducted on the effect of LFPPV-$ECCO_2R$ in patients with severe ARDS.[88] The investigators enrolled forty patients meeting the original NIH-ECMO entry criteria. Nineteen patients were randomized to LFPPV-$ECCO_2R$ and twenty-one to control mechanical ventilation. Survival was equivalent in the two groups: seven survivors in the $ECCO_2R$ and eight in the control group. The investigators and accompanying editorialists[89] concluded that extracorporeal support is not recommended in ARDS.

A more balanced interpretation of this study, however, must take into account several considerations.[90–92] The incidence of uncontrollable bleeding, leading to premature interruption of the treatment in seven of nineteen patients, was extremely high. More surprisingly, of seven $ECCO_2R$ survivors, five had been disconnected as an emergency because of severe bleeding. Average transfused blood products (packed red cells plus fresh-frozen plasma) was 3.39 L/day (4.79 L/day in the survivors). A problem in the management of blood clotting or the surgical procedure to control bleeding appears obvious when related to contemporary published experience. This study suggests that despite a high rate of catastrophic bleeding in the $ECCO_2R$ group, the net outcome was not worse in the $ECCO_2R$ group. As such, $ECCO_2R$ may prove beneficial, provided that the associated bleeding problems are handled effectively.

TABLE 21-4: OUTCOME WITH $ECCO_2R$ IN MILAN-MONZA (1979 TO 2008; ADULT PATIENTS)

	Survivors	Nonsurvivors	p
No. Patients	49 (40%)	75 (60%)	
Age	33.9 ± 14.4	34.6 ± 15.2	NS
Days from intubation	11.9 ± 13.5	11.6 ± 9.1	NS
Pa_{O_2}/FI_{O_2}	92.9 ± 44.6	76.3 ± 40.2	0.0353
Qs/Qt	0.46 ± 0.12	0.51 ± 0.10	0.0179
Pa_{CO_2} mm Hg	54.8 ± 17.2	63.9 ± 20.2	0.0106
PEEP cm H_2O	11.8 ± 5.5	13.2 ± 4.2	NS
PIP cm H_2O	41.8 ± 8.0	45.9 ± 10.5	0.0279
Cardiac index (L/min)	5.3 ± 1.6	4.9 ± 1.3	NS
Heart rate (bpm)	132 ± 19	125 ± 20	NS
BP mm Hg	84.5 ± 14.1	80.9 ± 13.7	NS
CVP cm H_2O	11.1 ± 5.7	11.3 ± 5.1	NS
PAP mm Hg	33.1 ± 8.9	35.3 ± 7.9	NS
WP mm Hg	13.1 ± 6.5	13.9 ± 5.0	NS
On vasopressor	6 (12%)	25 (32%)	0.0174
Days of $ECCO_2R$	15.7 ± 21.9	15.7 ± 16.3	NS

BP, arterial blood pressure, mean; *CVP*, central venous pressure; *PAP*, pulmonary artery pressure, mean; *PIP*, peak inspiratory pressure; *Qs/Qt*, intrapulmonary shunt; *WP*, pulmonary artery wedge pressure.

RECENT CLINICAL DEVELOPMENTS: ARTERIOVENOUS BYPASS

Venovenous $ECCO_2R$ still remains a complex procedure, reserved for centers with experience and capabilities to run it safely in very diseased patients. In an effort to simplify extracorporeal respiratory assist, Barthelemy et al[93] reported that an animal could be supported for up to 24 hours by a pumpless artery-to-vein extracorporeal system in combination with apneic oxygenation. Subsequently, Awad et al[94] demonstrated the feasibility of arteriovenous CO_2 removal ($AVCO_2R$) for up to 7 days in sheep. Young et al[95] evaluated $AVCO_2R$ in a femorofemoral arteriovenous (AV) model, both with and without a blood pump. A step forward in pumpless $AVCO_2R$ came with the design of very-low-resistance membrane lungs.[96] A pumpless system is expected to minimize the foreign-surface interactions and blood-element shear stress.

$AVCO_2R$ (also termed *interventional lung assist* [iLA] or *pumpless extracorporeal lung assist*) was studied in normal animals and in experimental lung-injury models.[97–100] Short-term feasibility and safety phase I trials were performed successfully in patients,[101] showing that an AV shunt coupled with a low-resistance membrane lung can achieve

an $ECCO_2R$ between 70% and 100% of the total CO_2 production. Reng et al[102] published a collection of ten patients treated by what they named "pumpless ECLA." In 2006, a paper from the same institution reported ninety patients with ARDS treated with $AVCO_2R$, with a survival rate of 41%.[103] The authors pointed out that the contribution of the bypass to oxygenation was moderate, while the removal of CO_2 averaged 140 mL/min allowing a consistent decrease in ventilation. The paper also reported a high rate of complications, up to 24%, mainly related to the arterial cannulation. More recently Zimmerman et al[104] reported a higher survival rate (50.9%) and fewer complications (11%) with a reduction of arterial cannula size, allowing a residual lumen equal to or greater than 30% of the vessel diameter. The iLA Registry,[105] updated to 500 cases by July 2010, mostly ARDS (268 cases, 53.6%) and chronic obstructive pulmonary disease exacerbations (125 cases, 25%), points out that early institution of iLA produces a 42% higher survival rate. We are now awaiting the results from the prospective randomized Extrapulmonary Interventional Ventilatory Support for Lung Protection in Severe Acute Respiratory Distress (Xtravent) trial that completed enrollment on January 2011.[106]

AV bypass can be established quickly, it is simple and does not require specialized personnel. The clinical application is limited to patients whose cardiovascular system can tolerate the increased cardiac output and whose arterial blood pressure can drive enough blood to achieve a sufficiently high CO_2 removal (shunt flows are 1 to 2.5 L/min). Although vasopressors can be added to increase shunt blood flow, no direct intervention is possible to otherwise regulate it. Lastly, $AVCO_2R$ consists of pure CO_2 removal: with the exception of extremely severe hypoxemia, the amount of oxygen that can be transferred to arterial blood can influence the systemic oxygenation only marginally.[107] In contrast to venovenous $ECCO_2R$, no simple conversion to ECMO is possible. The technique is fascinating and promising in its extreme simplicity, however. Very-low-resistance, surface-heparinized membrane lungs are now available for clinical use.[97]

Pumpless devices have been recently used as bridge to lung transplantation[108–110] with interesting results. The rapid implementation and extreme simplicity of the iLA system makes it suitable for the aerial transportation of critically ill patients with respiratory failure.[111,112]

NEW TRENDS: LOW FLOW PARTIAL CARBON DIOXIDE REMOVAL

The clinical application of $PECO_2R$, originally described by Marcolin et al,[40] was successfully implemented in a patient with severe and persisting bilateral bronchopleural fistulas.[9] The technique consisted of a very low flow (0.4 to 0.6 L/min) venovenous bypass, allowing a rapid liberation from mechanical ventilation to spontaneous breathing and healing of the fistulas.

More recently, Livigni[1] et al[13] described the application of a modified continuous venovenous hemofiltration circuit comprising ultrafiltrate recirculation and a membrane lung to achieve partial CO_2 removal in sheep. In 2009, Terragni et al[114] reported on the successful application of the same device to decrease tidal volume to levels lower than the standard 6 mL/kg predicted body weight (Fig. 21-6) in patients

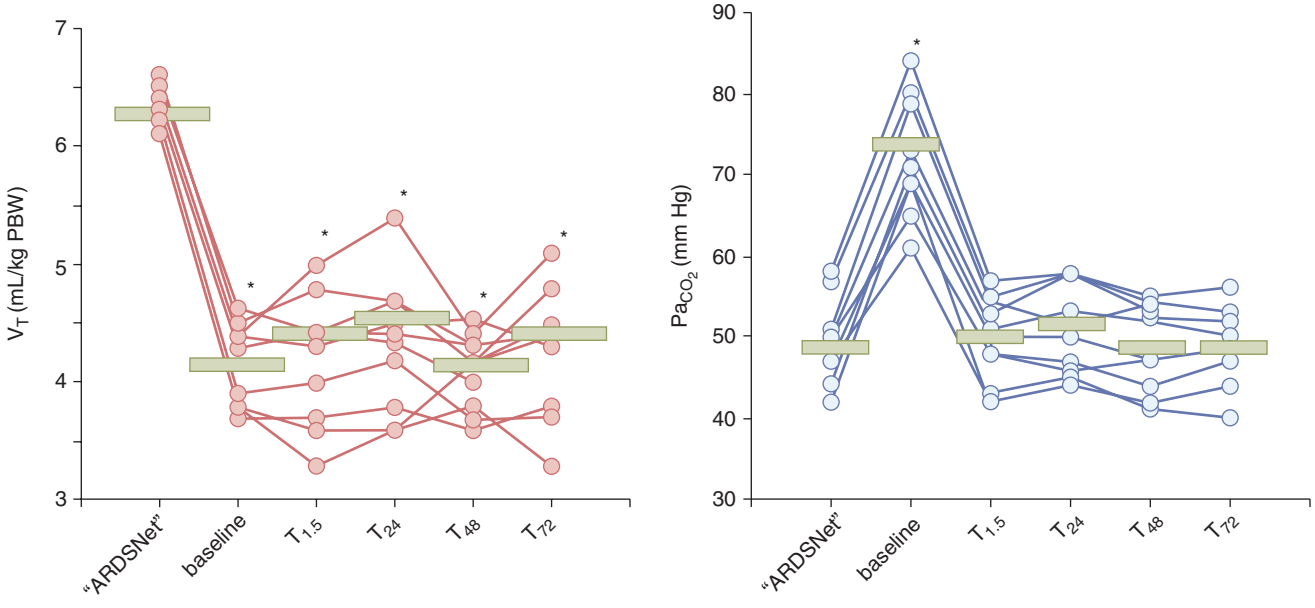

FIGURE 21-6 Individual and average (*horizontal bar*) values of tidal volume (V_T) and Pa_{CO_2} during Acute Respiratory Distress Syndrome Network ("*ARDSNet*") strategy, after lowering V_T and before initiating carbon dioxide removal (*baseline*), and 60 to 90 minutes (T1.5), 24 hours (T24), 48 hours (T48), and 72 hours (T72) after initiation of carbon dioxide removal. * P versus ARDSNet strategy. The data show how CO_2 removal is able to maintain normocapnia despite a reduced, noninjurious tidal volume. (Reproduced, with permission, from Terragni PP, Del Sorbo L, Mascia L, et al. Tidal volume lower than 6 ml/kg enhance lung protection: role of extracorporeal carbon dioxide removal. *Anesthesiology*. 2009;111:826–835.)

suffering lung hyperinflation in spite of lung-protective ventilation. The same investigator group[115] reported that at least 30% of patients with ARDS undergo lung hyperinflation despite limiting tidal volume to 6 mL/kg.

Batchinsky et al[116] successfully applied a new device (Hemolung) in swine that was able to remove a substantial proportion (72 mL/min) of an animal's CO_2 production at blood flows comparable to those used in dialysis or hemofiltration (400 to 500 mL/min). Preliminary clinical experience in five spontaneously breathing patients with chronic obstructive pulmonary disease has been recently reported.[117]

Zanella et al[118] achieved the remarkable result of a CO_2 removal of more than 150 mL/min from a blood flow of 500 mL/min in pigs. The technique includes the administration of a metabolizable acid (lactic acid) to convert blood bicarbonate to gaseous CO_2 before the membrane lung.

CONCLUSIONS

$ECCO_2R$ is a fascinating approach to the management of respiratory failure and is a powerful tool for overcoming any ventilatory problem. For patients with the most severe form of ARDS, a venovenous circuit with the possibility of shifting to modern full venovenous ECMO (if needed) may be a better solution. Venovenous $ECCO_2R$ should be limited to centers where appropriate technical skills, motivations, personnel, and experience are available.

In its purest conceptual application, $ECCO_2R$ is achieved by an arteriovenous pumpless shunt. Exciting perspectives are offered by the development of low or very low blood flow extracorporeal CO_2 removal techniques.[113–118] Their applications open up the possibility of substantially limiting the invasiveness of mechanical ventilation, to decrease the rate of failure of noninvasive ventilation, to limit the use of endotracheal intubation, and therefore substantially limit the incidence of ventilator associated pneumonia (actually an intubation-related disease). The need for increased airway pressure could be essentially covered by invasive or noninvasive continuous positive airway pressure, and sedation needs might as well be markedly decreased.

The dream of a fully awake, nonintubated, eating, drinking, and communicating patient connected to something like a hemodialysis machine, rather than a fully sedated, intubated, mechanically ventilated patient might finally have a chance of becoming true.[119,120]

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TRANSTRACHEAL GAS INSUFFLATION, TRANSTRACHEAL OXYGEN THERAPY, EMERGENCY TRANSTRACHEAL VENTILATION

Umberto Lucangelo
Avi Nahum
Lluis Blanch

Clinical evidence highlights the importance of limiting airway pressure during mechanical ventilation. In addition, experimental results suggest the importance of avoiding lung overdistension and cyclic end-expiratory airspace collapse and reexpansion, indicating that both phenomena promote mechanical damage and release of inflammatory mediators.[1–3] Unfortunately, interventions that can attenuate the structural insult caused by mechanical ventilation, such as the use of low tidal volume, high positive end-expiratory pressure, and reduced respiratory rate, can limit total minute ventilation.[4,5] In this context, transtracheal oxygen therapy and tracheal gas insufflation (TGI) could have a role as adjuncts to mechanical ventilation.[6–10]

BASIC PRINCIPLES

Mechanism of Action

TGI attempts to minimize dead space by delivering fresh gas through an intratracheal catheter to flush the anatomic dead space free of CO_2. During TGI, low-to-moderate flows of fresh gas introduced near the carina, either continuously or in phases, dilute the CO_2 in the anatomic dead space proximal to the catheter tip. Because CO_2 is washed out during expiration, less CO_2 is recycled back into the alveoli during the subsequent inspiration. Any catheter flow during inspiration contributes to the inspired tidal volume (V_T) but bypasses the anatomic dead space proximal (mouthward) to

the catheter tip. At higher catheter flow rates, turbulence generated at the tip of the catheter by the jet stream can enhance gas mixing in regions distal to the catheter tip, thereby contributing to CO_2 removal.[11–14] The fresh gas stream exiting the catheter tip rapidly establishes an expiratory front beyond the catheter tip between CO_2-rich alveolar gas and CO_2-free fresh catheter gas.[13] This front is practically abolished by inverting the catheter tip and directing the catheter jet mouthward, thus eliminating the distal effect of TGI.[12] These observations indicate that the primary mechanism of CO_2 elimination during TGI is expiratory washout, and the forward-directed TGI penetrates a substantial distance into the central airways, extending the compartment susceptible to CO_2 washout with a smaller contribution of turbulence beyond the straight catheter tip. Consequently, partial pressure of arterial carbon dioxide (Pa_{CO_2}) during TGI falls as a nonlinear function of catheter flow rate. Initially, modest flow rates achieve large decrements in Pa_{CO_2}, but once the anatomic dead space is flushed free of CO_2, the effect on Pa_{CO_2} diminishes as catheter flow rate increases.[6,11]

Modes of Operation

During TGI, fresh gas can be delivered continuously, or delivery can be timed to occur in phases during a specific portion of the respiratory cycle by gating a solenoid valve that either directs the flow to the catheter or diverts it to the atmosphere.[15,16] During continuous TGI, closure of the expiratory valve during inspiration causes catheter flow to deliver variable portions of the inspired V_T.[17,18] Phasic inspiratory TGI can be used as the only source of fresh gas, thereby bypassing the anatomic dead space proximal to the catheter tip.[16] It can also be combined with a conventional ventilator to augment alveolar ventilation. During continuous or phasic inspiratory TGI, the catheter-delivered portion of the inspired V_T is a function of catheter flow rate and inspiratory time. During phasic expiratory TGI, catheter flow is timed to occur during all or part of expiration and does not contribute appreciably to the inspired V_T.

The effect of insufflating fresh gas during specific phases of the respiratory cycle has been examined under different catheter-flow conditions. Catheter flow only during inspiration (inspiratory bypass) effectively avoids the "anatomic" dead space proximal to the catheter tip (extending from the ventilator's Y piece). Insufflation during late expiration (expiratory washout) washes the proximal dead space free of CO_2. Limiting TGI to the final 60% of expiration effectively reduces Pa_{CO_2} (not different from panexpiratory TGI) while limiting exposure of the trachea to TGI gas and reducing the potential for TGI-induced hyperinflation (Fig. 22-1).[16,19,20] Although experimental studies suggest that restricting the flow of TGI gas to some portion of the expiratory phase preserves effectiveness, a rigorous engineering analysis showed that applying TGI flow solely within the final 50% of the expiratory phase yields a near maximal effect of expiratory TGI (Fig. 22-2), and this approach could simplify implementation and decrease adverse consequences.[21]

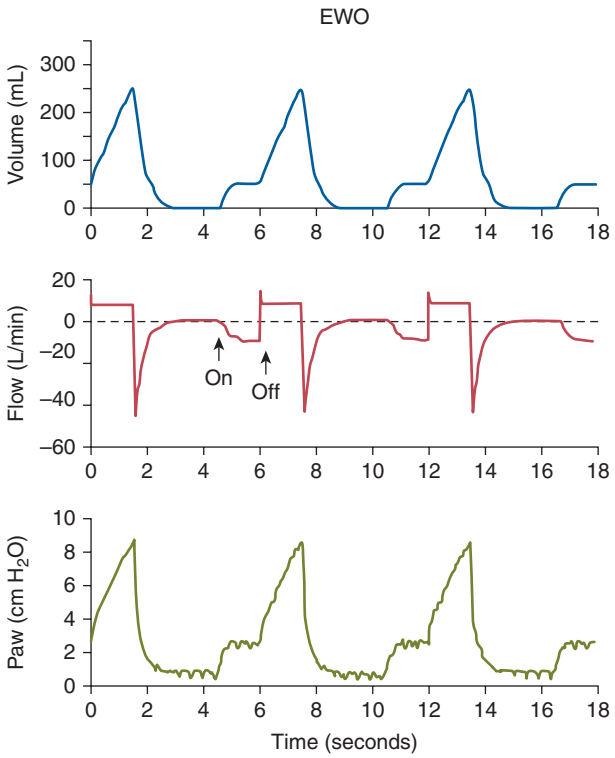

FIGURE 22-1 Simultaneous tracings during expiratory washout (EWO) at 10 L/min catheter flow. (*Above*) Plethysmographic lung volume relative to the end-expiratory lung volume measured without catheter flow. (*Center*) Flow tracing measured in the inspiratory and expiratory limbs of the external circuit. (*Below*) Proximal airway pressure. Note that lung volume and proximal airway pressure tracings show preinspiratory step changes. These deflections indicate that gas flows both antegrade (volume tracing) and retrograde (flow tracing) from the catheter tip during this period. (Used, with permission, Burke WC, Nahum A, Ravenscraft SA, et al. Modes of tracheal gas insufflation: comparison of continuous and phase-specific gas injection in normal dogs. *Am Rev Respir Dis.* 1993;148:561–568.)

Continuous TGI increases alveolar ventilation more than inspiratory bypass or late-expiratory washout.[16] Bidirectional continuous TGI delivery produces less hyperinflation than antegrade delivery, even with small diameter endotracheal tubes (ETT).[22]

PHYSIOLOGIC EFFECTS

TGI reduces anatomic dead space and increases alveolar ventilation for a given frequency and V_T combination. TGI's main effect is to enhance CO_2 removal by flushing the dead space from the carina to the Y of the ventilator circuit. The catheter and the TGI jet effect, however, oppose expiratory flow and favor air trapping at end-expiration and auto–positive end-expiratory pressure (auto-PEEP).[6,11,23–28]

TGI reduces Pa_{CO_2} during hypoventilation[16,29–32] although TGI's efficacy in lowering Pa_{CO_2} diminishes when an increased alveolar component dominates the total physiologic dead space.[18,32,33] An inverse correlation between

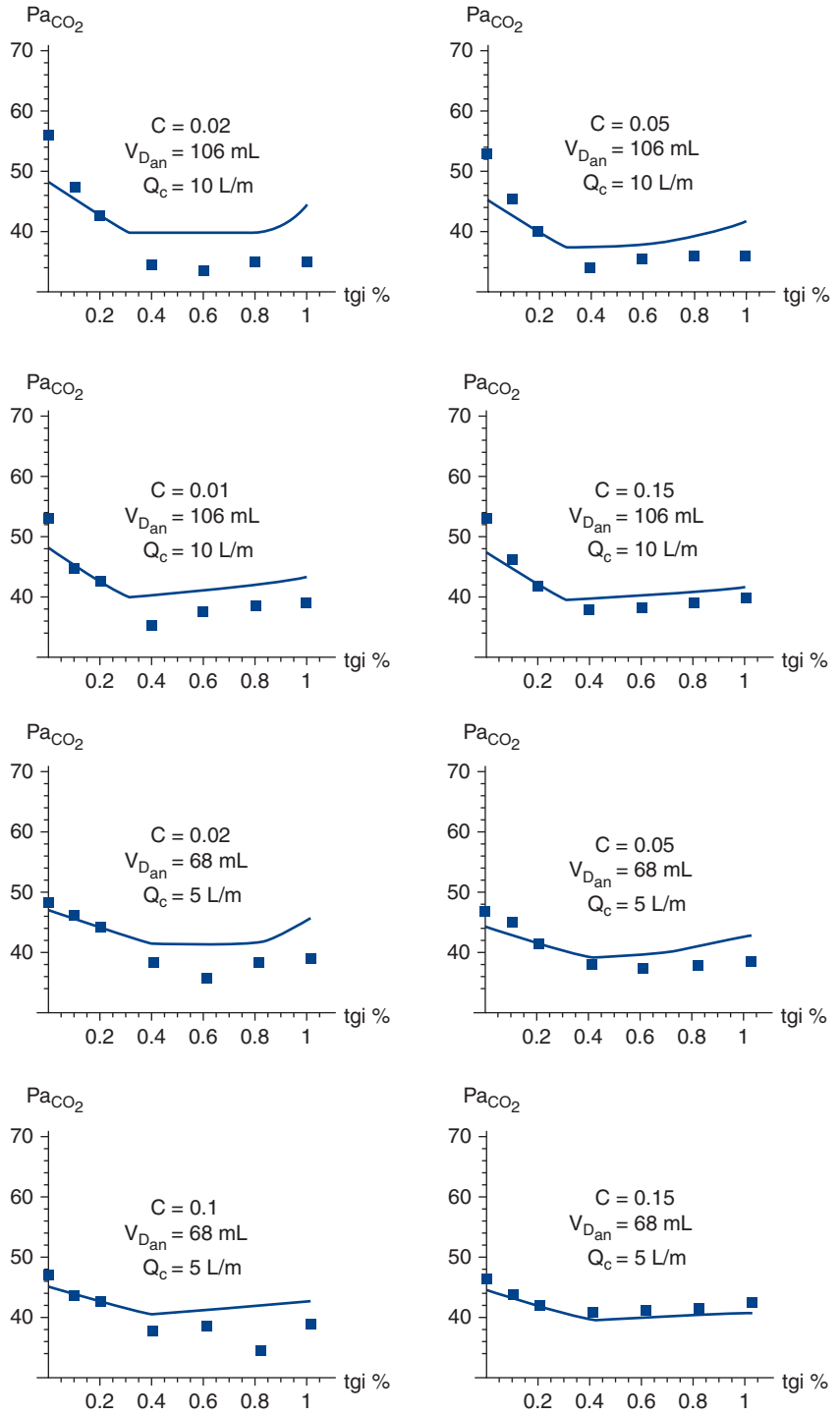

FIGURE 22-2 Partial pressure of CO_2 in alveolar gas (Pa_{CO_2}) vs. duration of tracheal gas insufflation (*TGI*) as a percentage of expiratory time. Comparison of experimental data (*boxes*) with mathematical model (*line*). V_T = 500 mL, Re = 5 cm $H_2O \cdot L^{-1} \cdot sec^{-1}$, and D = 0.33. *VT*, tidal volume; *Re*, compartmental resistance during expiration. Decreasing compliance (*C*), elevated dead space ($V_{D_{an}}$), and higher catheter flow (*Qc*) all magnify the effect of TGI on CO_2 clearance. Of particular note is that, with rare exception, the maximal decrease in Pa_{CO_2} is observed at catheter flow durations between 40% and 60% of the expiratory phase, suggesting that more prolonged application of TGI accrues little additional benefit with regards to CO_2 clearance over a broad range of impedance variables. (Used, with permission, Hota S, Crooke PS, Adams AB, Hotchkiss JR. Optimal phasic tracheal gas insufflation timing: an experimental and mathematical analysis. *Crit Care Med.* 2006;34:1408–1414.)

respiratory rate and Pa_{CO_2}[34] indicates that lower breathing frequencies (or longer expiratory times) favor TGI efficiency (reductions in Pa_{CO_2} and physiologic dead space).

Increase in lung volume is a serious limitation of TGI and should be avoided. Solutions to minimize expiratory TGI-induced auto-PEEP include using lower TGI flows, delivering TGI during pressure-controlled ventilation (PCV), and optimizing mechanical ventilation during TGI. During PCV, a TGI-induced increase in airway pressure automatically results in decreased V_T, and the lack of expiratory TGI-induced auto-PEEP is associated with less efficient CO_2 elimination. Likewise, reducing TGI flow reduces CO_2 clearance.[27,35–37]

INDICATIONS AND CONTRAINDICATIONS

Transtracheal Oxygen Therapy

Transtracheal oxygen therapy (TTO) administers gas directly into the trachea in nonintubated patients (Fig. 22-3). Long-term oxygen therapy is an established treatment for chronic lung disease with hypoxemia. Oxygen is usually delivered via a nasal cannula, irritating the nasal mucosa and the skin of the upper lip and ears. In 1982, Heimlich described a method for delivering oxygen directly into the trachea, bypassing the anatomic dead space and using the main airways as a reservoir.[38] Numerous studies have since found clear clinical benefits for TTO, including reductions in hematocrit,[39] pulmonary vascular resistance,[40] work of breathing,[41] dyspnea,[42] and incidence of cor pulmonale.[39] Other advantages are decreased oxygen cost and air pollution, decreased frequency of hospitalization, and improved exercise tolerance with better physical, psychological, and social function.[43]

FIGURE 22-3 Level of insertion and position of the indwelling tracheal catheter. (Used, with permission, Christopher KL, Schwartz MD. Transtracheal oxygen therapy. *Clin Chest Med.* 2003;24:489–510.)

THE TECHNIQUE

The Spofford-Christopher Oxygen Optimizing Program is a four-step protocol for TTO:[44]

1. Patient evaluation, selection, and procedure preparation. Refractory hypoxemia and discomfort during maximal nasal cannula therapy are specific indications. Patients with chronic obstructive pulmonary disease (COPD) must also guarantee adequate bronchial hygiene and good pharmacologic control of airway activity throughout the program.
2. A tracheocutaneous fistula is created by a modified Seldinger technique or a surgical Lipkin procedure. Low predicted compliance with treatment (as in anxious patients) and neck anatomic alterations (as in severely obese patients) are strong contraindications to the tracheocutaneous fistula. The Lipkin method has fewer complications than modified Seldinger technique.[45]
3. Tract maturation management. Patients must learn to clean the catheter and prevent inadvertent catheter displacement.
4. Mature tract management. This phase aims to prevent complications and educate the patient.

HOW TO VENTILATE THE PATIENT

The choice of equipment for oxygen supply and delivery depends on the setting (hospital or home) and on the patient's ability to move; choices for home treatment include compressed gas cylinders, liquid oxygen, and molecular sieve oxygen concentrators. TTO usually requires an oxygen flow rate ranging from 0.25 to 1.5 L/min, but flow rates up to 2.9 L/min can be delivered through larger catheters to guarantee adequate oxygenation in severe refractory hypoxemia.[46]

Oxygen flow requirements with TTO are 25-50% lower than with continuous flow therapy via a nasal cannula; 0.5 L/min of oxygen by the catheter is equivalent to 4 L/min by nasal prongs, because the tracheal effect acts as an anatomic reservoir that stores oxygen during the last part of exhalation. Oxygen flow requirements during exercise are also reduced by approximately 30% with concomitant reduction in patient sense of dyspnea. Moreover, the equipment is lighter and mobility may be improved.

COMPLICATIONS

The main complications are subcutaneous emphysema, barotrauma, and bleeding from catheter misplacement. Patients

receiving long-term TTO are at risk for catheter lumen occlusion by inspissated secretions, inadvertent catheter removal (particularly dangerous during the maturation phase), and chronic tract problems like infections and keloids.[43]

Emergency Transtracheal Ventilation

In the rare emergency situation in which it is impossible to guarantee adequate ventilation by facial mask, supraglottic device, or endotracheal intubation,[47] usually because of laryngeal stenosis, foreign bodies, tumors, or facial trauma, transtracheal ventilation is recommended.[48]

THE TECHNIQUE

Since the first report by Jacobs et al of a series of patients who were successfully ventilated in emergency conditions using a catheter placed through the cricothyroid membrane,[49] many transtracheal emergency ventilation strategies have been reported.[50] Current techniques consist of directly inserting a 14- to 18-gauge intravenous catheter between the tracheal rings or through the cricoid membrane. The device is connected to a syringe and advanced through the skin until the airway lumen is punctured. After air aspiration confirms placement, the cannula is connected to the oxygen delivery system. Percutaneous transtracheal emergency ventilation is performed; dedicated kits[51] or self-made devices can also be used.[52]

HOW TO VENTILATE THE PATIENT

Although manual or automatic jet ventilation is the reference standard for oxygen administration during transtracheal emergency ventilation, many techniques have been proposed to deliver oxygen with or without the aid of a jet valve. Commercially available resuscitation bags require great effort to ventilate through a 14-gauge catheter and make it impossible to guarantee adequate V_T.[50] Tubing that supplies oxygen can be coupled with a three-way stopcock, effectively creating a manual jet valve; however, tank and wall oxygen using flow regulators do not provide sufficient flow rates and, consequently, despite acceptable oxygenation, lead to hypercapnia. Only when the flow regulator is placed in the "wide open" position, an estimated flow of 65 L/min can be generated and physiologic V_T can be delivered.[50] Experimentally, both bidirectional manual respiration valves and active expiration using ejector-based expiratory ventilation assistance have proved useful in conditions of high expiratory resistance and occluded upper airway.[53–55]

COMPLICATIONS

Complications of transtracheal emergency ventilation mainly result from the need to operate under emergency conditions and ensure ventilation as soon as possible.[56] Bleeding and posterior tracheal wall lesions are the most common, although kinking and inability to ventilate patients have also been reported when standard intravenous catheters are used.[57] Moreover, catheters equipped with safety systems sometimes do not allow a syringe to be connected. Other complications can arise with chronic therapy (e.g., infection and tracheal stenosis).[43]

In conclusion, TTO can be an effective and safe alternative to nasal prongs for long-term home oxygen administration, and transtracheal ventilation using commercially available intravenous catheters and manual jet ventilation valves or wall oxygen supply can ensure emergency lung ventilation.

Chronic Respiratory Failure

In patients with end-stage pulmonary disease and chronic CO_2 retention, continuous insufflation of fresh gas (oxygen and/or air) through an intratracheal catheter has been used to provide continuous oxygen therapy, decrease oxygen flow requirements,[7–9,58] provide a method for oxygen delivery, decrease dyspnea, and increase exercise tolerance.[59] A continuous low flow (4 to 5 L/min) delivered to the tracheostomy tube reduces dead space, V_T, and minute ventilation without affecting Pa_{CO_2} in the acute state and maintains or reduces Pa_{CO_2} in the chronic state, presumably by reducing dead space. In patients with the most severe forms of COPD, TGI resulted in oxygen consumption and CO_2 production, as well as a less-demanding respiratory pattern.[9]

Patients with chronic respiratory failure may experience dynamic hyperinflation that may be relieved when minute ventilation decreases and expiratory time increases during high-flow insufflation. Brack et al[60] found an almost immediate decrease in end-expiratory lung volume during high-flow insufflation compared to low-flow oxygen insufflation. To investigate whether this drop in end-expiratory lung volume was caused by active expiration, they performed a Konno-Mead analysis of rib cage-abdominal volume loops. The absence of a systematic change in loop configuration and the unaffected inspiratory and expiratory asynchrony indices did not suggest increased abdominal expiratory muscle recruitment during high-flow insufflation. Therefore, the drop in end-expiratory lung volume coinciding with the reduction in minute ventilation, respiratory rate, and prolongation of expiratory time after transition to high-flow insufflation was most likely caused by the reversal of dynamic hyperinflation (Fig. 22-4).

Acute Lung Injury and Acute Respiratory Distress Syndrome

One of the most important features of TGI is that it can maintain normocapnia or a given level of Pa_{CO_2} while V_T is decreased, allowing a reduction in minute ventilation. Therefore, TGI can be used to decrease the forces acting on the lung and thereby minimize ventilator-induced lung injury in patients with acute respiratory distress syndrome (ARDS).[36,61–63]

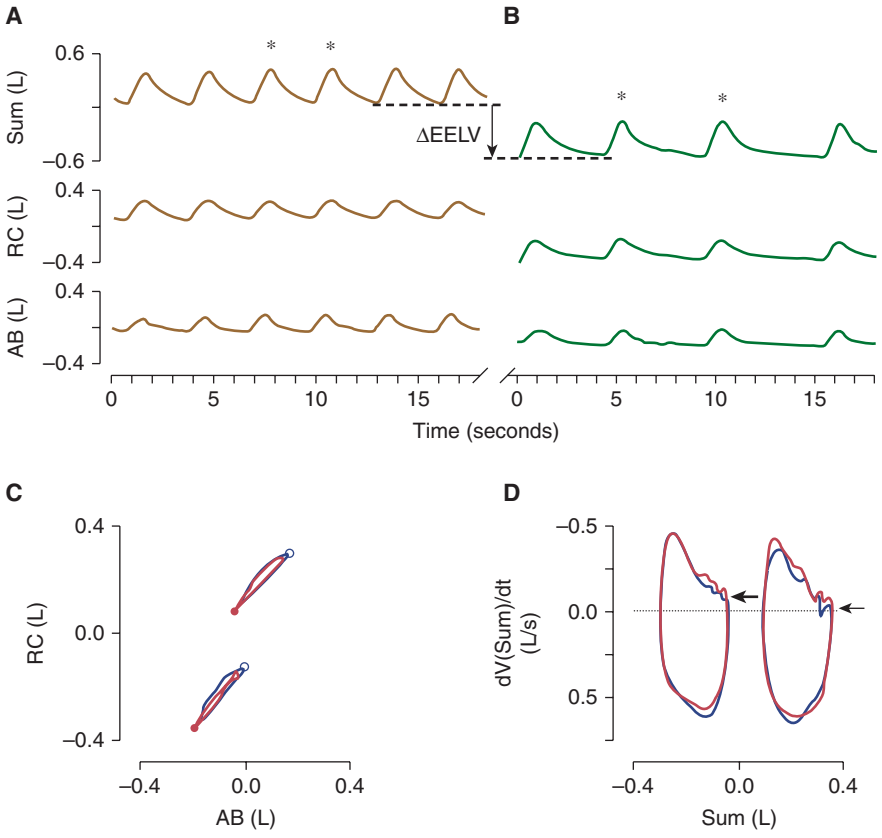

FIGURE 22-4 Time series of inductive plethysmographic rib cage (*RC*), and abdominal (*AB*) signals along with instantaneous lung volume (*Sum*) during transtracheal insufflation of oxygen at 1.5 L/min (low-flow insufflation, *top left*, *A*) and with an oxygen-air mixture at a rate of 15 L/min (high-flow insufflation; *top right*, *B*). Note the marked reduction of respiratory rate and end-expiratory lung volume (*vertical line with arrow*) during high-flow insufflation. For two breaths during low-flow insufflation and high-flow insufflation (marked with *asterisks*, respectively) rib cage versus abdominal volume loops (*bottom left*, *C*), and flow-volume loops (i.e., time derivative of the sum volume vs. the sum volume loops) (*bottom right*, *D*) are plotted. The loops at lower volumes in *bottom left*, *C*, and *bottom right*, *D*, correspond to high-flow insufflation. In *bottom left*, *C*, the major downward and minor leftward displacement of the loops with high-flow insufflation indicates that the drop in lung volume was predominantly related to deflation of the rib cage. The closed and open circles in *bottom left*, *C*, correspond to end-expiration and end-inspiration, respectively. During high-flow insufflation (*top right*, *B*), the expiratory flow approaches zero at end-expiration, as indicated by the *small, horizontal arrow* in *bottom right*, *D*. In contrast, during low-flow insufflation (*top left*, *A*), inspirations commence before expiratory flow has ceased (*large arrow*, *bottom right*, *D*), suggesting dynamic hyperinflation. (Used, with permission, Brack T, Senn O, Russi EW, Bloch KE. Transtracheal high-flow insufflation supports spontaneous respiration in chronic respiratory failure. *Chest.* 2005;127:98–104.)

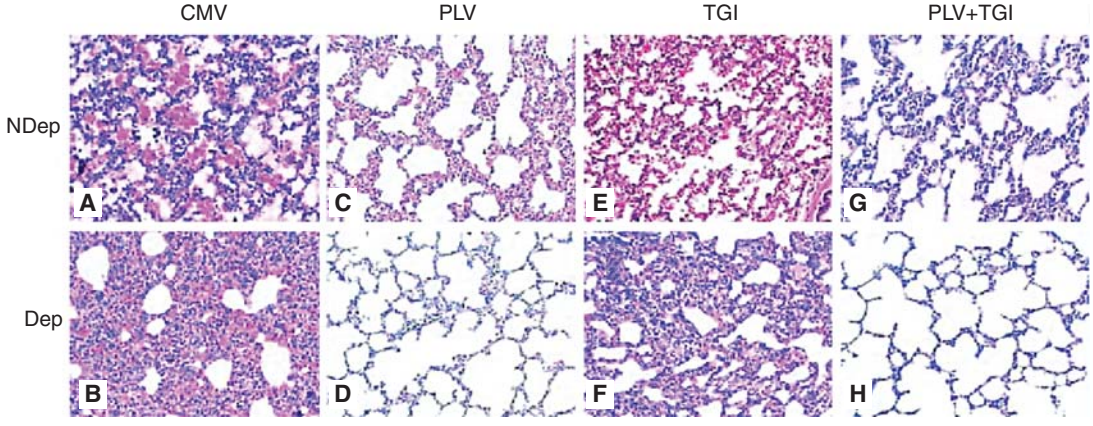

FIGURE 22-5 Representative photomicrographs (×100) of lung sections obtained at 4 hours after lung injury and stained with hematoxylin and eosin. The samples were from nondependent (*NDep*) and dependent (*Dep*) regions for mechanical ventilation (*CMV*, *A* and *B*), partial liquid ventilation (*PLV*, *C* and *D*), continuous tracheal gas insufflation (*TGI*, *E* and *F*), and combination (*PLV + TGI*, *G* and *H*) groups. Intraalveolar and interstitial inflammation and hemorrhage, atelectasis, edema, and exudation were severe, especially in the dependent regions in CMV group. Dependent region damage was significantly less in the PLV and in PLV+TGI groups. (Used, with permission, Guo ZL, Liang YJ, Lu GP, Wang JC, Ren T, Zheng YH, Gong JY, Yu J. Tracheal gas insufflation with partial liquid ventilation to treat LPS-induced acute lung injury in juvenile piglets. *Pediatr Pulmonol.* 2010;45:700–707.)

Experimental studies on lung injury show that TGI results in lower ventilator requirements (airway pressures, V_T, and dead space), more favorable alveolar surfactant composition, and a more favorable histologic trend than conventional mechanical ventilation.[64,65] Similarly, in experimental bilateral or unilateral lung injury, the combination of TGI and partial liquid ventilation is more effective than conventional mechanical ventilation or either modality alone (Fig. 22-5).[66–69] In this regard, TGI helps partial liquid ventilation to offset diffusional issues, remove partial pressure of arterial carbon dioxide (Pa_{CO_2}), and decrease the demands for ventilator gas pressures and V_T. Perfluorocarbon liquids provide cytoprotection and low-pressure mechanical support to the atelectatic lung, and these combined effects may offset lung inflammation associated with higher V_T. The combined application of TGI and partial liquid ventilation, however, is still in the early experimental stages.

In patients with ARDS who are ventilated with a permissive hypercapnia strategy,[63] the combination of increasing respiratory rate to the limit of inducing auto-PEEP, elimination of unnecessary instrumental dead space, and reduction in external PEEP when TGI-induced auto-PEEP increases (to maintain the total PEEP constant) seems a suitable pressure-limited ventilator strategy in combination with TGI[36,70] (Fig. 22-6).

In ARDS, high-frequency oscillation (HFO) improves oxygenation relative to conventional mechanical ventilation. Mentzelopoulos et al recently examined whether the combination of HFO and TGI (HFO-TGI) results in better gas exchange than standard HFO and conventional mechanical ventilation.[71] In fourteen patients with ARDS, the combination of HFO-TGI substantially improved oxygenation relative to both standard HFO and conventional mechanical ventilation according to the ARDS Network protocol. HFO-TGI also reduced shunt fraction and oxygenation index relative to conventional mechanical ventilation and HFO, respectively, but failed to improve Pa_{CO_2}. This study demonstrated the short-term feasibility of HFO-TGI, although its clinical utility in ventilator-induced lung injury remained uncertain. In subsequent studies, these authors compared standard HFO and HFO-TGI matched for tracheal pressure to determine whether TGI affects gas exchange independently from tracheal pressure. Compared to HFO alone, HFO-TGI resulted in a higher partial-pressure-of-arterial-oxygen-to-fractional-inspired-oxygen-concentration ratio at similar tracheal pressures, lower Pa_{CO_2} (at the higher tracheal pressure level),[72] and less nonaerated lung tissue below the carina.[73] These results imply enhanced lung recruitment and/or gas transport and alveolar ventilation during HFO-TGI in ARDS (Fig. 22-7).

TGI-associated reduction in Pa_{CO_2} is a potentially important maneuver in patients with cerebrovascular injury with intracranial hypertension and concomitant acute lung injury and/or ARDS, who need lung-protective ventilation and aggressive treatment to maintain intracranial pressure as low as possible. Both anecdotal case reports[74,75] and case series[76] show that TGI in patients with acute lung injury and/or ARDS and severe head trauma allows a more protective ventilator strategy while Pa_{CO_2} is reduced or remains constant; more importantly, no short-term deleterious effects on hemodynamics or cerebral parameters occurs (Fig. 22-8).

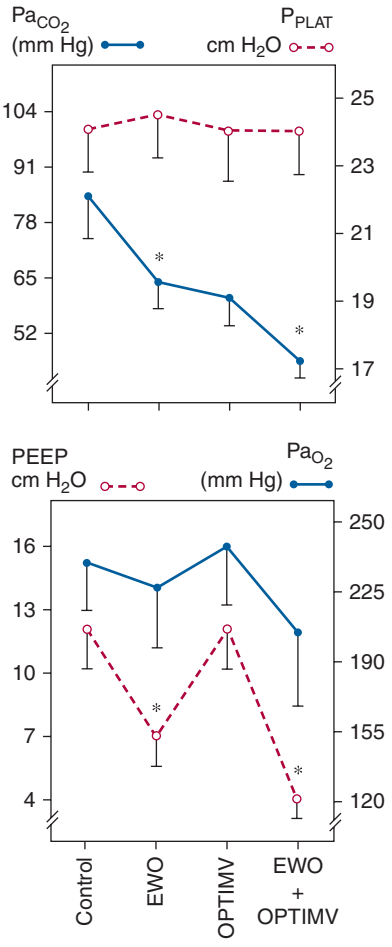

FIGURE 22-6 Changes in Pa_{CO_2}, inspiratory plateau airway pressure (P_{PLAT}), PEEP, and Pa_{O_2} induced by optimized mechanical ventilation (*OPTIMV*), expiratory washout (*EWO*), and the combination of *OPTIMV* and *EWO* in six patients with severe acute respiratory distress syndrome. Extrinsic PEEP had to be reduced by 5.3 ± 2.1 cm H_2O during EWO and by 7.3 ± 1.3 cm H_2O during the combination of OPTIMV and EWO, whereas it remained unchanged during OPTIMV alone. Plateau pressure did not change significantly, suggesting that lung hyperinflation was not produced. In patients with severe ARDS, the combination of OPTIMV and EWO has additive effects and resulted in partial pressure of arterial carbon dioxide (Pa_{CO_2}) levels close to normal values. (Used, with permission, from Richecoeur J, Lu Q, Vieira SRR, et al. Expiratory washout versus optimization of mechanical ventilation during permissive hypercapnia in patients with severe acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 1999;160:77–85.)

Liberation from Mechanical Ventilation

Failure of the respiratory muscle pump is the most common cause of unsuccessful weaning from mechanical ventilation. Indeed, patients with COPD who fail weaning trials exhibit not only an almost immediate rapid and shallow breathing pattern but also progressive worsening of pulmonary mechanics with inefficient CO_2 clearance. Worsened pulmonary mechanics in these patients is characterized by

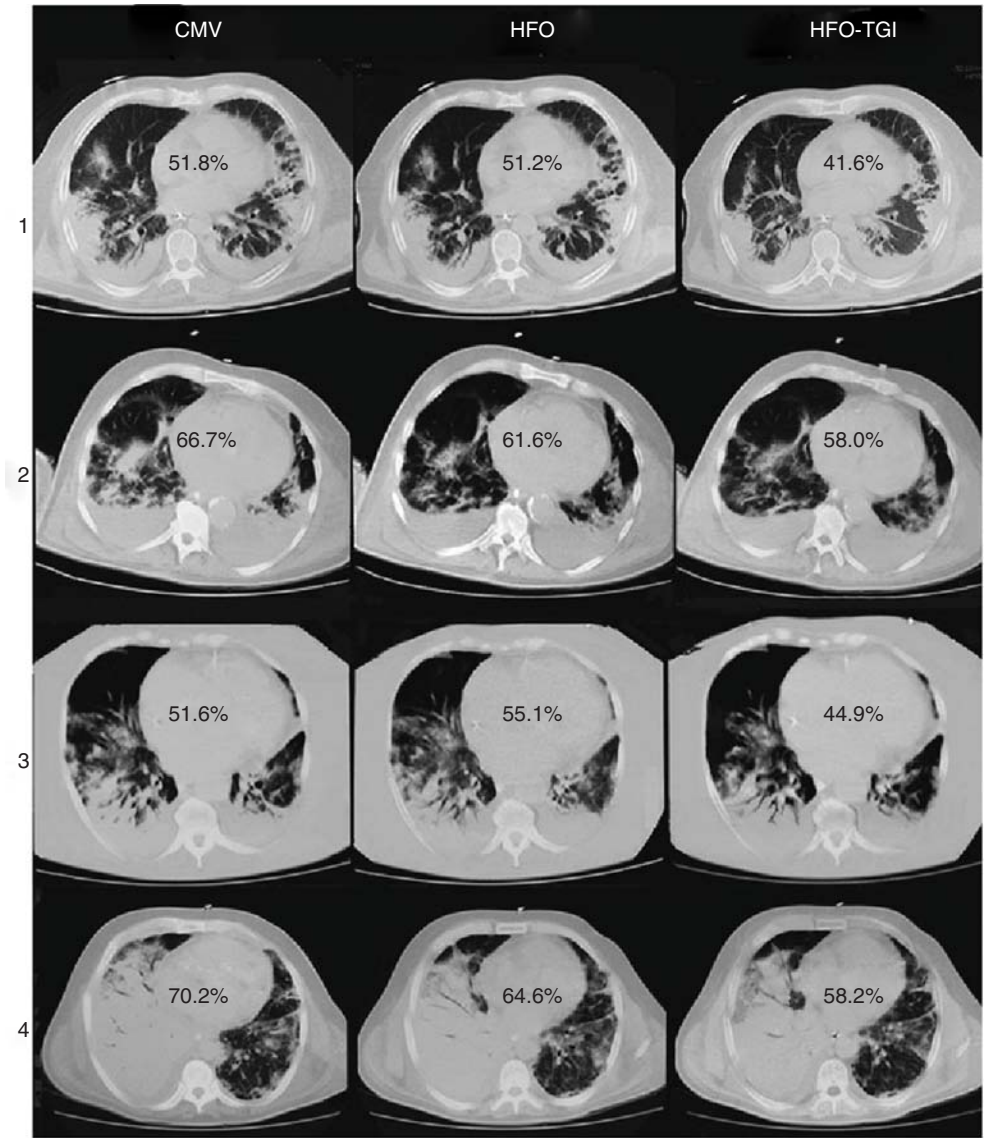

FIGURE 22-7 Computed tomography (CT) sections of the lower lung from four representative patients (*1* to *4*). CT sections correspond to 7 cm below the carina. In patients 1 and 3, HFO preceded HFO-TGI. In patients 2 and 4, HFO-TGI preceded HFO. Percentages reflect proportions of nonaerated lung-tissue weight in lower-lung CT sections. Regional gas volume was higher during HFO-TGI versus CMV and HFO. In the nondependent lower lung, there was a HFO-TGI–related decrease in the percentage of nonaerated parenchyma versus CMV and HFO. The corresponding regional lung volume and tissue weight were higher during HFO-TGI versus CMV and HFO; HFO-TGI resulted in a higher gas volume versus CMV, and a trend toward higher gas volume versus HFO. *CMV*, conventional mechanical ventilation; *HFO*, high-frequency oscillation; *TGI*, tracheal gas insufflation. (Used, with permission, from Mentzelopoulos SD, Theodoridou M, Malachias S, et al. Scanographic comparison of high frequency oscillation with versus without tracheal gas insufflation in acute respiratory distress syndrome. *Intensive Care Med.* 2011;37:990–999.)

increased auto-PEEP and inspiratory resistance, together with decreased dynamic lung compliance.[77] Therefore, TGI could facilitate liberation from ventilator support by enhancing CO_2 clearance.

In spontaneously breathing sheep with acute lung injury,[78] the combination of continuous positive airway pressure (CPAP) and TGI reduced the inspiratory work of breathing. The beneficial effect of TGI with CPAP on the work of breathing was attributed to a favorable balance between decreased ventilatory requirements and low workload superimposed by the apparatus and TGI. TGI may increase the work needed to open the demand valve and trigger the ventilator; this problem may be surmounted by a system that stops TGI flow before end-expiration.[79]

Case series[34,80] on the effects of TGI on lung function in patients undergoing weaning from mechanical ventilation have reported a flow-dependent reduction in V_T, minute ventilation, Pa_{CO_2}, and physiologic dead space when gas is delivered through an orotracheal tube. Moreover, distal positioning of the TGI catheter is more effective than proximal positioning, and the effects are less pronounced in patients with tracheostomies. Interestingly, the improvement

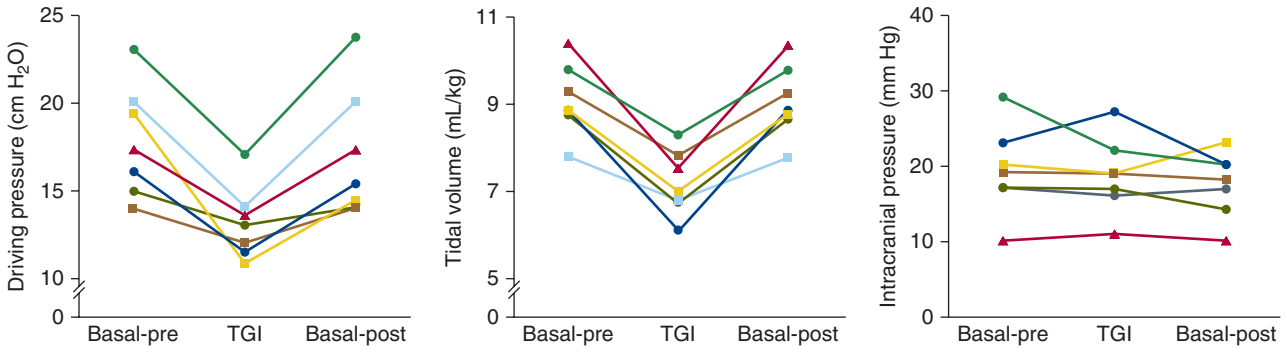

FIGURE 22-8 Individual values of driving airway pressure (difference between plateau pressure and PEEP) (*left*), tidal volume (*center*), and intracranial pressure before (*basal-pre*), during (TGI), and after (*basal-post*) application of expiratory TGI in patients with severe head trauma and acute lung injury. Expiratory TGI allowed the targeted Pa_{CO_2} level to be maintained, together with substantial reductions in tidal volume and driving pressure, without deleterious effects on cerebral parameters. (Used, with permission, from Martinez M, Bernabe F, Peña R, et al. Effects of expiratory tracheal gas insufflation in patients with severe head trauma and acute lung injury. *Intensive Care Med.* 2004;30:2021–2027.)

in ventilatory efficiency from the reduction of dead space yielded a decrease in Pa_{CO_2} at the same respiratory rate and at lower V_T.[81]

OPERATIONAL CHARACTERISTICS OF TRANSTRACHEAL GAS INSUFFLATION

Catheter Position

In TGI, a single catheter is usually placed above the main carina, making this technique simple to use. Nonetheless, more distal catheter placement may improve the efficiency of TGI in two ways.[31] First, with more distal placement, a greater volume lies proximal to the catheter tip, permitting additional expiratory flushing of CO_2-laden dead space. Moving the catheter toward the carina also advances the jet-generated turbulence zone closer to the lung periphery, thereby improving TGI efficacy. The clinical benefit, however, of introducing TGI catheters deeper than the main carina is doubtful. In a series of animal studies, the effect of TGI on Pa_{CO_2} was strongly dependent on catheter flow rate, but catheter tip position was not crucial provided it was within a few centimeters below or above the main carina.[13,26,31] Similar findings have been reported in critically ill patients.[82] Bronchoscopic guidance may not be necessary for TGI catheter placement because the position of the catheter can be verified on a chest radiograph by estimating the distance from the tip of the ETT to the main carina.

Catheter Flow Rate

TGI usually employs modest catheter flow rates. Most animal and human studies of TGI have used a flow rates of 4 to 10 L/min. CO_2 elimination during TGI depends primarily on catheter flow rate,[31,61,82,83] with turbulence generated at higher flows enhancing distal gas mixing and CO_2 elimination.[12] Once fresh gas sweeps the proximal anatomic dead-space free of CO_2, further increases in flow rate are unlikely to wash out more CO_2. Because expiratory washout of the proximal anatomic dead space is the primary mechanism of action of TGI, both curtailing expiratory time and prolonging lung deflation may diminish the efficacy of TGI unless catheter flow rate is very high. Decreasing expiratory time would decrease the volume of fresh gas delivered to the central airways per respiratory cycle (Fig. 22-9). In situations of short expiratory times, higher flow rates are required to preserve TGI efficacy. At high catheter flow rates, the high impact pressure and shear of the inflow jet can damage the bronchial mucosa.[84,85]

The optimal flow rate in terms of the decrement in Pa_{CO_2} afforded by TGI is a complex function of the volume of anatomic dead space proximal to the catheter tip, the volume of fresh gas delivered per expiration, the pattern of CO_2 exhalation from the lungs, and the CO_2 exchange characteristics of the respiratory system before TGI. Once dead space proximal to the catheter tip has been almost completely flushed by the fresh gas during expiration, any catheter-flow dependence of Pa_{CO_2} is likely to be secondary to enhanced turbulent mixing in the airways distal to the catheter tip. Consequently, Pa_{CO_2} continues to decrease with increasing flow rate as catheter flow rate rises but at a slower pace.[12,31] In most TGI systems, the effect of increasing flow rate diminishes considerably when flow rate exceeds 10 L/min.

Catheter Shape

To benefit from the distal turbulence produced by TGI, the catheter must direct the jet stream toward the periphery of the lung.[14] Inverting the catheter mouthward eliminates the distal effects and decreases CO_2 removal. Inverting the catheter within the ETT, however, avoids directing the jet stream onto the bronchial mucosa, which may cause bronchial injury.[84–86] Alternatively, the catheter tip can

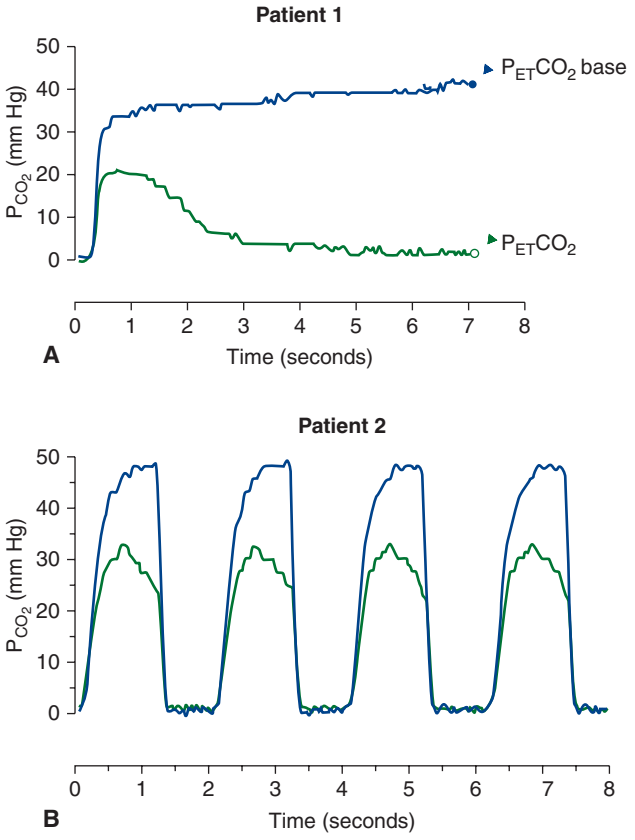

FIGURE 22-9 Representative exhaled capnograms in two patients without TGI and with TGI at 6 L/min insufflation flow. A greater reduction in end-tidal CO_2 ($P_{ET}CO_2$) from the $P_{ET}CO_2$ base value corresponded with a larger reduction in Pa_{CO_2}. At a given insufflation flow, efficiency to clear CO_2 is a function of the time available to flush proximal dead space. (Used, with permission, from Ravenscraft SA, Burke WC, Nahum A, et al. Tracheal gas insufflation augments CO_2 clearance during mechanical ventilation. *Am Rev Respir Dis.* 1993;148: 345–351.)

be positioned within the ETT so that the jet hits the ETT wall. The orientation of the ETT holes with respect to the catheter (end or side) appears to have little impact on catheter efficiency.[31] Nevertheless, catheter shape directly influences the extent (or lack of) dynamic hyperinflation caused by TGI.[87]

Humidification

The fresh gas delivered by TGI should be heated and humidified to prevent mucous plug formation and to prevent TGI gas from causing bronchial injury via cooling and dehydration of the bronchial mucosa. Few studies have systematically examined the occurrence of bronchial mucosal injury during TGI. Similarly, few studies have examined the effect of conditioning TGI gas on the extent of injury to bronchial mucosa. TGI can cool tracheal gas significantly. The extent of cooling is greatest at high flow rates with continuous TGI and can be compensated only partially by conditioning the ventilator-delivered inspired gas during panexpiratory TGI.[88,89] Case series have reported either no damage or no encrustation,[86] whereas other investigators found intratracheal catheter obstruction after 2 days of continuous use.[62]

Endotracheal Tube Design

In most human studies, a small-caliber catheter is introduced through an angled sidearm adapter attached to the ETT and positioned just above the main carina.[61,62,82,90] Placing a catheter through the ETT interferes with suctioning and can increase airway resistance by partially occluding the airway. Moreover, the catheter is not fixed in space and may cause injury to bronchial mucosae if it whips within the trachea at high flows. Alternatively, the catheter can be placed outside the ETT along the trachea. This technique requires visualization of the vocal cords and deflation of the ETT cuff and risks puncturing the cuff.

Designs incorporating channels within the ETT wall would solve these problems and simplify TGI application. Boussignac et al[91,92] embedded small capillaries in the walls of an ETT for TGI, and also used this modified ETT to deliver high-velocity jets of O_2 at the carinal orifice to prevent arterial O_2 desaturation during suctioning.[93] The modified ETT can be used to make mechanical ventilation less aggressive in different clinical scenarios.[94,95] Future clinical applications of TGI will probably use a modified ETT that incorporates the catheter in its wall attached to a standardized circuit for gas delivery. In any case, TGI should never require reintubation.[96]

Other systems allow aspiration of anatomic and instrumental dead space in the late part of expiration, and replacing the aspirated volume with fresh gas through the inspiratory line of the ventilator improves CO_2 clearance.[97] This aspiration system has allowed reductions in airway pressure and V_T while keeping Pa_{CO_2} constant in healthy humans,[98] as well as in patients with ARDS [99] and COPD.[100] This aspiration system might avoid the problems associated with jet streams of gas or with gas humidification without developing auto-PEEP.

ADJUSTMENTS AT THE BEDSIDE

Inspired Oxygen Fraction

The actual fraction of inspired carbon dioxide (FI_{O_2}) during TGI depends on two factors: the contribution of TGI to total inspired V_T and the FI_{O_2} of the catheter gas. If, however, the FI_{O_2} of the catheter gas is matched to ventilator FI_{O_2}, the actual inspired FI_{O_2} will always be identical to that delivered by the ventilator.

Airway Opening Pressure

During TGI, the jet stream increases flow through the ventilator circuit during expiration and creates a region where bidirectional flows exist. Both effects change the resistance characteristics of the respiratory system and modify the relationship between airway opening (Pao) and alveolar (Palv) pressures observed at baseline (catheter flow rate, 0 L/min). Because expiratory resistance increases during TGI, Pao tends to underestimate Palv (and functional residual capacity [FRC]) when the system is switched from baseline to TGI conditions. During panexpiratory TGI, catheter flow ceases during inspiration, and inspiratory Pao provides as much useful information regarding Palv as during conventional mechanical ventilation. In contrast, during continuous TGI, inspiratory Pao (measured at the tip of the ETT) differs from the tracheal pressure (Fig. 22-10). During expiration under both continuous and expiratory TGI conditions, however, catheter flow pressurizes the respiratory system, so Pao underestimates tracheal pressure.[84] During expiration, the extent that Pao underestimates tracheal pressure increases with catheter flow rate and depends on the geometry of the system and the orientation of the catheter with respect to the trachea.

Effect of Transtracheal Gas Insufflation on Lung Volume

Catheter flow delivered during inspiration contributes to total inspired V_T. This contribution is eliminated if TGI is timed to occur only during expiration.[16] In most TGI circuits, however, this volume is small (approximately 10 to 20 mL at a catheter flow rate of 10 L/min). The effect of TGI on total inspired V_T depends on the ventilator mode and on FRC in a flow-dependent fashion.[12,82] TGI can increase FRC in three ways. First, part of the momentum of the discharging jet stream is transferred to the alveoli.[101] Second, the catheter decreases the cross-sectional area of the trachea, increases expiratory resistance, and delays emptying. Third, catheter flow through the ETT, expiratory circuit, and expiratory valve can build up a backpressure that impedes deflation and is the major determinant of dynamic hyperinflation.[102] Continuous TGI increases FRC more than expiratory TGI, especially when the inspiratory time fraction is prolonged.[102]

Dynamic hyperinflation caused by TGI may represent either a problem or a therapeutic option[36] and can be manipulated by using an inverted-jet insufflator to achieve a venturi effect.[12,86] Monitoring dynamic hyperinflation during TGI requires a means of external lung-volume measurement, such as impedance plethysmography. Guided by the plethysmograph signal, ventilator-set PEEP can be adjusted to maintain FRC constant as flow rate is varied.[26,32] Alternatively, if the TGI system allows an end-expiratory hold maneuver, the ventilator-set PEEP can be adjusted to maintain total PEEP constant.[37,103] Alternatively, during PCV, a flow-relief valve automatically compensates for the extra gas introduced into the system by TGI and eliminates the need for ventilator adjustments to control total PEEP.[104]

Transtracheal Gas Insufflation–Ventilator Interactions

During flow-controlled, volume-cycled ventilation, total inspired V_T can be maintained relatively constant during continuous TGI by decreasing the ventilator-set V_T.[26,61] During PCV, TGI application does not change the total inspired V_T, provided TGI does not pressurize the respiratory system beyond the set pressure. As catheter flow rate increases, ventilator-delivered V_T declines, but the total inspired V_T remains the same.[26,83] If inspired V_T delivered by the catheter (V_Tc) exceeds the V_T generated by PCV in the absence of TGI, then TGI will overpressurize the circuit, and peak Pao will be greater than that produced by the ventilator-set pressure. Consequently, excessive pressures can be produced within the respiratory system if V_Tc is too large. When this happens, the Pao-time profile becomes a hybrid of PCV and constant-flow volume-cycled ventilation, resembling that generated during volume-assured pressure-support ventilation. This problem can be circumvented by introducing a pressure-release valve into the ventilator circuit that dumps circuit pressure above a set threshold.[105]

The interactions between TGI and ventilator mode, V_T, and Pao that result in development of auto-PEEP deserve mention. During volume-controlled ventilation, when ventilator PEEP is left constant, V_T remains constant, but end-expiratory pressure and Pao increase because of TGI-induced auto-PEEP. During PCV, when ventilator PEEP and peak airway pressure are kept the same as baseline, V_T excursions (and hence minute ventilation) are reduced because of TGI-induced auto-PEEP. When ventilator PEEP is reduced by an amount equivalent to TGI-induced auto-PEEP, V_T, peak airway pressure, and total PEEP remain the same as baseline during PCV [37–88].

During CPAP delivered by a mechanical ventilator in combination with TGI, additional inspiratory effort is required to overcome the insufflation flow and trigger the ventilator valves. Bench studies have found that TGI might interfere with ventilator triggering at low peak inspiratory flow rates, suggesting that weak patients may fail to open the demand valve at high catheter flow rates.[106]

MONITORING

Careful monitoring of delivered volumes and pressures is necessary to ensure safe application and to evaluate the effect of TGI on lung function. A catheter inside the ETT may increase both inspiratory and expiratory resistances, particularly when small endotracheal or tracheostomy tubes are used.[6,11,32,107,108]

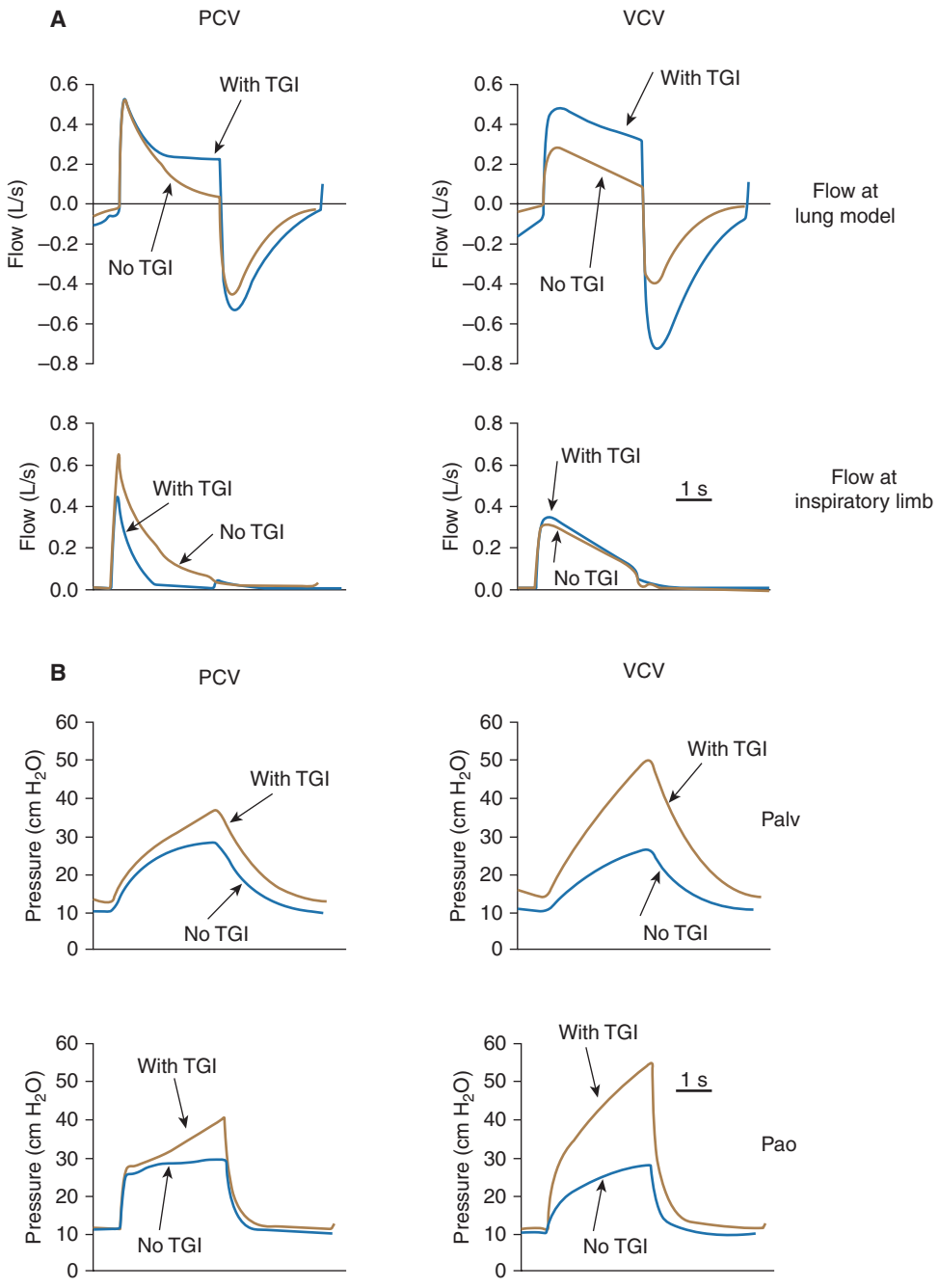

FIGURE 22-10 **A.** Flow-versus-time tracings of delivered gas flow measured both at airway opening and distal to the entrance of tracheal gas insufflation (*TGI*) during both pressure-controlled ventilation (*PCV*) and volume-controlled ventilation (*VCV*) with and without the addition of 12 L/min TGI in a lung model. **B.** Pressure-versus-time tracings of system pressure measured both at the airway opening (*Pao*) and distal to the entrance of the TGI flow (*Palv*) during both PCV and VCV with and without the addition of 12 L/min of TGI flow in a lung model. Regardless of whether VCV or PCV was used, continuous TGI increases Pao and peak carinal pressure (*B*). In association with these changes there is an increase in tidal volume. During VCV (*A*), the flow from TGI is additive to the flow from the ventilator. During PCV, the addition of the TGI flow caused the flow from the ventilator to decelerate more rapidly; once ventilator flow reached zero, a square wave flow pattern derived entirely from the TGI system persisted. (Used, with permission, from Kacmarek RM. Complications of tracheal gas insufflation. *Respir Care.* 2001;46:167–176.)

Because TGI introduces an external flow source independent of the ventilator, it can hinder the ventilator's ability to monitor pressures and volumes and may cause the ventilator alarm to go off incessantly. Catheter flow during expiration disables the monitoring role of the ventilator's expiratory pneumotachograph, triggering ventilator alarms when the difference between the measured inspired and exhaled volumes exceeds a certain value. More importantly, external

flow that can pressurize the ventilator circuit interferes with the ventilator's ability to detect leaks. Using the end-expiratory occlusion technique to measure auto-PEEP may increase lung volume dramatically if TGI flow is not interrupted simultaneously. The same effect will occur with continuous TGI during end-inspiratory occlusions.[6,30] TGI may also interfere with clinicians' ability to measure lung mechanics like respiratory system compliance and auto-PEEP.

Continuous-flow TGI could increase delivered V_T, airway and alveolar pressures, and total PEEP with both PCV and with volume-controlled ventilation. Moreover, in PCV, when ventilator flow reaches zero, continuous flow from continuous TGI increases V_T and airway pressures. These increases occur because the exhalation valve of the ventilator is not active during the inspiratory phase.[24] Overpressurization can be identified by examining the airway pressure tracing,[11] and can be remedied by placing a pressure-relief valve in the ventilator circuit to dissipate insufflated flow that produces excess pressure.[78,109] Complete obstruction of the outflow can cause overinflation of the lungs in seconds, with the potential for pneumothorax or hemodynamic compromise.

The efficacy of TGI can be monitored by capnography. Expiratory capnograms provide an indicator of the effect of TGI on the CO_2 concentration in the gas remaining in the proximal anatomic dead-space compartment at the onset of inspiration.[62,82,90] Although end-tidal P_{CO2} is a poor estimate of Pa_{CO_2}[110,111] in patients with respiratory failure, changes in end-tidal P_{CO2} induced by TGI correlate significantly with changes in Pa_{CO_2} and justify routine measurement of end-tidal P_{CO2} during TGI[33,62,82,90] (Fig. 22-11).

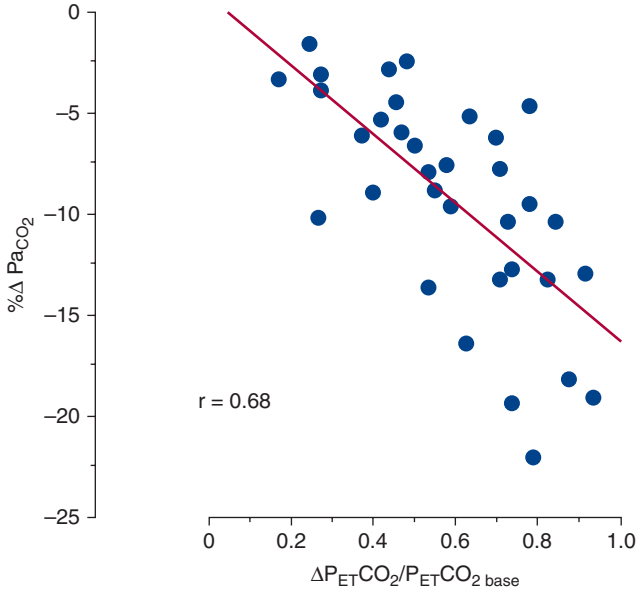

FIGURE 22-11 Percentage reduction in arterial P_{CO2} (Pa_{CO_2}) from baseline as a function of the reduction in partial pressure of end-tidal P_{CO2} ($P_{ET}CO_2$) from the baseline value ($P_{ET}CO_2$ base). As the difference between $P_{ET}CO_2$ and $P_{ET}CO_2$ base widened, larger reductions in arterial P_{CO2} were observed. (Used, with permission, from Ravenscraft SA, Burke WC, Nahum A, et al. Tracheal gas insufflation augments CO_2 clearance during mechanical ventilation. *Am Rev Respir Dis.* 1993;148:345–351.)

UNKNOWNS

The delivery of catheter gas at higher flows must be examined with regard to the need for humidification and the potential for tracheal damage with long-term use. Only inconclusive, limited data are available on the clinical safety of TGI.[85,87,112] Turbulent gas conditions promote shear stress, increased gas impact on the airway walls, and the transfer of a higher kinetic energy to the tracheal mucosa.[101,103] The end-hole TGI catheter mode could theoretically cause more airway damage than large-caliber reverse-thrust catheters because the flow exiting the end-hole catheter is closer to the carina and points directly at it. Further studies are needed to assess clinical safety before broad clinical application.[113–114]

THE FUTURE

TGI remains a promising technique that is only used as an investigational or late option at the bedside. TGI should be weighed against established invasive and noninvasive modes of ventilation. Evidence demonstrating better patient–ventilator interaction and the absence of significant adverse effects must be accumulated before TGI can be considered suitable for standard intensive care practice. Future TGI devices must include certain features:[30,84,105,109,115] (a) good coordination with the ventilator, (b) monitoring capabilities like automatic TGI flow shutoff to prevent overpressurization of the ventilator circuit and airways, (c) contextual alarms for TGI settings and TGI-ventilator–patient interaction, and (d) commercially available devices and catheters.

SUMMARY AND CONCLUSION

TTO therapy is safe for long-term administration of home oxygen. Transtracheal ventilation, using commercially available intravenous catheters and manual jet ventilation valve or wall oxygen supply, can ensure emergency lung ventilation. Experimentally, TGI is very effective at reducing lung volume while maintaining similar levels of Pa_{CO_2} during permissive hypercapnia in patients with ARDS. Similarly, TGI has been successfully used in patients with concomitant severe brain and lung injury and in patients with chronic respiratory failure. Nevertheless, concerns regarding patient application, safety, monitoring, and interaction with the ventilator remain. Further investigations are necessary before TGI can be routinely employed in intensive care units.

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VIII

VENTILATOR SUPPORT IN SPECIFIC SETTINGS

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23

MECHANICAL VENTILATION IN THE NEONATAL AND PEDIATRIC SETTING

Peter C. Rimensberger
Jürg Hammer

Respiratory disease in its various forms remains the most common cause of pediatric and neonatal morbidity and mortality. One of the most common reasons for admission to pediatric or neonatal intensive care units is the need for ventilatory support for acute or impending respiratory failure. The major challenge for these units is to deal with a very heterogeneous population of patients who are characterized by enormous differences in age and size and marked developmental changes in organ physiology during growth. In particular, the pediatric intensive care unit population is characterized by a wide variety of rare and unique medical problems that make large clinical trials, even on general topics such as ventilator support, very difficult to conduct.[1,2] Despite worldwide daily use of mechanical ventilation in pediatric and neonatal intensive care units, many clinical and practical questions remain unresolved. Answers are often extrapolated from the results of adult studies. This may seem sensible for older children but is dangerous when applied to neonates, infants, and children up to the age of 12 years, because of developmental alterations in the physiology of their organ systems, particularly (but not only) their respiratory system.

PECULIARITIES IN PHYSIOLOGY AND RESPIRATORY MECHANICS

The considerable differences in respiratory physiology and anatomy between infants and adults[3] explain why infants and young children have a higher susceptibility to more severe manifestations of respiratory diseases, and why respiratory failure is a common problem in neonatal and pediatric intensive care units (Table 23-1). The appreciation of the peculiarities of pediatric respiratory physiology is essential for correct management of critically ill and/or ventilated infants and children.

Metabolism

The basal metabolic rate is approximately twofold higher in infants than in adults (7 mL/kg/min at birth vs. 3 to 4 mL/kg/min in the adult). Hence, the normal resting state in infants is already one of high respiratory and cardiovascular activity. This means that infants have less metabolic reserve if O_2 consumption needs to be increased during critical illnesses.

TABLE 23-1: PHYSIOLOGIC REASONS FOR THE INCREASED SUSCEPTIBILITY FOR RESPIRATORY COMPROMISE OF INFANTS IN COMPARISON TO ADULTS

Cause	Physiologic or Anatomic Basis
Metabolism ↑	↑ O_2 consumption
Risk for apnea ↑	Immaturity of control of breathing
Resistance to breathing ↑	
Upper airway resistance ↑	Nose breathing Large tongue Airway size ↓ Collapsibility ↑ Pharyngeal muscle tone ↓ Compliance of upper airway structures ↑
Lower airway resistance ↑	Airway size ↓ Collapsibility ↑ Airway wall compliance ↑ Elastic recoil ↓
Lung volume ↓	Numbers of alveoli ↓ Lack of collateral ventilation
Efficiency of respiratory muscles ↓	Efficiency of diaphragm ↓ Rib cage compliance ↑ Horizontal insertion at the rib cage Efficiency of intercostal muscles ↓ Horizontal ribs
Endurance of respiratory muscles ↓	Respiratory rate ↑ Fatigue-resistant type I muscle fibers ↓

From Hammer J, Eber E. The peculiarities of infant respiratory physiology. In: Hammer J, Eber E, eds. *Paediatric Pulmonary Function Testing. Prog Respir Res.* Basel, Switzerland: Karger; 2005;33:2–7.

Control of Breathing

A considerable amount of maturation of the control of breathing occurs in the last few weeks of gestation and in the first few days of life, which explains the high prevalence of apnea in infants born prematurely.[4] The breathing pattern of newborn, especially premature, infants is irregular with substantial breath-to-breath variability and periodic breathing at times, which increases the risk of prolonged, potentially life-threatening apnea under certain circumstances. The responses to hypercapnia or hypoxia are decreased and of variable sensitivity, making the young infant much more vulnerable to any noxious stimuli and disturbances of the respiratory control mechanisms.[5]

Ineffective breathing can lead to hypoxemia and bradycardia that may be severe enough to require the use of continuous positive airway pressure (CPAP) or intubation and mechanical ventilation, especially in the very preterm baby. Methylxanthines (such as caffeine) are effective in reducing the need of ventilator support for apnea of prematurity.[4] Feedback from vagal stretch reflexes, rib cage muscles, and the changing mechanical state of the respiratory system during each breath influence respiratory activity. If inflation is small, there is little inhibitory vagal feedback. If inflation is excessive, inspiration is inhibited. This inspiratory–inhibitory reflex, the *Hering-Breuer inflation reflex,* is very potent in the preterm and less so in the term newborn and young infant during the first weeks of life.[6] This inflation reflex facilitates passive measurement of respiratory mechanics, but may interfere with ventilator triggering. Babies may become apneic after a mechanical inflation, especially if an excessively prolonged inspiratory time (T_I), is used.[7] Fortunately, CPAP seems to enhance a baby's ability to adjust to increased respiratory loads, possibly by the elimination of the Hering-Breuer deflation reflex.[8]

Upper and Lower Airways

In the newborn, nasal breathing is obligatory, or at least strongly preferential, secondary to the configuration of the upper airways. The epiglottis is relatively large, floppy, and positioned high in the pharynx so that it is in contact with the soft palate, thereby favoring nasal over mouth breathing.[9] The larynx, trachea, and bronchi are considerably more compliant than in the older child, thus making the infant's airway highly susceptible to distending and compressive forces.[10] Thus, with any obstruction of the upper airway, significant dynamic inspiratory collapse of upper airway structures can occur during forceful inspirations, which further adds to the obstruction already present. With lower-airway obstruction, forced expiratory efforts result in increased intrathoracic pressure and dynamic expiratory lower airway collapse further limiting expiratory flow. Positive end-expiratory pressure (PEEP) may help to stent collapsing airways during expiration in some patients (e.g., those with tracheobronchomalacia; Fig. 23-1).[11]

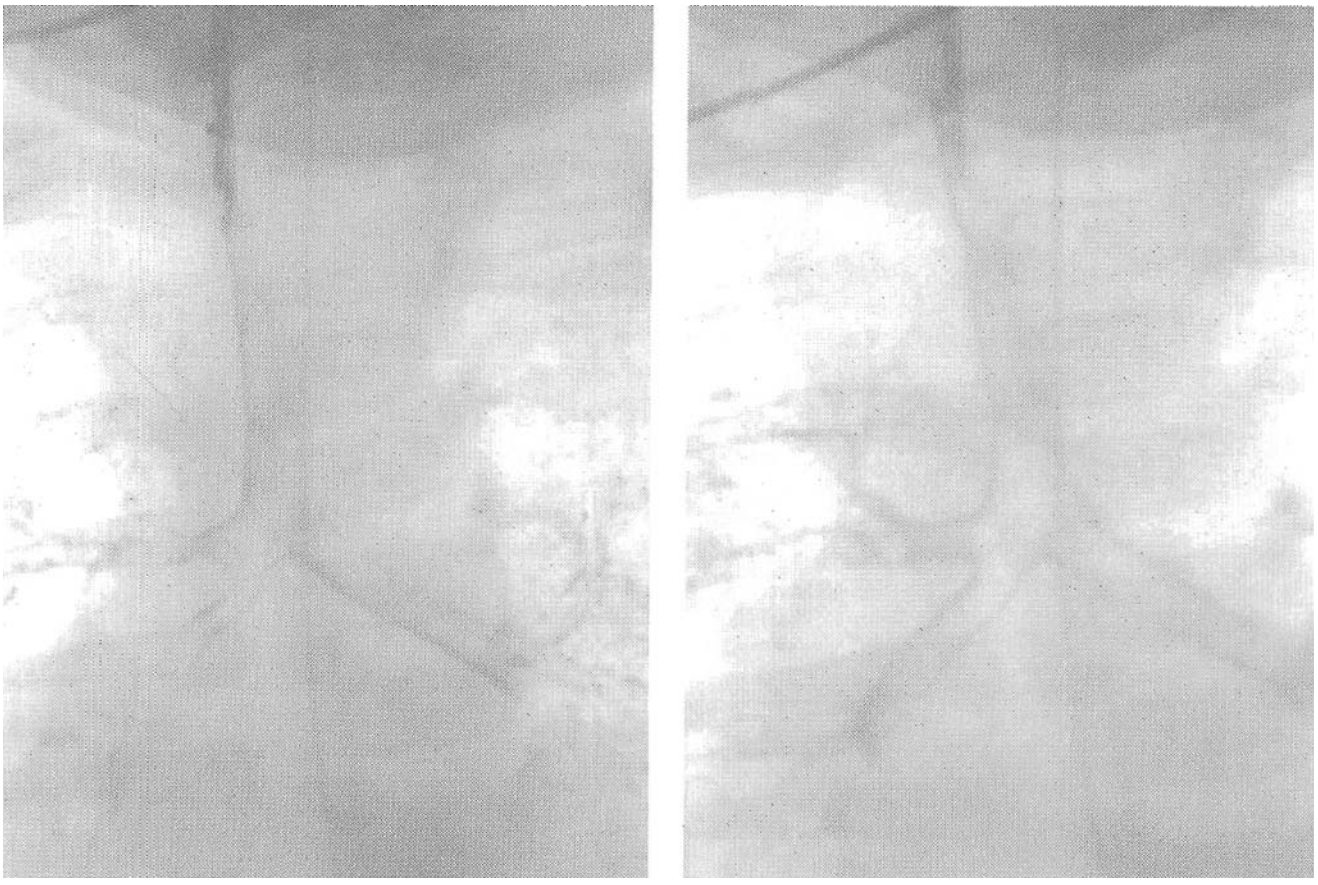

FIGURE 23-1 Bronchography in patient with tracheobronchomalacia without application of positive airway pressure (*left*) and with 10 cm H_2O of positive airway pressure (*right*). Application of positive airway pressure produces stenting of the trachea and the bronchial tree. (Courtesy Quen Mok, Great Ormond Street Hospital for Children, London, UK.)

Small peripheral airways contribute approximately 50% to the total airway resistance in the infant lung (compared to approximately 20% in the adult). As airway diameter and length increase with age and growth, airway resistance falls tremendously from birth to adulthood.[12] Therefore, diseases that affect the small airways and cause large changes in peripheral resistance may be clinically silent in an adult, but can cause significant problems in infants (e.g., bronchiolitis).

The airways of a child are relatively large in comparison with those of an adult, although in absolute terms they are small. Airway resistance in spontaneously breathing infants is normally 20–30 cm H_2O/liter per second; values in intubated infants are 50 to 150 cm H_2O/L/s, consequent to the diameter of the endotracheal tube (ETT).[13] For many years it was thought that small infants could not breathe spontaneously through an appropriately sized ETT (because of the high resistance imposed by the small lumen), but this view is no longer maintained. Under normal tidal flow conditions, resistance imposed by a small tube is not substantially higher than that with larger tubes.[14]

Lung and Chest Wall

Because of its shape, high compliance, and deformability, the contribution of the rib cage to tidal breathing is limited in newborns and infants. The ribs are horizontally aligned and allow for less anteroposterior movement of the chest wall and less efficiency of the intercostal muscles during respiration. The highly compliant chest wall is easily distorted, so that under conditions of respiratory impairment, much energy is wasted by sucking in ribs rather than fresh air. This paradox inward movement of the chest wall during inspiration is a common sign of almost any disorder causing respiratory distress in infants, but is most pronounced in upper-airway obstruction.

The elastic tissue in the septa of the alveoli surrounding the conducting airways provides the elastic recoil that enables the airways to remain open. Early in life there are few relatively large alveoli that provide little support for the airways, which are thus able to collapse easily. Addition of alveoli continues throughout early childhood by septal division, providing more elastic recoil and a decreased tendency for airway collapse with increasing age.[15] Elastic recoil increases

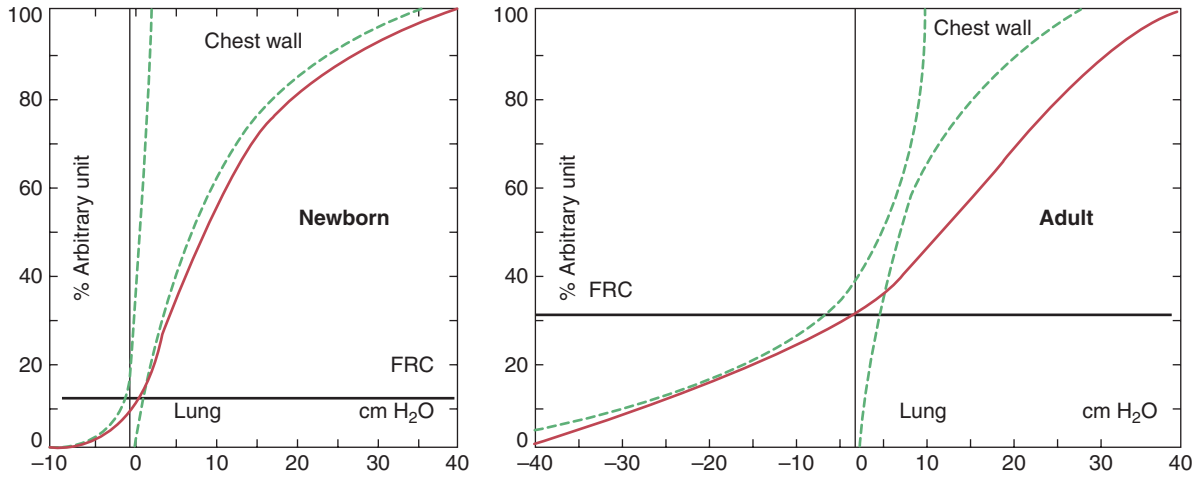

FIGURE 23-2 Characteristics of lung and chest wall mechanics in newborns compared to adults. The compliant chest wall in the newborn leads to lower functional residual capacity (*FRC*) in the newborn. (Based on data published in Agostoni E. Volume-pressure relationships of the thorax and lung in the newborn. *J Appl Physiol.* 1959;14:909–913.)

until adolescence and declines again with aging. Collateral pathways of ventilation (intraalveolar pores of Kohn and bronchoalveolar canals of Lambert) do not appear until 3 to 4 years of age,[16,17] which excludes alveoli beyond obstructed airways to be ventilated by these alternate routes and predisposes the infant to the development of atelectasis.

The balance between the chest and lung recoil pressure that determines the static resting volume of the lung is set at lower lung volumes in infants compared with older children (Fig. 23-2).[18] The highly compliant chest wall results in relatively low transpulmonary pressures at end-expiration that leads to an increased tendency for collapse of the small peripheral airways and ventilation inhomogeneity. The infant adopts several strategies to constantly establish lung volumes, including (a) a higher respiratory rate with insufficient time to exhale to the elastic equilibrium volume, (b) laryngeal adduction during exhalation to increase the resistance to airflow, and (c) constant postinspiratory diaphragmatic muscle activity (i.e., tonic diaphragmatic activity). A PEEP of 5 to 6 cm H_2O is necessary to maintain end-expiratory lung volume in infants under neuromuscular blockade.[19] The highly compliant chest wall also explains the generally high cardiovascular tolerance of infants to high airway pressures that are less efficiently transmitted to the pleural space. The low elastic recoil of the chest, together with a low percentage of slow-muscle fibers in both the diaphragm and intercostal muscles, explain why very little airway pressure is needed to expand the chest wall during inspiration in healthy babies.

Circulatory Changes Pertinent to Mechanical Ventilation after Birth

Before birth, only approximately 10% of blood flow passes through the lungs as a result of high pulmonary vascular resistance, patent ductus arteriosus, open foramen ovale, and the low-resistance placental component to the systemic circulation. Pulmonary vascular resistance falls rapidly in the first minutes of life, but is still elevated and falls only gradually to normal levels over days to weeks. Under certain circumstances (e.g., birth asphyxia, chronic hypoxia, or neonatal septicemia with or without metabolic acidosis), pulmonary vascular resistance increases or remains high, leading to right-to-left shunting through the ductus arteriosus and sometimes even through the foramen ovale. This persistent pulmonary hypertension of the newborn (PPHN) leads to poor systemic oxygenation, as revealed by low postductal transcutaneous saturation levels or desaturation of all four extremities when the right-to-left shunt at the level of the foramen ovale is important.

High inflation pressures to recruit lung volume and improve oxygenation should be used with caution because of the risk of increased pulmonary vascular resistance by overdistension and compromised cardiac output. First-line treatment is directing toward known determinants of pulmonary vascular resistance (Table 23-2) such as acidosis or high interstitial pressures. Second-line therapy includes specific pulmonary vasodilators, such as inhaled nitric oxide (iNO)[20–22] after excluding congenital heart disease with

TABLE 23-2: MAIN DETERMINANTS OF PULMONARY VASCULAR RESISTANCE

Increase in Pulmonary Vascular Resistance	Decrease in Pulmonary Vascular Resistance
High interstitial pressure	Low interstitial pressure
High lung volumes (alveolar overdistension)	Normal lung volumes
Low lung volumes (atelectasis)	
Low alveolar P_{O_2}	High alveolar P_{O_2}
Low arterial pH	High arterial pH

P_{O_2}, partial pressure of oxygen.

duct-dependent systemic circulation, which may deteriorate when pulmonary vascular resistance is lowered (e.g., total anomalous pulmonary venous return or hypoplastic left-heart syndrome).[23]

Oxygen Transport

Fetal hemoglobin is the predominant type of hemoglobin at birth and decreases steadily over the first 6 months. 2,3-Diphosphoglycerate (2,3-DPG) has a lower affinity to fetal hemoglobin and shifts the dissociation curve to the left. This facilitates loading and unloading of O_2, ensuring, together with the high O_2-carrying capacity of fetal hemoglobin, adequate tissue oxygenation despite low partial pressure of arterial oxygen (Pa_{O_2}) values in utero (15 to 30 mm Hg). The predominance of fetal hemoglobin makes it possible, if necessary, to tolerate lower Pa_{O_2} values (but not really arterial oxygen saturation [Sa_{O_2}]) better in early postnatal life than is possible later in life.

Preterm babies can maintain their growth in utero with a mean Pa_{O_2} of 3.2 kilopascals (kPa; approximately 24 mm Hg), equivalent to Sa_{O_2} of approximately 70%. In neonatal intensive care units, clinical practice has long been to keep oxygen levels in preterm newborns in line with those of term infants until neonatal morbidities induced by oxygen have been better understood. To date, there is insufficient evidence to suggest what would be the optimal Sa_{O_2} or Pa_{O_2} values in preterm infants to avoid potential oxygen toxicity while ensuring adequate oxygen delivery to tissues. There is, however, ample evidence to support the notion that a "restrictive" oxygen approach does more good than harm in preterm babies.[24]

SOME SPECIAL CONSIDERATIONS FOR VENTILATOR MANAGEMENT IN NEONATES, INFANTS, AND CHILDREN

The basic objectives of ventilator support remain the same from early life to adulthood[25,26] but ventilator strategies, modes, and targets are not always fully identical to those established in adults.

Lung-Protective Ventilation

Barotrauma zones, safe peak inspiratory pressure and PEEP, are less-well defined in the younger age group, especially the very premature infant. Neonatologists tend to limit peak inspiratory pressure to 30 cm H_2O or lower; some favor the use of high-frequency oscillation ventilation (HFOV) in this age group. Studies investigating lung-protective ventilation in neonates have mainly focused on comparing high-frequency ventilation with conventional mechanical ventilation (CMV), leaving unanswered the important question as to whether reducing tidal volume or increasing PEEP is also lung protective.[27] HFOV is best used with a high-lung-volume strategy, but offers no benefit over conventional ventilation when a lung-protective strategy is applied.[28]

A lung-protective strategy is commonly advocated similar to recommendations for adults following the publication of the ARDS Network trial.[29] Recent observational cross-sectional studies, however, revealed that commonly used tidal volume (V_T) varies between 6 and 10 mL/kg (mean: 8.3 ± 3.3 mL/kg) in children,[2,30] and between 4 and 6 mL/kg (mean: 5.7 ± 2.3 mL/kg) in neonates.[31] Interestingly, V_T up to 10 mL/kg in children does not seem to be associated with increased mortality. Moreover, higher V_T within this range is associated with more ventilator-free days, particularly in patients with less-severe disease.[30] In a recent prospective, multicenter, observational study, higher maximum and median tidal volumes were associated with reduced mortality, even when corrected for severity of lung disease.[32] There is even less data available for neonates than for children to confirm or reject the hypothesis that small-volume ventilation, V_T of 4 to 6 mL/kg, is the best lung-protective approach.[27]

Allowance for Hypercapnia or Hypocapnia, Respectively

Overventilation and hypocapnia have been shown to contribute to adverse neurodevelopment in preterm infants and also in the neonate with hypoxic ischemic encephalopathy.[33–35] Any rapid reduction in partial pressure of arterial carbon dioxide (Pa_{CO_2}), which may occur with surfactant therapy or change in ventilator mode, may lead to cerebral vasoconstriction, increasing the risk of cerebral hemorrhage and/or leukomalacia. Both extremes and fluctuations of Pa_{CO_2} are associated with severe intraventricular hemorrhage. It may be prudent to avoid extreme hypocapnia and hypercapnia during the period of risk for intraventricular hemorrhage in preterm infants. Both minimum partial pressure of carbon dioxide (P_{CO_2}) and cumulative P_{CO_2} less than 35 mm Hg are associated with poor outcome in neonates with hypoxic ischemic encephalopathy.[34]

Volume-Targeted Ventilation in Neonates

Modern neonatal ventilator modes can target a set tidal volume as an alternative to traditional pressure-limited ventilation. Volume-targeted ventilation (VTV) aims to produce a more stable V_T so as to reduce lung damage and stabilize Pa_{CO_2}. Infants receiving VTV had lower rates of death and chronic lung disease compared with infants ventilated using pressure-limited ventilation modes.[36,37] Further studies are needed to identify whether VTV modes improve neurodevelopmental outcomes and to compare and refine VTV strategies.

VTV has some technical limitations. First, the displayed VT can be misleading in the presence of a high ETT leak. Such leak is common in neonatal practice where uncuffed tubes are commonly used and may be noted in approximately 75% of all ventilated neonates, usually without greater clinical relevance.[38] Leaks are associated with an inability to detect the patient's inspiratory effort or autotriggering of the ventilator. The latter also occurs if tubing is not kept dry and if there is water accumulation in the expiratory limb. This complication is more common in the neonate and young infant. Second, inaccurate V_T delivery under specific conditions, especially when rapid changes in respiratory system mechanics occur, has been described with various neonatal ventilators that offer VTV. Such discrepancies between the set V_T and the delivered inflations can be harmful in clinical situations, especially in newborns. Their clinical relevance needs to be clarified with safety studies in the neonatal population, before the "uncritical" use of such new hybrid modes could be advocated for all neonates and for various clinical conditions.[39]

Setting Ventilator Parameters According Respiratory Mechanics

There is a tendency towards using very short inspiratory times in premature infants with respiratory distress syndrome (RDS) secondary to the very low compliance of the lungs. An increase in inspiratory time may sometimes result in lower peak inspiratory pressures and more homogenous ventilation. A good knowledge of respiratory mechanics is helpful to decide on the best settings. In addition, there exists the erroneous belief that expiratory times have to be longer than inspiratory times. While this is the case in obstructive airways disease, it does not apply to the healthy or the stiff lung in neonates and children.

Small Endotracheal Tubes

The small and narrow ETTs are prone to mucus plugging and kinking. Many clinicians believe that for an infant or young child, breathing through a small ETT is equivalent to breathing through a straw, thereby imposing an unacceptable work of breathing. This notion is contrary to both clinical observation and physiology.[14,40] A 3-kg infant accepts a 3-mm inner-diameter ETT, whereas a 60-kg adult can tolerate a 9-mm inner-diameter ETT—a 20-fold increase in body size but only a threefold increase in ETT size. The narrower tube is irrelevant because it is shorter and because lower flows are generated by the infant compared to the adult. The net effect is that the infant is breathing through a hose rather than a straw when compared to the adult. Hence, if an infant or young child cannot sustain a spontaneous breathing trial on CPAP or a T-piece for several hours, he or she is as likely to fail extubation as when pressure support is applied. Furthermore, the addition of pressure support is likely to mask respiratory insufficiency and contribute to a higher failed extubation rate.[41]

Tracheotomy for Long-Term Ventilation

Tracheotomy is withheld for a longer period in critically ill children than in adults. Infants tolerate prolonged intubation much better than adults, although complications, such as subglottic stenosis,[42] can occur. Furthermore, indications for tracheotomy are different between children and adults: Tracheotomy is more often appropriate for bypassing congenital or acquired upper-airway obstruction than for supporting long-term mechanical ventilation.[43]

Closed Suction Systems

There is probably no medical device other than closed-suction systems that has been as enthusiastically accepted in intensive care unit practice without the requirement to prove benefit in a randomized controlled trial. There is still insufficient evidence to decide between endotracheal suctioning with or without disconnection.[44] In the injured lung, however, closed suction is much less effective than open suction, irrespective of the type of secretions.[45] The negative effects of suction on lung volume, heart rate, and Sa_{O_2} are transient and highly variable with both open-suction and closed-suction methods in spontaneously breathing infants.[46] This suggests that it is time to reassess the role of open suction, especially in ventilated infants with narrow tubes and respiratory disease resulting in large amounts of copious secretions.

COMMON CLINICAL CONDITIONS

Neonates

RESPIRATORY DISTRESS SYNDROME (HYALINE MEMBRANE DISEASE)

RDS is characterized by pulmonary surfactant deficiency and transudation of plasma proteins into the alveolar spaces. It typically occurs in preterm infants, and its severity correlates with the degree of immaturity of the lungs and is aggravated by concomitant infection, oligohydramnios, and a variety of other factors. The results are stiff lungs and a tendency to atelectasis. Initial ventilator management aims to recruit collapsed alveoli, restore functional residual capacity, and achieve adequate alveolar ventilation. Technical and pharmacologic advances, with improved understanding of pathophysiology and causes of lung injury, have significantly enhanced the ventilator management of preterm infants with RDS. Ventilator modalities have shifted towards early noninvasive ventilation and decreased and shortened use of invasive forms of ventilation in most preterm infants.

Nasal CPAP applied by various devices has become the primary respiratory support for RDS. When used early, it reduces respiratory failure, the need for surfactant, and the duration and invasiveness of respiratory support without impairing neonatal outcome.[47] It therefore offers a valuable

alternative to intubation and surfactant in preterm infants.[48] It has not, however, proven to allow for better outcome than intubation and mechanical ventilation in preterm infants.[49] Nasal CPAP improves respiration in preterm infants by increasing functional residual capacity and chest wall stability, as well as decreasing upper-airway collapsibility and upper-airway resistance.[50]

Recently, heater-humidifier devices that use novel methods for conditioning respiratory gases from an external source have been introduced. The addition of sufficient warmth and high levels of humidification to a gas has enabled the use of higher flow rates from a nasal cannula. High-flow nasal cannula can be used to provide high concentrations of O_2 and may deliver PEEP. At present, there is insufficient evidence to establish the safety or effectiveness of high-flow nasal cannula as a form of respiratory support in preterm infants. When used following extubation, high-flow nasal cannula seems to result in a higher rate of reintubation than does nasal CPAP.[51]

When positive-pressure ventilation was first introduced in newborn infants with RDS, the use of high peak inspiratory pressures was associated with high mortality rates, air leaks, and the development of bronchopulmonary dysplasia (BPD).[52] In the 1970s, the incidence of pneumothoraces was reduced by adopting a strategy using long T_I values and slower rates.[53] This strategy was widely adopted and only given up after the benefit of PEEP was better understood.[54] Administration of exogenous surfactant and advancements in ventilator technology, which decrease patient–ventilator asynchrony, have further improved the management and outcome of RDS. It is now widely accepted that severe RDS, characterized by poorly compliant lungs and very short time constants, is best managed with short T_I values (0.26 to 0.34 seconds), rapid rates (60/breaths/min or more), and PEEP.[55,56] Such general recommendations help in avoiding major errors when initiating mechanical ventilation in infants suffering from severe RDS. Nevertheless, inspiratory and expiratory time, respiratory frequency, and PEEP need to be customized to an individualized assessment of a patient's respiratory mechanics, which change over the course of disease or with therapeutic interventions such as surfactant administration. The availability of low-dead-space-flow sensors enables continuous measurement of V_T, and eliminated much of the guesswork in setting the ventilator. Volume-targeted modes have now become increasingly popular in the neonatal intensive care unit to improve the stability of ventilation and to reduce unnecessarily high peak pressures.[37] This strategy aims at reducing Pa_{CO_2} fluctuations in very preterm infants (although it is not always as successful as hoped[57,58]), which are associated with the development of intraventricular hemorrhage and leukomalacia. Hence, much emphasis is placed on using ventilator strategies that should best guarantee a constant Pa_{CO_2} and at the same time use of the lowest fractional inspired oxygen concentration (FI_{O_2}) to achieve sufficient tissue oxygenation.

The underlying pathophysiology, decreased lung compliance, high chest wall compliance, and dynamically maintained functional residual capacity above closing volume make RDS a perfect candidate for an open-lung strategy and use of HFOV. Despite many studies of HFOV versus conventional ventilation (and three meta-analyses of these trials) involving 3652 infants, neonatologists remain unsure about the potential benefits and harms of HFOV for support of preterm infants with surfactant-deficient lungs. The Prevention of Ventilator Induced Lung Injury Collaborative Group (PreVILIG collaboration) recently concluded that HFOV seems equally effective to conventional ventilation in preterm infants.[59] Current results do not support selection of preterm infants for HFOV on the basis of gestational age, birthweight for gestation, initial lung disease severity, or exposure to antenatal corticosteroids.[59] Why data from animal models predicted a larger effect size than that observed in human infants remains an unanswered question. Recent data, however, support the usefulness of first-intention HFOV strategy in managing selected subpopulations, such as very-low-birthweight newborns complicated by severe RDS not antenatally treated with glucocorticoids.[60]

Exogenous surfactant therapy has been part of routine care of preterm neonates with RDS since the early 1990s. Animal-derived exogenous surfactants are the present treatment of choice, with few adverse effects. The few adverse effects are largely related to changes in oxygenation and heart rate during surfactant administration.[61] The optimal dose is usually 100 mg/kg. Both prophylaxis and early treatment are successful in infants with established RDS, but prophylaxis appears to produce greater benefit.[62] The concept of using surfactant early in patients with low oxygen needs (FI_{O_2} <0.45), combined with the so-called INSURE approach (intubation-surfactant-extubation to nasal CPAP), has decreases the need for mechanical ventilation, incidence of BPD, and air leak syndromes as compared to subsequent use of INSURE when FI_{O_2} exceeds 0.45.[47,63]

Persistent fetal circulation is a complication of RDS in preterm infants. At present, there is no clearcut evidence in favor of using iNO for preterm infants requiring mechanical ventilation.[64] Clinicians continue to make case-by-case decisions for the treatment of preterm infants with hypoxia unresponsive to other therapies.[65]

PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN

PPHN is the result of elevated pulmonary vascular resistance to the point that venous blood is shunted to some degree through fetal channels (e.g., ductus arteriosus and foramen ovale) into the systemic circulation. By bypassing the lungs, it causes systemic arterial hypoxemia. It is associated with (a) pulmonary parenchymal disease such as RDS or meconium aspiration and (b) hypoplasia of the lungs, most often in the form of diaphragmatic hernia. It (c) also can occur without an evident cause.

Traditionally, these infants have been hyperventilated to achieve mild hypocapnic alkalosis in an attempt to attenuate

hypoxic pulmonary vasoconstriction. iNO is an approved adjunct to improve oxygenation in term and preterm infants with severe hypoxemic respiratory failure secondary to PPHN and has been shown to reduce the need for extracorporeal membrane oxygenation.[66] Alveolar recruitment should be optimized to achieve best iNO effects on oxygenation.[23] Hence, HFOV is an ideal method to combine with iNO.

MECONIUM ASPIRATION SYNDROME

Meconium aspiration syndrome affects mature infants and is characterized by a mixture of inflammatory pulmonary disease, secondary surfactant deficiency, obstruction of small airways, and pulmonary hypertension. The result is a very inhomogeneous lung with areas of atelectasis and hyperinflation. In terms of pathophysiology and ventilator management, meconium aspiration syndrome resembles acute respiratory distress syndrome (ARDS) of pulmonary origin, favoring the use of similar ventilator strategies (open lung concept, permissive hypercapnia, and so on). Despite the introduction of innovative ventilatory treatments for this disease over the last two decades (e.g., surfactant-lavage, HFOV, iNO, extracorporeal membrane oxygenation), most infants can be successfully managed with CPAP or mechanical ventilation alone.[67,68]

CONGENITAL DIAPHRAGMATIC HERNIA

Congenital diaphragmatic hernia (CDH) is characterized by lung hypoplasia, surfactant deficiency, and an extremely reactive hypoplastic pulmonary vascular system. The hypoplastic lungs are very vulnerable to injury from aggressive ventilation with high inspiratory pressures. Treatment is no longer focused on immediate surgery, but rather on delaying repair until all reversible problems are resolved (i.e., stabilization period).[69,70] The concept of delaying repair until pulmonary hypertension resolves and the patient is hemodynamically stable has increased survival from below 50% to as high as 80%.[69,71] Although high airway pressures may be required with secondary parenchymal injury to ensure adequate oxygenation, special care is necessary to avoid alveolar distension in the setting of pulmonary hypoplasia. Neither the use of HFOV nor early rescue extracorporeal membrane oxygenation, however, has significantly improved outcome in CDH patients, the best survival rates with these options are approximately 80%.[72–77] The discussion on optimal treatment strategies for CDH, in addition to the commonly accepted need for early lung-protective ventilation to avoid lung injury, is not closed.[78]

Pediatric Patients

VIRUS-INDUCED HYPOXEMIC FAILURE

Two distinct patterns of disease occur in infants with virus-induced respiratory failure.[79,80] The primary causative agent is respiratory syncytial virus. The most frequent pattern is acute bronchiolitis characterized by an obstruction of small airways with air trapping and a moderate degree of parenchymal disease from atelectasis. This leads to increased respiratory resistance, a prolonged time constant, intrinsic PEEP, and decreased respiratory compliance.[81] Radiographic findings include hyperinflation, perihilar infiltrates, and atelectasis. The second pattern, which affects approximately 25% to 30% of infants with respiratory syncytial virus-induced respiratory failure, consists of severe restrictive parenchymal disease (usually termed *respiratory syncytial virus-pneumonia*). Typically, respiratory compliance and lung volumes are decreased markedly without significant airway obstruction or air trapping. Alveolar consolidation is the main radiographic feature. This subgroup also usually fulfills the criteria of ARDS. Patients require prolonged ventilation compared with a brief duration (4 to 8 days) for the bronchiolitic pattern.[79,80]

No consensus exists on optimal ventilator strategy. Nasal CPAP appears useful in the early stages of severe bronchiolitis by decreasing the work of breathing needed to overcome the intrinsic PEEP. The evidence supporting the use of CPAP to reduce P_{CO_2} and respiratory distress in bronchiolitis, however, is of low methodologic quality, reporting only short-term effects,[82] and there is no conclusive evidence that CPAP reduces the need for intubation.[83,84] More recently, high-flow nasal cannula, if used early in the treatment of severe bronchiolitis, appears to reduce the need for intubation in infants with viral bronchiolitis.[85]

Pressure-controlled ventilation (PCV) is the mode used most commonly in virus-induced respiratory failure because the decelerating flow pattern achieves a lower mean airway pressure than volume-controlled ventilation (VCV). Most patients need peak inspiratory pressures of 25 to 35 cm H_2O to achieve adequate ventilation. Infants with obstructive disease have long expiratory time constants. They are best ventilated with slow rates and inspiratory-to-expiratory (I:E) ratios of at least 1:3 to prevent breath "stacking" and further hyperinflation. Conversely, patients with restrictive disease may require faster rates and lower I:E ratios. Permissive hypercapnia, to avoid high peak inspiratory pressures and barotrauma, can be used with both pathophysiologic patterns.

Obstructive patients may do poorly with HFOV, although this statement is not as absolute as often thought.[86] Patients with predominant restrictive disease, however, are better candidates for HFOV.

PEDIATRIC ACUTE RESPIRATORY DISTRESS SYNDROME

The causes of ARDS in pediatric patients are the same as in adults, although viral or bacterial respiratory infections are more common in children.[79] Ventilator strategies are the same as in adult patients and include high PEEP and limiting peak inspiratory pressure to below 30(–35) cm H_2O.

Lung-protective ventilation strategies are commonly recommended, although there is doubt as to the best V_T.

Although no single ventilation mode has proven superior, the most common modes are PCV and HFOV,[2,30,87] despite the absence of solid data on the use of HFOV in pediatric patients beyond the neonatal period. Prone positioning is used commonly, but without proven benefit.[88,89] iNO cannot be recommended for routine use, although it is used as rescue therapy (for a short time) in the very early stages of life-threatening hypoxemia and severe pulmonary hypertension.

STATUS ASTHMATICUS

Most complications in patients with asthma receiving ventilation occur during or immediately after intubation. They result largely from gas trapping that causes hypotension, O_2 desaturation, pneumothorax, and cardiac arrest. Institution of positive-pressure ventilation in patients with asthma alters cardiocirculatory and respiratory dynamics dramatically, leading to diminished venous return and hypotension.

The optimal ventilator mode for status asthmaticus is not established. Randomized, controlled trials comparing different modes in pediatric asthma patients are virtually impossible.[90] Most clinicians prefer pressure-limited ventilation, keeping peak inspiratory pressure below 35 to 40 cm H_2O and accepting hypercapnia.[91] Because of their decelerating flow pattern, PCV and pressure-regulated VCV allow for lower peak inspiratory pressures but result in higher mean airway pressures than VCV with identical V_T. Ventilator rates are set well below normal and require an extremely long expiratory and reasonably long inspiratory time. Externally applied PEEP should be, in general, just below auto-PEEP to decrease trigger work but not increase hyperinflation. Duration of mechanical ventilation for status asthmaticus is usually of 1 to 4 days. Children with rapid-onset near-fatal asthma may have a shorter duration of ventilation than children with asthma that progresses slowly to respiratory failure.[92]

HFOV, pressure-support ventilation (PSV), and noninvasive ventilation have been tried in status asthmaticus. HFOV is believed to be contraindicated in children with severe airflow obstruction, although recent experience challenges this belief.[93] PSV enables active exhalation, which may decrease hyperinflation. PSV allows patients to determine their own respiratory pattern (rate, T_I, and V_T) and may decrease patient–ventilator dyssynchrony. PSV decreases work of breathing by partially unloading the respiratory muscles. Careful selection of PEEP decreases the work of triggering during PSV. PSV of 22 to 37 cm H_2O has been used successfully in children with asthma requiring full or near-full support, resulting in rapid improvement in gas exchange.[94] Noninvasive PSV is often poorly tolerated without sedation, and its role in avoiding intubation in children with status asthmaticus remains unclear.[95,96]

CORRECT TIMING OF EXTUBATION

Avoidance of unnecessary weaning delays is important for reducing the risk of nosocomial infection, ETT damage to the airway, development of chronic lung disease in neonates, and prolonged dependency on narcotic drugs.[97,98] Aggressiveness with early weaning, however, must be balanced against the risk of extubation failure that occurs in 2% to 20% of children[41,99] and up to 40% of neonates,[100] and which is associated with increased mortality.[101]

Extubation Readiness

Several indices have been developed to predict successful weaning and extubation. Although these indices have been used in research studies, they have not found widespread use in clinical care, likely because of their complexity and lack of proven benefit over clinical judgment. A trial of spontaneous breathing with a T-piece or the use of 10 cm H_2O of PSV for up to 2 hours has been successful in predicting extubation failure in children.[102] A modified rapid shallow breathing index, also known as frequency-to-tidal-volume ratio, and the compliance, rate, oxygenation, and pressure index has been proposed for weaning prediction in children.[103]

There is fertile ground for future research to identify simple predictors of extubation readiness that would likely shorten the duration of ventilation, decrease length of intensive care unit stay, and potentially reduce ventilator-induced lung injury.[41] Table 23-3 lists proposed clinical and laboratory criteria for weaning failure during 2 hours on CPAP of 5 cm H_2O or a T-piece. The single most common cause

TABLE 23-3: CRITERIA FOR EXTUBATION READINESS TEST FAILURE

Proposed criteria for failure of extubation readiness during 2 hours on CPAP <5 cm H_2O or T-piece

Clinical Criteria:
Diaphoresis
Nasal flaring
Increasing respiratory effort
Tachycardia (increase in heart rate >40 bpm [breaths per minute])
Cardiac arrhythmias
Hypotension
Apnea
Laboratory Criteria:
Increase in end-tidal CO_2 >10 mm Hg
Decrease of arterial pH <7.32
Decline in arterial pH >0.07
Pa_{O_2} <60 mm Hg with an FI_{O_2} >40 (P/F O_2 ratio <150)
Sp_{O_2} declines to <5%

From Newth, et al. Weaning and extubation readiness in pediatric patients. *Pediatr Crit Care Med.* 2009;10:1–11.

of extubation failure in children, however, is upper-airway obstruction, which is difficult to predict with an ETT in place. The air-leak test (an audible air leak when airway pressure ≥25 cm H_2O), although often recommended, has repeatedly been shown to have low sensitivity for testing extubation readiness.[104–106]

Extubation failure is more frequent in children with chronic respiratory disorders, neuromuscular and chronic neurologic disorders, and upper-airway problems.[101] The most common cause of extubation failure in preterm infants is apnea with bradycardia.[107]

Developing reliable thresholds for indices for weaning extremely low-birthweight preterm infants has proven equally difficult as for older children.[108] The percentage of time spent below a target value of spontaneous expiratory minute ventilation (<125 mL/min/kg) during a 2-hour CPAP trial appears promising but requires further testing.[109,110] Another option might be a spontaneous breathing trial of 3 minutes on CPAP after minimal ventilator settings have been reached.[111]

Weaning Modes and Adjuncts to Weaning

The most common approach to weaning infants and children is gradual reduction of ventilator support by decreasing rate and airway pressures during synchronized intermittent mandatory ventilation (SIMV). Other weaning methods include PSV and volume-support ventilation. Both methods involve patient-triggered pressure support. With PSV, the level of PSV is adjusted gradually by the physician to a minimal level that achieves an acceptable breathing pattern. With volume-support ventilation, the level of PSV is adjusted continuously by the ventilator to achieve minimum minute ventilation. It is common practice to extubate infants and children from a low level of ventilator support. Gradual weaning is often unnecessary after the underlying disorder has resolved.[102,112]

Today, many modes have been developed to facilitate weaning by reducing work imposed by the respiratory apparatus.[113,114] Misperceptions about the impact of the ETT resistance may interfere with weaning management. Although it has become fashionable to use pressure support with PEEP, rather than CPAP or T-piece breathing, to overcome ETT resistance, physiologic and scientific evidence shows that the increase in resistance caused by an appropriately sized tube is minimal and the additional work of breathing negligible. Hence, an infant or young child should be able to sustain a spontaneous breathing trial on CPAP or a T-piece for several hours, if he or she is likely to be successfully extubated. A spontaneous breathing trial using pressure support set at higher levels for smaller ETTs overestimates readiness for extubation in children and contributes to a higher failed extubation rate.[115]

The classic approach to weaning neonates from CMV is to extubate them from a rate of about 15 breaths/min to supplemental O_2 or nasal CPAP. Weaning strategies involve decreasing rate (except for patient-trigger ventilation) and positive inspiratory pressure to maintain the V_T at 4 mL/kg or greater. PSV may be combined with SIMV. Newer options include volume-assured pressure support and proportional-assist ventilation.[116] In neonates, direct extubation from a low ventilator rate showed a trend toward greater successful extubation than did extubation after a period of endotracheal CPAP.[117] Weaning from HFOV is performed by switching to CMV or by extubation after gradual reduction of mean airway pressure and amplitude to very low values.

Nasal CPAP, noninvasive positive-pressure ventilation, and methylxanthines are evidence-based treatments to facilitate weaning and extubation of preterm infants, but only the first two can be recommended for routine use. In contrast to adults, steroids are not recommended for prevention of postextubation stridor in pediatric or neonatal populations.[118]

In conclusion, neonates and children can be weaned much quicker than adults, and weaning protocols have proven to be of little or limited value in pediatric patients.

COMMON TECHNIQUES FOR RESPIRATORY SUPPORT

The following invasive and noninvasive techniques are commonly used in infants and children to support spontaneous ventilation or to apply controlled mechanical ventilation:

1. CPAP during spontaneous breathing
2. PSV to assist spontaneous breathing
3. PCV or VCV
4. Intermittent mandatory ventilation (IMV) or SIMV, with or without PSV
5. High-frequency ventilation (HFV) with or without spontaneous breathing

Clinical experience with most of these modes in neonates and infants, although less in children, is distinctly different from that in adults. There is a long-standing neonatal experience of nasal CPAP and HFV. Conversely, assist modes only recently became available in the neonatal field because of difficulties in providing sufficiently sensitive trigger systems, especially for end-expiratory flow termination during PSV. This latter may be enhanced through the availability of neurally adjusted ventilatory assist (NAVA), which appears to lessen asynchrony.[119] All modes, with the exception of HFV, are also used during noninvasive ventilatory support, either by nasal or nasopharyngeal prongs or cannula, nasal or nasofacial masks, or the helmet.

Continuous Positive Airway Pressure in Neonates

In infants, CPAP is commonly applied via the nasal route with a short binasal cannula (nasal prongs), a single

nasopharyngeal cannula, or a soft nasal mask. Short binasal prongs seem to be more effective than a single prong.[120] The feasibility of using a helmet as CPAP interface was documented recently.[121] To apply CPAP, various methods, such as electronic feedback control, underwater seal, flow opposition, and flow opposition with fluidic flow reversal on expiration have been used. Each method imposes a different resistive load and there is ongoing discussion whether one is better than another[122–125] in reducing work of breathing. For practical reasons, it is simpler to divide the commercially available devices into two types: continuous and variable flow systems.

Continuous flow systems adjust the CPAP level by either modulation of the resistance created by an valve in the expiratory circuit (the case for some ventilators with inbuilt CPAP modes) or by placing the expiratory tubing under water, the depth of the tubing allowing for blow-off at a certain CPAP level (the case for bubble CPAP systems). These systems require relatively high constant flow rates (often above 8 L/min) to ensure that flow during inspiration at least matches a patient's peak inspiratory flow. Simple high-flow systems can also be used for CPAP;[51] their efficiency remains doubtful, and pressure variations are poorly controlled.[126]

Variable flow systems maintain a set CPAP level by rapid adjustments in the flow rate. Flow modulation can result from either fast modulation of inspiratory flow or, with a special nosepiece, by entrainment of gas at the inspiratory jets (Infant Flow system) or with a jet device at the nasal prongs (Benenviste system).[127] With the latter systems, CPAP is changed by increasing or decreasing flow. The pressure generated should be measured with an accurate manometer and linked to an alarm.

No clear evidence favors any particular nasal interface[120] or flow pattern.[128] A recent randomized controlled trial that compared various CPAP systems (bubble vs. infant flow) suggested certain advantages with a bubble CPAP system in terms of secondary outcome measures, such as a higher rate of successful extubation or shorter duration of CPAP in infants recovering from RDS.[129] A crossover study in premature infants showed better oxygenation with bubble CPAP when compared to ventilator-derived CPAP.[125] Such observations are intriguing and question the belief that modern expensive CPAP devices perform better than older, simple, and relatively cheap devices.

Nasal CPAP is now used as first-line support in the neonatal field, mainly for premature infants presenting with various forms of respiratory distress (classically, infant RDS). Many unanswered questions remain,[130] such as optimal pressure or flow to be used,[131] whether early CPAP for RDS reduces mortality and morbidity (chronic lung disease remaining a significant problem in neonatal intensive care) as compared with intubation and mechanical ventilation (a large trial failed to give a definitive answer[49]), and the lack of clear criteria to indicate when an infant is unresponsive to nasal CPAP.[132]

Conventional Mechanical Ventilation in Neonates and Infants

TIME-CYCLED, PRESSURE-LIMITED VENTILATION

Pressure-control techniques have been used in neonates for many years. Such neonatal *pressure controllers* deliver a continuous, constant flow during inspiration and expiration, and the inspiratory and expiratory pressure levels cycle at regular intervals (time-cycled, pressure-limited [TCPL] ventilation). In that inspiratory flow characteristics of TCPL ventilation differ from classic PCV, which modulates inspiratory flow in a decelerating pattern (Fig. 23-3), a classic neonatal ventilator that offers TCPL ventilation is nothing more than a simple and easy-to-operate *flow driver.* To achieve an inspiratory plateau pressure, relatively high flow rates are required (6 to 10 L/min), especially when short T_I values (0.3 to 0.4 second) are used to keep mean airway pressures low.

On several occasions, pressure-limited ventilators have failed to provide adequate alveolar ventilation in newborn babies; this can be a problem when T_I is too short or with insufficient inspiratory flows. A second and perhaps more important problem with TCPL ventilation is that delivered V_T varies from breath to breath, coupled with the fact that many flow drivers still do not offer measurements or display of delivered V_T. The same problems, however, hold true for any pressure-control mode.

A third problem with TCPL ventilation is the slow buildup of pressure and cycle to pause as the pressure target is achieved. There is argument as to whether this leads to slow intratidal recruitment of the airways during the insufflation phase, the quantity of which depends on the pressure delivered. This may create less shear force in the airways than does classic PCV with a decelerating flow pattern. Conversely, a potential disadvantage of TCPL ventilation is that as soon as the inspiratory pause time commences, unstable airways are prone to collapse as gas is redistributed to areas with longer time constants. Consequently, a situation arises whereby collapse is already commencing during the inspiratory phase. Conversely, if a fast regulation system is used (variable flow delivery in a pressure-controlled mode) that promptly delivers flow, tightly regulated by pressure, previously collapsed airways will continue to expand; others with a longer time constant experience a chance of opening throughout inspiration. This implies that there is no pause during the inspiratory period and that the regulation system is active even during the "no-flow" phase. Flow during this "no-flow" phase is seen only on high resolution but adds to the efficacy of recruitment by providing extra time for lung inflation; this behavior is best explained by the power law of avalanches.[133]

PRESSURE-CONTROLLED VENTILATION

Classic PCV has been introduced in neonatal ventilation only recently. It differs from TCPL ventilation in that inspiratory

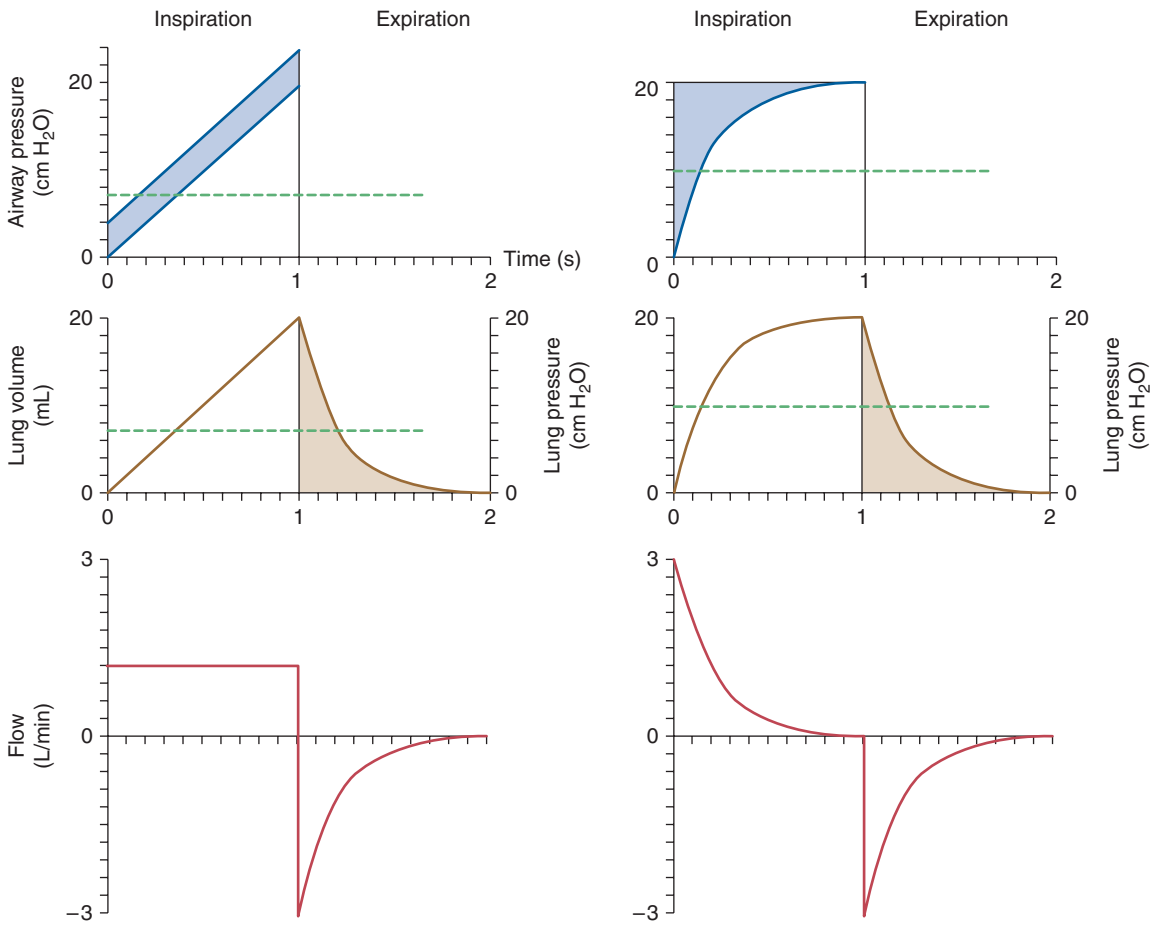

FIGURE 23-3 Graphic representation of the equation of motion for a constant inspiratory flow pattern (*left*) and a constant inspiratory pressure pattern (*right*). The *dotted lines* indicate mean airway and lung pressures. The *shaded sections* represent equal geometric areas proportional to the pressure required to overcome flow resistance. The *unshaded sections* represent equal geometric areas proportional to the pressure required to overcome elastic recoil. Note that for the same tidal volume and mean inspiratory flow rate (i.e., tidal volume-to-inspiratory time, V_T/T_I), the constant flow pattern produces a higher peak airway pressure and lower mean airway pressure but the same peak lung pressure. (Reprinted, with permission, from Chatburn RL. Principles and practice of neonatal and pediatric mechanical ventilation. *Respir Care*. 1991;36:569–595.)

flow is variable (decelerating flow pattern). Peak inspiratory pressure can be reached early during inspiration. This leads to fast increases in circuit and airway pressures, which may help to overcome high airway resistance. For years, this was considered harmful, but no evidence supports this concern.

VOLUME-CONTROLLED VENTILATION

VCV in neonatology was abandoned in the early 1980s mainly because of difficulties in measuring very small V_T values under low-flow conditions. A second concern was the slow rise to peak pressures (with constant inspiratory flow), eventually causing unequal lung-volume distribution within the lung. A third concern was the frequent occurrence of an ETT leak (not using cuffed tubes), which can alter effective delivery of volume substantially. All these concerns are mere assumptions and not supported by clear scientific evidence. Because of technological advances and discussion of small V_T values for lung protection, there is growing interest in this mode again. A single-center, randomized, controlled trial has compared pressure-limited ventilation versus VCV, with identical V_T values in both arms, in newborns presenting with RDS.[134] There was a small benefit, in terms of ventilator duration and significantly less intraventricular hemorrhages and abnormal periventricular echo densities on ultrasound scans, in favor of VCV. The lower rate of cerebral complications with VCV may reflect better P_{CO_2} stability.

VOLUME-TARGETED VENTILATION

Recognition that volume rather than pressure causes ventilator-induced lung injury has led to the development of various techniques that combine features of pressure-limited and volume-limited ventilation in a mode, usually referred to as *volume-targeted ventilation* (VTV; i.e., volume guarantee, pressure-regulated volume control, or volume-assured pressure support). With this, delivery of a set V_T is "guaranteed" by adjusting inspiratory pressure according to changes

in compliance, resistance, or respiratory drive. This usually requires a learning period over a number of breaths, during which dynamic compliance and respiratory system resistance are assessed by the ventilator. Small studies show only small breath-to-breath variability in V_T,[57,135] although there is concern about overshooting volume delivery over several breaths (learning period effect) if compliance or resistance change rapidly.[39] Along the same lines, inbuilt algorithms may cause an increase in airway pressure resulting in larger than targeted V_T over the next few breaths if a spontaneously breathing infant's efforts have interrupted his or her expiration by diaphragmatic braking.[136] Therefore, the safety of these devices may need to be reconsidered.

Recent meta-analytic data suggests that the use of VTV in premature infants with RDS might improve pulmonary and neurodevelopmental outcome.[37] Cross-sectional surveys document a rapid increase in the routine use of VTV,[31,137,138] but with a considerable variation in VTV practice. However, despite the fact that some have provided practical advice on use of VTV in premature infants,[138] we are still far away from establishing best VTV practice.

PATIENT-TRIGGERED VENTILATION

Synchronized Intermittent Mandatory Ventilation. Asynchrony may cause poor gas exchange and air trapping, leading to pneumothorax, hemodynamic instability, changes in cerebral blood flow, and intracranial hemorrhage in newborns.[139] Synchronization of spontaneous inspiration with the ventilator has been attempted, initially with SIMV, which conducts a search for a spontaneous effort within a predefined time frame (Fig. 23-4). Although SIMV was thought to be superior to IMV, no evidence supports this suspicion.[140]

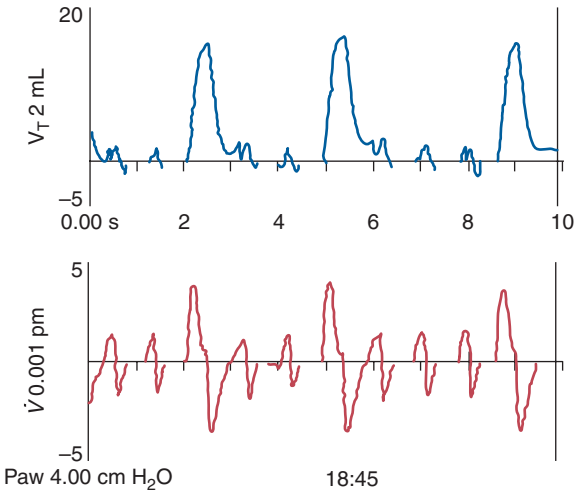

FIGURE 23-4 Volume (*above*) and flow (*below*) waveforms in a patient receiving synchronized intermittent mandatory ventilation (SIMV). The SIMV breaths occur at somewhat irregular intervals because of the timing windows, during which the machine waits to detect spontaneous effort by the patient. *Paw,* airway pressure; *V,* flow; V_T, tidal volume. (Reprinted, with permission, from Donn S. Invasive and noninvasive neonatal mechanical ventilation. *Respir Care*. 2003;48:426–439.)

Assist-Control, Intermittent Mandatory, and Pressure-Controlled Ventilation. Assist-control ventilation, IMV, and PCV were developed to assist all spontaneous breaths that exceed a trigger threshold; in the case of apnea or bradypnea, a mechanical breath is provided by the machine according the rate set. The inspiratory time is set by the operator. Asynchrony occurs when the machine's T_I exceeds the infant's T_I.

Pressure-Support Ventilation. It is possible to terminate a machine breath based on a decline in inspiratory flow to below a certain percentage of peak inspiratory flow, as with PSV. Algorithms such as this help to synchronize patient effort with ventilator assistance.[141] PSV increases inspiratory pressure to a preset level and is intended to decrease the work of breathing. Flow delivery is variable and proportional to patient effort. Initially, PSV was viewed mainly as a weaning mode, but subsequently, it was used more widely in the adult field.[142] Since the development of sensitive flow triggers and variable inspiratory flow termination, PSV can be used in neonates.[143]

SIMV, assist-control ventilation, IMV, pressure-control ventilation, and PSV can be grouped under the generic term of *patient-triggered ventilation.* In neonates, and especially in preterm infants, the trigger needs to sense any weak spontaneous breathing effort. It also must minimize artifacts that may result from other sources: heartbeat-induced variations in intrathoracic pressure or variations in pressure oscillations induced by rainout in the ventilator tubing. Various trigger signals have been used: flow or pressure triggers, abdominal or thoracic impedance methods, and detection of abdominal motion. Flow triggering is more sensitive than pressure triggering for neonatal ventilation.[144] Two major sources of patient–ventilator dyssynchrony are (a) inappropriate long delays in inspiratory triggering (preterm infants with a short T_I may have completed much of the inspiratory phase before ventilator assistance commences) and (b) inappropriately selected inspiratory flow termination ("cycling off" or "flow termination" setting given as a percentage of maximum inspiratory flow; if set too low, inflation times will be too long). With this, the flow at which the ventilator cycles to exhalation does not coincide with the end of patient T_I.

Neurally Adjusted Ventilatory Assist. NAVA offers a new approach to patient-triggered ventilation. This mode provides ventilator support triggered by, and proportional to, the electrical activity of the diaphragm (see Chapter 13). Experience with NAVA in the neonatal field is sparse. In a small series of premature infants, better patient–ventilator synchronization (more appropriate cycling off) was observed as compared to PSV.[145] This was the case even with large air leaks, suggesting that NAVA may improve ventilator synchrony during noninvasive ventilation through nasal prongs or masks. Whether this will decrease the need

for intubation in infants with RDS is unknown. In pediatric patients, synchrony has undergone less evaluation, although neural triggering has been shown to precede pneumatic triggering in more than two-thirds of breaths during NAVA.[119]

Conventional Mechanical Ventilation in Children

In pediatric intensive care units, conventional mechanical ventilation is used in a similar fashion to adult intensive care units. With today's ventilators, which offer various control (pressure or volume control) or assist (mainly PSV) modes, trigger systems (flow or pressure), and cycle criteria (time or flow based), even small children can be satisfactorily assisted. In the pediatric setting, PCV and PSV are most commonly used,[2] although volume control or VTV are sometimes preferred and useful for assuring stable P_{CO_2} values in patients with pulmonary hypertension (reactive pulmonary vasculature) or increased intracranial pressure. Otherwise, there is no proven benefit for these latter modes in children.

High-Frequency Ventilation in Neonates and Infants

HFV is defined by a frequency that greatly exceeds the normal respiratory rate and a V_T that approximates anatomic dead space (see Chapter 19). There are three major types of HFV:

1. *High-frequency positive-pressure ventilation* (rate: 60 to 150 Breaths/min)
2. *High-frequency jet ventilation* (HFJV; rate: 100 to 600 Breaths/min)
3. HFOV (rate: 180 to 1500 oscillations/min or 3 to 25 Hz)

HFOV is the most commonly used method in pediatric and neonatal intensive care units. High-frequency positive-pressure ventilation and HFJV promote gas exchange in a conventional way with V_T greater than dead-space volume. Expiration is passive. In contrast, HFOV uses V_T values that are less than dead space, and expiration is active.

HFJV is used mainly during (adult) laryngeal surgery; few randomized, controlled trials exist in neonates, with conflicting results.[146,147] Concerns have been raised about prolonged HFJV not only in neonates but also in adults regarding airway damage, ranging from focal necrosis to complete airway obstruction with mucus and severe necrotizing tracheobronchitis.[148,149] Increased risk of adverse cerebral outcome has been reported.[150] Studies have not used consistent criteria for assessment, however, and HFJV systems have varied widely.

All these methods are highly effective in eliminating CO_2, but the effect on oxygenation is less uniform. This is one reason that these modes (especially HFOV) have failed to sustain their initial attraction. Within the context of ventilator-induced lung injury and lung-protective strategies, HFV could be viewed as the optimal protective mode. By providing very small VT values, it is possible to ventilate the lung within a safe zone of the pressure–volume curve of the respiratory system.[151] Side effects, such as from respiratory acidosis (permissive hypercapnia), are not associated with HFOV, and spontaneous ventilation can be often maintained, at least in neonates and small children. Thus, use of sedation is decreased, and muscle relaxants are avoided. In larger patients, inspiratory flow demands are higher; thus, spontaneous breathing is not managed as easily, and heavy sedation and/or paralysis may be required.

INDICATIONS AND TIMING FOR HIGH-FREQUENCY OSCILLATION VENTILATION IN NEONATES AND CHILDREN

HFOV is still used mainly as rescue therapy despite clear indicators from experimental and clinical experience that it is most beneficial when initiated before major lung injury has developed[152–155] because no ventilator strategy can repair preexisting lung injury.[156,157]

Classic indications for HFOV in neonatal patients include:

1. *RDS* characterized by surfactant deficiency, high chest wall compliance, and low functional residual capacity. This is the constellation for easy and efficient lung recruitment, at least with early disease.[153,156] Conceptually, the success of HFOV depends on its ability to recruit lung volume, which is not always easy late in disease when substantial ventilator-induced damage is superimposed on preexisting injury. Most randomized controlled trials, comparing HFOV to CMV in infants with RDS, produced controversial outcome data.[28,59,158] This has been partially attributed to flaws in study design and noncompliance with study protocols.[27] A recent small randomized controlled trial (HFOV vs. CMV) in a well-defined patient group (minimizing heterogeneity) and employing comparable ventilator strategies in both arms, showed a benefit[60] in favor of HFOV. This may revitalize the debate on the use of HFOV in neonates with RDS.
2. *CDH,* usually associated with alveolar and pulmonary vascular hypoplasia,[159] resulting in increased risk of ventilator-induced lung injury[160] and presenting with PPHN requiring aggressive P_{CO_2} control. Lung recruitment should be applied with great caution because of the difficulty in estimating the degree of lung hypoplasia.
3. *Air-leak syndrome,* such as pneumothorax or interstitial emphysema. HFOV can achieve early improvement and resolution of air leak in patients with interstitial emphysema, enabling better gas exchange and lower airway pressures than with CMV.[161]
4. *PPHN.* Although iNO is the classic treatment for PPHN, HFOV can enhance delivery of iNO by achieving adequate lung recruitment[162] and enable easier CO_2 control and correction of respiratory acidosis.

The classic indication for HFOV in pediatric patients is *diffuse alveolar disease* (*primary or secondary ARDS*)[152,163]

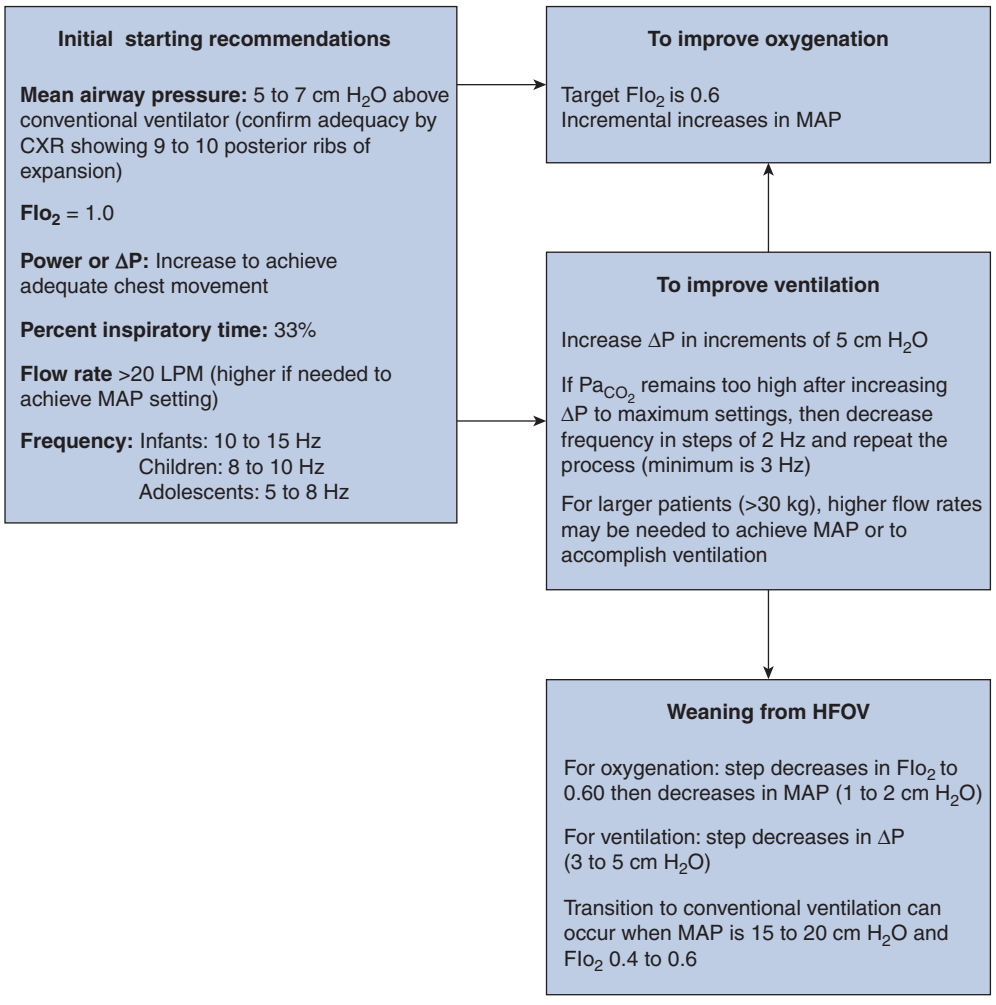

FIGURE 23-5 Recommendations for instituting high-frequency oscillatory ventilation (*HFOV*) and the transition to conventional ventilation during weaning. CXR, chest X-ray; LPM, liters per minute; MAP, mean airway pressure. (Courtesy Martha Curley, Children's Hospital Boston, Harvard Medical School. See also ref. 89.)

as rescue therapy to improve oxygenation. The only pediatric randomized controlled trial[152] did not show any difference in survival or duration of ventilation duration, although duration of supplemental O_2 was shorter with HFOV than with CMV. Recommended strategies for use of HFOV (Fig. 23-5) are empirical and derive mainly from the neonatal field and experience with HFOV in adult patients.[164]

UNIQUE NEONATAL AND PEDIATRIC MACHINES AND INTERFACES

Neonatal and Pediatric Ventilators

Conventional pediatric and/or neonatal ventilators can be divided in three groups: (a) neonatal ventilators, (b) pediatric ventilators (which generally are identical to adult ventilators), and (c) all-age-group ventilators (from neonates to adults). Traditionally, a neonatal ventilator was used for neonates or toddlers up to a body weight of 10 kg. Neonatal ventilators were mainly constant-flow generators that build up pressure and cycle to pause as the pressure target is achieved (TCPL ventilators). This type of ventilators are limited to neonates and infants, because inspiratory flow does not allow a buildup of sufficient airway pressure in bigger patients and such ventilators are not able to adapt to the high inspiratory peak flows of bigger patients with spontaneous breathing activity. Today, some neonatal ventilators, mainly all-age-group ventilators, also offer classic pressure-control and volume-control modes.

The following are the characteristics of a good neonatal ventilator: (a) small apparatus dead space; (b) stiff but flexible circuit tubing; (c) reliable tidal-volume measurement device (hot-wire or pressure-differential flow meter or fixed or variable orifice device) placed between the Y piece

and ETT; (d) highly sensitive trigger device (flow triggering preferred to pressure triggering at least in premature infants,[144] which provides adjustable inspiratory flow triggering and in PSV modes cycles off criteria ranging from 5% to 25% or more of peak inspiratory flow); (e) built-in leak compensation, which can be turned off if there is a large leak around the ETT (this is important with PSV to enable inspiratory flow termination so as to avoid excessive T_I in relation to patient need); and (f) airway humidification with cascade humidifiers and heated-wire ventilator circuitry.[165]

The new-generation all-patient units offer all these neonatal requirements and perform as well as those designed specifically for neonatal and pediatric patients.[166] Detailed specifications on "only neonatal" and "all-patient" ventilators can be found in Tables 23-3 and 23-4 in the second edition of this book.

High-Frequency Ventilators

Important differences in performance characteristics of devices for HFV have been shown repeatedly.[167–170] Thus, it is not possible to compare settings from one device to another. Three major systems are used: HFOV, HFJV, and HFV with a flow-interrupter (HFFI) device.

HIGH-FREQUENCY OSCILLATION VENTILATION

HFOV is characterized by use of mean airway pressure (continuous distending pressure), on top of which square-wave or sinusoidal pressure swings are added by means of a piston, diaphragm, or bidirectional high-velocity flow in the expiratory limb. This leads to a more or less active aspiration during the "expiratory" phase of the oscillatory cycle. The best studied and most widely applied HFOV system is the SensorMedics 3100 high-frequency oscillator (VIASYS Healthcare, Palm Springs, CA). This exists in two versions: the 3100A for neonatal use and the 3100B for pediatric and adult use. The Humming V (Metran Medical Instruments, Saitama, Japan) exhibits similar performance to the SensorMedics 3100A in vitro and bench studies and also can be switched to CMV. Other neonatal ventilators combine conventional and HFOV. There is tendency to use the term HFOV for various forms of HFV, but to qualify as an oscillator, a device has to generate a waveform that has both positive and negative pressure deflection. Each system has a slightly different design (piston or diaphragm, Venturi-valve or jet injector) for creating biphasic pressure waveforms (high frequency oscillations). Therefore, the oscillation power of each machine is slightly different from the other, which explains their various ability to support children only to a certain weight limit.

A new development in many neonatal oscillators (Fabian, Leoni-plus, and VN500) is the ability to servo-control the delivered V_T (measured as exhaled or inhaled tidal volume at the airway opening) by means of HFOV+Volume Targeted Ventilation (volume guarantee) option. This allows the user to preset a V_T during HFOV. Whether this new mode offers any advantage is unknown; using target V_T ventilation during HFOV has no sound background and it goes against the principle of maintaining a mean airway pressure for lung-volume optimization and superimposing the lowest amplitude needed for acceptable CO_2 washout. We still do not know which V_T is appropriate in the various situations, given that V_T during classic HFOV shows large variations (0.5 to 2.5 mL/kg). V_T depends on the oscillation frequency and there is no consensus on the optimal frequency in various settings. Given these unknowns, HFOV with the VTV option should not be used until more data on its safety are available. Making extrapolations based on protective V_T during conventional ventilation to V_T during HFOV is inappropriate because of completely different gas-exchange mechanisms (convection vs. molecular diffusion) between the two modes.

HIGH-FREQUENCY JET VENTILATION

HFJV is characterized by the delivery of small, high-velocity breaths at fast rates coupled with passive exhalation. HFJV allows the application of relatively low airway pressure to maintain reasonable oxygenation. Pulses of gas are delivered at high velocity through an orifice at frequencies of 10 to 100 Hz. The orifice may be in a T-piece connected to a conventional ETT or a narrow tube incorporated in the wall of a special ETT or at end of a fine-bore catheter placed in the trachea. Available HFJVs for pediatric use include the Acutronic Monsoon Deluxe Jet Ventilator (Acutronic Medical Systems, Hirzel, Switzerland), and for pediatric and neonatal use the Life Pulse High Frequency Ventilator (Bunnell, Salt Lake City, UT). In the pediatric field, indications for HFJV are available in the operating room during endolaryngotracheal surgery.[171] In the neonatal field, HFJV has been proposed as rescue treatment for severe pulmonary dysfunction in infants with RDS, CDH, and meconium aspiration syndrome.[147,172–174] Although promising results have been reported with HFJV as early or late rescue[172] treatment in infant RDS, benefit in terms of pulmonary or neurodevelopmental outcome has not been documented.[175]

HIGH-FREQUENCY FLOW-INTERRUPTER

For HFFI (basically a CMV mode) gas flow from a high-pressure source is interrupted at a high rate. Expiration is passive, but additional negative pressure generated by a Venturi effect on the expiratory side may enhance lung emptying. The Infrasonics Infant Star 950 (Nellcor Puritan-Bennett, Inc., Pleasanton, PA) is an example. HFFI devices are available only for neonatal ventilation, and little data exist on their clinical use.[176,177]

Interfaces

Much progress has been made in improving interfaces. For the invasive airway management, improvements in ETT design have changed the traditional teaching to avoid use of cuffed ETTs in infants and children younger than 8 years of age because of increased risk of subglottic injury. This dogma had inhibited research on this topic despite major technological advances with the development of low-pressure, high-volume cuffs and new material. Recent studies show that cuffed tubes can be safely used in children of all ages, provided the correct size is used and cuff pressure is continuously monitored, without an increase in postextubation stridor.[178,179] Advantages include a lower reintubation rate, and control of leakage causing less autotriggering and more stable ventilation. Pediatric advanced life support recommendations have also changed and now suggest the use of cuffed tubes of appropriate size for emergency tracheal intubations in children.[180]

For noninvasive ventilation, the fit and comfort of an interface together with patient–ventilator synchrony are the most important factors for success. There have been significant improvements in mask designs and in plastic materials used for mask seal interfaces (air-cushion seal, gel interfaces). The availability of bilevel-pressure masks for pediatric patients, however, is still very limited, and one has often to rely on petite versions of adult masks.[181] Aside from the known complications related to nasal mask ventilation (skin irritation or breakdown, headache, eye irritation, gastric distension, leakage), certain problems and complications are unique or more pronounced in children. Leakage can simulate patient effort, causing some bilevel generators to autotrigger when set in spontaneous or timed mode. In these circumstances, the ventilator can be set in a timed or control mode at a rate that overrides the patient's respiratory drive during sleep. The pressure on facial structures from a nasal mask is associated with flattening of facial structures, especially the midface, leading to malocclusion with retrusion of the maxillary ridge.[182,183] The choice of the interface also influences the type of ventilator used. Nonvented masks are designed for use with more sophisticated intensive care unit-type ventilators (requiring an active exhaust valve), whereas vented masks are used for the more traditional flow-cycled bilevel-pressure home ventilator (not requiring an active exhaust valve).

MONITORING OF MECHANICAL VENTILATION: SPECIFIC PEDIATRIC AND NEONATAL CONSIDERATIONS

Several specific pediatric and neonatal issues about respiratory monitoring must be noted. First, ventilator-circuit dead space should be kept as small as possible when monitoring devices are added. Second, flow measurements must be made as close as possible to the airway opening to get true delivered V_T.[184,185] Third, with standard practice of using uncuffed ETTs air leakages around the ETT are observed in approximately 70% of all ventilated neonatal infants, rendering tidal volume monitoring less reliable.[186] Fourth, little is known about the reliability of end-tidal CO_2 measurements in the presence of ETT leakage (>30%).[187] Fifth, accurate measurements of exhaled CO_2 in pediatric and especially neonatal patients is challenging because of limitations in size of the analyzer chamber (to reduce instrumental dead space), the amount of flow that must be suctioned by side-stream devices, and the need for fast response times because of rapid respiratory rates. Therefore, small dead-space volume mainstream sensors, which have a faster response time (than side-stream devices) and do not need suction flow, are preferred.[188] Recently, a microstream capnograph (suction flow of only 30 mL/min) with a miniaturized sample chamber was developed, thus, improving the measurement accuracy of end-tidal CO_2 in intubated infants.[189,190] Volumetric capnography, measuring CO_2 elimination per breath (V_{CO2}), may assist with optimal PEEP titration: atelectatic or overdistended areas reduce alveolar ventilation and therefore CO_2 elimination.[191,192] The concept is used by companies that offer inbuilt volumetric capnography (e.g., "the open lung tool" on the Servo-I ventilator by Maquet, Solna, Sweden). V_{CO2} monitoring has also been proposed for guiding weaning but the concept has been questioned.[193]

COMPLICATIONS OF MECHANICAL VENTILATION

In addition to barotrauma (e.g., pneumothorax and interstitial emphysema), three other complications include postextubation stridor, development of chronic lung disease or BPD (classic in the preterm infant), and ventilator-associated pneumonia.

Postextubation Stridor

Acquired subglottic stenosis became a well-recognized problem with use of long-term endotracheal intubation. Serious tube trauma and postextubation stridor have decreased markedly with improvements in material and tube design and greater care in choosing appropriately sized tubes. Tube complications usually arise from incorrect size, traumatic or multiple intubations, up-and-down movements of the tube, and inadequate analgesia and sedation, causing intubated infants to struggle. Poor design can result in a cuff being positioned too high within the larynx (Fig. 23-6), causing severe trauma.[194] These observations have led to new design for ETTs.[195,196] With newly designed cuffed-ETTs (cuff pressure held ≤20 cm H_2O), side effects, such as an increased rate of postextubation stridor, were not observed in large observational studies[178,197–199] and in one randomized controlled trial.[179] Specifically designed cuffed ETTs, such as the Microcuff PET tubes, have proven safe in neonates of birthweight greater than 3 kg and in children,[200] and no real arguments remain against their use.[201] Other risk factors of postextubation stridor include duration of intubation,

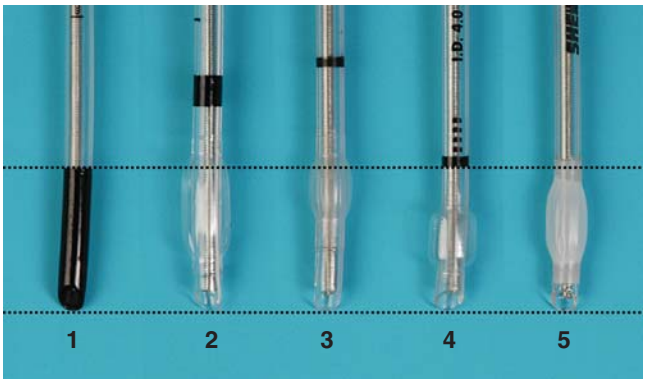

FIGURE 23-6 Positioning of the cuff on various endotracheal tubes: (*1*) uncuffed tracheal tube, inside diameter 4.5 mm; (*2*) Rueschelit Super Safety Clear, inside diameter 4 mm; (*3*) Mallinkrodt Hi-Contour P, inside diameter 4 mm; (*4*) Microcuff PET, inside diameter 4 mm; and (*5*) Sheridan CF, inside diameter 4 mm. Note that only tube 4 has a cuff of appropriate size and positioning. (Courtesy Markus Weiss, Pediatric Anesthesia, Children's Hospital of Zurich, Switzerland.)

gastroesophageal reflux, and tracheobronchial infection. Checking for a cuff leak is of little help in predicting postextubation problems in young children.[104]

Most injuries causing postextubation stridor are superficial and include nonspecific changes such as laryngeal edema, granulation tissue, and ulcerations. Stridor usually resolves with medical therapy. Inhaled epinephrine is successful in treating subglottic edema. If reintubation is required, a smaller ETT should be used to prevent additional trauma. The nasal route is preferred to optimize tube stabilization and to minimize the tube shifting with head movement. The child should be weaned rapidly from the ventilator to humidified O_2 delivered via a light T tube. These measures prevent infants from pushing out the tube with their tongue and allow for better head movements, thereby minimizing risk of further trauma. Alternatively, the child must be heavily sedated and eventually receive neuromuscular blockade. In most cases of simple subglottic edema, extubation is successful after a rest period of approximately 2 to 3 days with or without a short course of dexamethasone (1 to 2 mg/kg/day in divided doses). It is reasonable to administer dexamethasone to patients at risk of stridor for 24 hours before and 24 hours after extubation. Such prophylactic steroids may reduce postextubation stridor and the rate of reintubation.[202]

Bronchopulmonary Dysplasia in the Preterm Baby

The pathogenesis of BPD is multifactorial.[203,204] The principal risk factors are lung immaturity, barotrauma, volutrauma, O_2 toxicity, prenatal and nosocomial infections, and increased pulmonary blood flow secondary to a patent ductus arteriosus.[205,206]

Changes in neonatal care of very-low-birthweight infants, including antenatal corticosteroids, postnatal surfactant, and modified respiratory support, have improved survival and have changed the clinical picture of BPD. "Old" BPD described above is a consequence of ventilator-induced lung injury, whereas "new BPD" is mainly a developmental disorder in which the immature lung fails to reach its full structural complexity.[204,207] Improved survival of very immature infants has led to more infants with this disorder. Changes in clinical practice have improved the clinical course and outcomes for infants with BPD over the past decade, but the overall incidence has not changed[208] and there are large variations among centers.[153,209–214] This wide range reflects the heterogeneity of study populations, management practices, and disease definitions. The initial description of BPD by Northway et al[52] and Bancalari et al[215] was based on O_2 requirements at 28 days of age. As newborns of lower gestational age survived, Shennan[216] later proposed the term *chronic lung disease.* The diagnosis of BPD is currently based on the need for supplemental oxygen for at least 28 days after birth, and its severity is graded according to the respiratory support required at 36 postmenstrual weeks.[217]

Management of BPD includes minimizing ventilator duration and avoiding high O_2 concentrations. Fluid restriction, diuretics, and bronchodilators are helpful but do not alter disease course. Pulmonary vasodilators are not beneficial for BPD-associated pulmonary hypertension.[218] Dexamethasone can accelerate ventilator weaning and shorten the period of O_2 supplementation but is associated with worse neurologic outcome (increased leukomalacia, impaired brain growth) and more frequent severe gastrointestinal complications.[219,220] Dexamethasone therapy, if given at all, should be brief[221] and early, but initiated only beyond the first week of life.[219] Hydrocortisone has been recommended in place of dexamethasone because the latter may impair neurodevelopment. The efficacy of hydrocortisone, however, is questionable.[222] Inhaled steroids have some efficacy, but only in ventilated patients.[223] Despite several attempts for severity grading and various approaches for treatment and prevention, long-term prognosis remains uncertain.[224,225]

Ventilator-Associated Pneumonia

Ventilator-associated pneumonia (VAP) is the second most common nosocomial infection in the pediatric intensive care unit.[226–228] VAP occurs in approximately 5% of ventilated children, and nearly 20% of affected children die. *Pseudomonas aeruginosa,* enteric gram-negative bacilli, and *Staphylococcus aureus* are isolated most commonly from endotracheal aspirates, particularly with VAP of late onset.[229] Specific risk factors associated with pediatric VAP include the presence of a genetic syndrome, tracheal reintubation, transport out of the pediatric intensive care unit, subglottic or tracheal stenosis, trauma, and tracheostomy.[230] VAP is

associated with increased pediatric intensive care unit length of stay, ventilator days, and mortality rates. Adherence to a VAP-prevention bundle decreases VAP rate in pediatric patients.[231] For diagnostic purposes, protected bronchial brushing (sensitivity 72%, specificity of 88%) offers an alternative to poorly supported bronchoscopic bronchoalveolar lavage.[232]

IMPORTANT UNKNOWNS

Mechanical ventilation has increased survival of acutely ill neonates and children. A better understanding of pathophysiology has led to newer ventilator strategies. Many of these strategies, however, have not been tested in the pediatric setting, but simply adapted from adult experience. Recent research suggests that comparable ventilator settings are more injurious in the adult than in the infant lung.[233] This latter is supported by conflicting results from observational cross-sectional studies investigating the relationship between V_T and outcome.[30,32]

Approaches to optimizing ventilation are based on bedside assessment of respiratory mechanics and blood-gas response. Unfortunately, no characteristic of the pressure–volume curve can predict end-expiratory atelectasis, overstretching, or optimal airway pressure.[234,235] Despite improved understanding of pediatric diseases and mechanical ventilation, we still do not know the best settings for an individual child. To date, evidence is confined to bad ventilator settings.

Noninvasive ventilation has proven safe and feasible in pediatric settings and can help to avoid intubation, although we do not know whether to avoid intubation is a wise decision in some conditions. This latter is true for the pediatric and neonatal field.[49,236,237] Ventilator discontinuation is believed to decrease several complications, but proof is limited.

THE FUTURE

Respiratory monitoring has been used to decrease complications and improve patient–ventilator interactions. We need to develop approaches whereby this knowledge can be used to improve patient outcome. Tools that provide continuous recordings of pulmonary function have yet to be incorporated into ventilator equipment. For example, the continuous monitoring of functional residual capacity might improve ventilator strategies and enhance assessment of lung recruitment. Newer imaging techniques, such as bedside ultrasonography, electrical impedance tomography,[238] or optoelectronic plethysmography,[239] may help to monitor regional ventilation.[240–242] In the end, such techniques will need to prove cost-effectiveness and/or improve outcome. Furthermore, we need a better description of what constitutes "standard" care.

SUMMARY AND CONCLUSION

Mechanical ventilation of infants or small children requires fundamental knowledge of the anatomic and functional characteristics of the respiratory system in a growing child. Clinicians also require good knowledge of specific pediatric pathologies, which sometimes results in a different approach to ventilation than in an adult patient. Nevertheless, adult experience has influenced many strategies applied in pediatric and even neonatal settings because it remains difficult to do well-controlled trials of mechanical ventilation in the pediatric intensive care unit.

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24

MECHANICAL VENTILATION DURING GENERAL ANESTHESIA

Paolo Pelosi
Claudia Brusasco
Marcelo Gama de Abreu

In the early years following the first demonstration of anesthesia with an inhalation device, different inhalation anesthetic agents were developed and tested in spontaneously breathing subjects. However, the increasing complexity of surgical procedures, the discovery and use of neuromuscular blocking as well as intravenous anesthetic agents, and the need to protect the airways resulted in the need for mechanical ventilation during general anesthesia. Accordingly, anesthesia ventilators were developed to match the particular needs of general anesthesia, which differ from those in other settings, such as the intensive care unit (ICU). Moreover, modern anesthesia is not restricted to the intraoperative period and mechanical ventilation may be required preoperatively and postoperatively.

This chapter provides a comprehensive review of aspects related to the principles and practice of mechanical ventilation during general anesthesia, as well as during the perioperative period.

RESPIRATORY EFFECTS OF ANESTHESIA AND SURGERY

General anesthesia has several effects on respiratory function, most notably on control of breathing and the activity of respiratory muscles, which influence the distributions of ventilation and perfusion within the lungs. Moreover, surgery-related positioning of patients, as well as manipulation or displacement of intraabdominal and thoracic organs may further affect ventilation and perfusion, with deterioration in pulmonary gas exchange.

Control of Breathing and General Anesthesia

OBJECTIVES OF THE CONTROL OF BREATHING

The main objective of control of breathing is the maintenance of blood gases, especially of arterial carbon dioxide (Pa_{CO_2}), which is kept within a relatively restricted range. Even a small

increase in Pa_{CO_2} may result in a significant increase in minute ventilation. The output of the respiratory center is less sensitive to reductions in partial pressure of arterial oxygen (Pa_{O_2}), but hypoxia may enhance the response to Pa_{CO_2}.[1] Another objective of the control of breathing is to maintain the brain pH. Because CO_2 is highly diffusible across the blood–brain barrier, this is achieved through modulation of alveolar ventilation, which regulates Pa_{CO_2}. Last but not least, control of breathing aims at optimizing breathing frequencies and maximizing the work output of the respiratory muscles to maintain adequate gas exchange.[2]

CONTROL OF BREATHING

The respiratory rhythm originates from complex neuronal network interactions throughout the nervous system.[3] This network consists of smaller and larger networks that interact in generating different breathing patterns, including the regular breathing (eupnea), but also sighs and gasping. The group of neurons responsible for the control of breathing is dispersed across a region in the brainstem termed the *respiratory centers*. These centers are located bilaterally in the reticular formation of the medulla oblongata and pons, beneath the floor of the fourth ventricle, and are grouped into inspiratory, pneumotaxic, and expiratory areas.[4]

The inspiratory area is located in the dorsal part of the medulla and generates rhythmic cycles that are transmitted to the diaphragm, upon contraction of which alveolar ventilation takes place. Impulses originating in peripheral and central chemoreceptors (e.g., in carotid bodies and in the brainstem, respectively), and lungs are transmitted through the vagus and glossopharyngeal nerves to the inspiratory area, downregulating its activity in a negative-feedback mechanism.[5] Impulses from the pneumotaxic center located in the pons inhibit the inspiratory area continuously, contributing to avoidance of overinflation and modulation of respiratory rate.[6] Normally, exhalation is a passive process resulting from the elastic recoil of the lungs and chest wall, and the expiratory center located in the ventral portion of the medulla is silent. This center, however, may be activated for increased alveolar ventilation, leading to recruitment of thoracic and abdominal muscles and forced expiration. In addition, alveolar ventilation is regulated by the cerebral motor cortex during voluntary control of breathing, and impulses bypass the respiratory centers being transmitted directly through corticospinal to respiratory motoneurons.[7]

EFFECTS OF ANESTHESIA AND ANALGESIA ON THE CONTROL OF BREATHING

Most drugs used to achieve hypnosis, sedation, and relief or suppression of the response to pain affect the control of breathing. Such drugs, which usually result in depression of the alveolar ventilation, have their effects mediated by direct interference with peripheral and central chemoreceptors, changes in behavioral control, suppression of the function of the motoneurons and respiratory muscles, and by general depression of the respiratory center.[8]

Volatile halogenated anesthetic drugs like halothane, isoflurane, enflurane, desflurane, and sevoflurane reduce the response of the respiratory center to hypoxia even at subanesthetic concentrations.[9–13] In addition, volatile anesthetics can potentiate the effects of neuromuscular blocking agents on the respiratory muscles in a dose-dependent and time-dependent fashion.[14] Intravenous anesthetic drugs like midazolam and propofol also blunt the response to hypoxia at subhypnotic concentrations,[15,16] while hypnotic concentrations of barbiturates are necessary for decreasing the ventilatory response to hypoxia.[17] Although anesthetics usually depress the respiratory center activity, subhypnotic concentrations of etomidate stimulate ventilation,[18] while during infusion of ketamine, the response to hypercapnia is fairly well maintained[19] or even increased.[20]

Opioids represent a mainline therapy for analgesia and anesthesia. These drugs, however, can reduce and make the respiratory rate irregular,[21] resulting both in hypercapnia and hypoxemia. Such effects are mediated mainly by opioid receptors expressed in the peripheral chemoreceptors.[22] When infused rapidly as boluses, opioids have the potential to abolish the respiratory center activity completely without producing unconsciousness. Furthermore, opioids can increase the resistance of the upper airway by enhancing the discharge activity in the recurrent laryngeal nerve, and reduce the compliance of the respiratory system through increases in tonic discharges from the expiratory area of the respiratory center.[23]

Even when administered in the intrathecal or epidural space, or intramuscularly, opioids have the potential to induce respiratory depression in approximately 1% of patients.[24] Respiratory depression induced by epidural opioids results either from systemic absorption, when delayed, or from cephalad migration through the cerebrospinal fluid, when it immediately follows the administration of the drug. Factors that magnify respiratory depression following intrathecal and epidural opioids are: (a) use of intravenous anesthetic drugs; (b) coughing, which may contribute to spread of the drug within the cerebrospinal fluid; (c) accumulation through higher and/or repeated doses; (d) use of morphine; (e) advanced age; (f) lack of opioid tolerance; (g) thoracic epidural placement; (h) general anesthesia; and (i) increased thoracic pressure.[24]

Pattern of Contraction of Respiratory Muscles and General Anesthesia

INSPIRATION

Depression of inspiratory muscle activity during anesthesia occurs not in a global but rather in a selective manner. The intravenous administration of the barbiturate thiopentone decreases the mean activity of the genioglossus, sternothyroid and sternohyoid (strap muscles), and scalene muscles in

patients.[25] Furthermore, tonic pattern of activity of the strap and scalene muscles disappears and those muscles become synchronized with inspiration.

Although diaphragmatic activity is fairly well preserved, the intercostal muscles become silent at concentrations between 0.2 and 1.0 of the minimal alveolar concentration.[26,27] As a result, a pattern of breathing originates where diaphragmatic activity expands the lower ribcage and the resulting negative intrathoracic pressure moves the upper ribcage inwards. Such pattern can be even more pronounced if the resistance of the upper airways is increased, for example, when narrow endotracheal tubes are used. In fact, it is conceivable that increased resistance solely determines the limited expansion of the ribcage during inspiration. It has been namely shown that one minimal alveolar concentration isoflurane does not reduce ribcage motion, unless hyperpnea occurs.[28] Accordingly, ribcage motion during inspiration is not depressed by anesthesia with ketamine.[29]

EXPIRATION

In contrast to the inspiratory muscles, the expiratory muscles are usually inactive in awake subjects, becoming active during anesthesia. In patients anesthetized with halothane, Warner et al[26] attributed active expiration to the motion of the internal intercostal muscles. In fact, most anesthetic agents have been implicated with active expiratory muscle activity.

The purpose of active expiration is not well determined, and its contribution in reducing functional residual capacity (FRC) during anesthesia is controversial.[30,31]

Functional Residual Capacity during General Anesthesia

Reductions in FRC of as much as 20% during general anesthesia have been reported in healthy individuals and can be larger in the presence of pulmonary comorbidities and obesity.[32] Such deterioration occurs early after induction of anesthesia and is stable over time.[33] Also, spontaneous breathing or increases in airway pressure cannot easily reverse a reduced FRC, which persists for hours after recovery from anesthesia.[32] Various mechanisms explain the reduction of FRC during anesthesia: (a) changes in the chest wall; (b) changes in the diaphragmatic shape and position; and (c) increase in thoracic blood volume.

CHANGES IN THE CHEST WALL

The loss of inspiratory muscle tone associated with anesthesia results in reduced outward recoil of the chest wall, and of the internal diameters of the ribcage,[32] leading to changes of approximately 200 to 300 mL in lung volume.[34–37] In addition, an increase in the anterior curvature of the border of vertebral bodies consistent with increased spinal curvature has been detected.[37]

CHANGES IN THE DIAPHRAGM SHAPE AND POSITION

Loss of muscle tone during induction of anesthesia may favor a cephalad movement of the diaphragm secondary to pressure of the intraabdominal organs. Although such a mechanism hypothesis has been supported by some authors,[34,38] it has been challenged by others. Using a dynamic spatial reconstructor technique, Warner et al[31] showed that it is not the position, but the shape of the diaphragm, that is altered during anesthesia. They[31] postulated that the most dorsal part of the diaphragm shifts cephalad, while the most ventral part shifts only minimally, or even caudally. Figure 24-1 schematically illustrates the concepts of change in diaphragmatic position and shape.

INCREASE OF THORACIC BLOOD VOLUME

Increases in intrathoracic blood volume resulting from redistribution of blood from the periphery could theoretically further reduce FRC, although this mechanism is controversial.[34,39]

Atelectasis Formation during General Anesthesia

The concept of atelectasis formation during general anesthesia was first proposed by Bendixen et al[40] in 1963 to explain a progressive decrease in oxygenation and compliance. Those authors, however, could not confirm that hypothesis using chest radiographs. In addition, other authors were not able to reproduce those findings, observing a prompt rather than gradual change in respiratory mechanics under anesthesia.[33]

Collapse of lung zones during anesthesia was first confirmed using computed tomography,[41] and it has been estimated that 90% of patients develop atelectasis under general anesthesia.[42] Several mechanisms have been suggested to explain the formation of atelectasis during anesthesia: (a) collapse of small airways; (b) compression of lung structures; (c) absorption of intraalveolar gas content; and (d) impairment of lung surfactant function. These mechanisms are not mutually exclusive and may interact with each other.

COLLAPSE OF SMALL AIRWAYS

A reduction in FRC below the closing capacity during anesthesia can result in collapse of lung units.[43] Two studies documented a decrease of closing capacity and FRC in anesthetized patients,[44,45] but this finding is not indisputable.[46] In the presence of increased smooth muscle tone of the small airways, collapse can occur even at FRC values above the closing capacity, for instance in patients with chronic obstructive pulmonary disease (COPD) and asthma, or those receiving anesthetic drugs that promote histamine release and cause bronchoconstriction (e.g., thiopental, atracurium, D-tubocurarine).

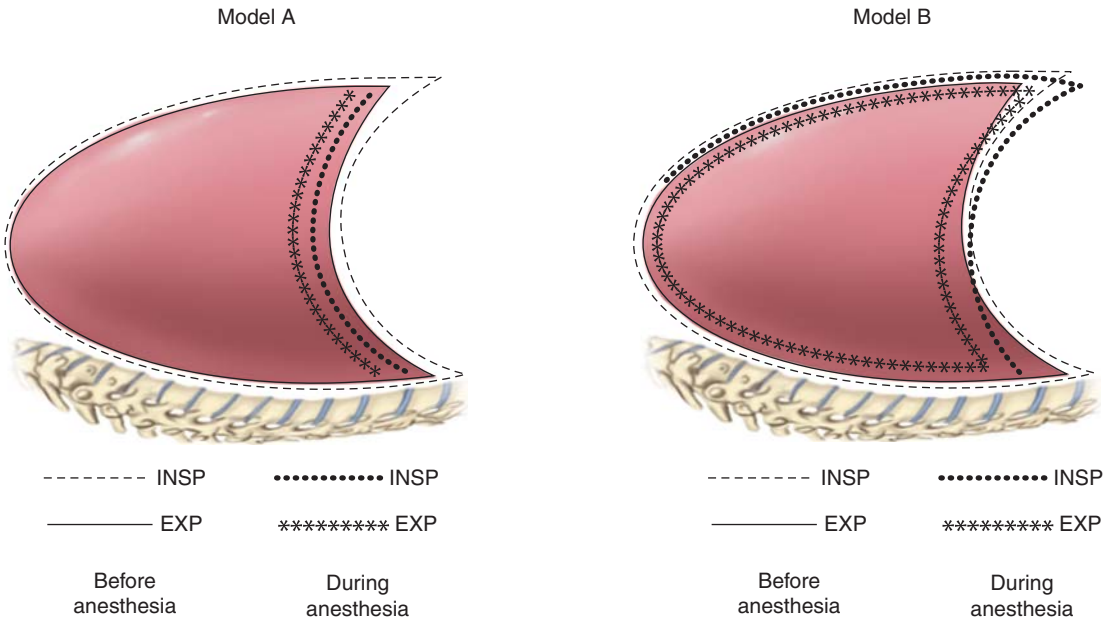

FIGURE 24-1 Models of chest wall and diaphragmatic displacement during general anesthesia. In model **A**, a cephalad shift of the diaphragm is postulated;[34] in model **B**, the displacement of the ventral part of the diaphragm is caudal, while the dorsal part shifts cranially.[31] Both models are associated with a decrease in functional residual capacity (FRC). *Exp*, expiration; *Insp*, inspiration.

COMPRESSION OF LUNG STRUCTURES

In the supine position, there is a ventral–dorsal gradient in the transpulmonary pressure.[47,48] This gradient is determined by the shape of the chest wall and lungs, as well as by lung height multiplied by the tissue density, which may promote atelectasis. Similarly, because the lung area under the heart is greater in the supine than in the prone position,[49] the weight of the heart could theoretically favor atelectasis during general anesthesia. Furthermore, the pressure of intraabdominal organs can be transmitted in part to the lung structures in the absence or reduction of diaphragmatic muscle tone.[50] In addition, increases in intrathoracic blood volume resulting from redistribution of blood from the periphery could theoretically further reduce FRC but this mechanism is controversial.[34,39]

ABSORPTION OF INTRAALVEOLAR GAS CONTENT

In the presence of an increased ventilation-to-perfusion ratio, high alveolar oxygen concentrations can lead to a progressive loss of alveolar total gas volume. A computed tomography study showed that 16% to 20% of lung tissue develops collapse or is poorly aerated in patients under general anesthesia.[51] Absorption atelectasis is most relevant when small airway closure occurs, as for instance following reduction of the FRC beyond the closing capacity. The pulmonary circulation then takes up the trapped gas enriched with oxygen, resulting in atelectasis. This mechanism is supported by the fact that lower oxygen fractions at induction of anesthesia limit the development of intrapulmonary shunt.[52] Mathematical modeling of gas exchange suggests that absorption atelectasis achieves a maximum as fast as 9 minutes if preoxygenation with 100% oxygen is performed over 3 minutes.[53]

IMPAIRMENT OF LUNG SURFACTANT FUNCTION

An early study implicated the volatile anesthetic agents halothane and chloroform in the reduction of lung volume of excised lung dogs. In rabbit lungs, the combination of halothane with higher inspiratory oxygen concentrations increased the permeability of the alveolar–arterial barrier, possibly because of additional effects on the lung surfactant. Also in patients without pulmonary disease, the inhalation of volatile anesthetics reduced the surface tension of tracheobronchial secretions.[54] Furthermore, inactivation of lung surfactant may occur as a result of large changes in alveolar surface area, which are associated with surfactant aggregate conversion.[55]

General Anesthesia and Distribution of Ventilation and Perfusion

Chapter 37 discusses the effects of mechanical ventilation on the distribution of alveolar ventilation ($\dot{V}_A$) and perfusion ($\dot{Q}$) in detail. Basically, mechanical ventilation is associated with $\dot{V}_A/\dot{Q}$ mismatching and increased intrapulmonary shunt, while diffusion limitation to O_2 plays a marginal role. General anesthesia and surgery have the potential to aggravate the deterioration of gas exchange by further impairment of $\dot{V}_A$ and diversion of perfusion from better ventilated lung zones.

Induction of anesthesia with certain barbiturates (thiopental and thiamylal[56]), opioids (morphine[57]), and neuromuscular blocking agents (atracurium and D-tubocurarine[58]) induces histamine release by mast cells, possibly resulting in bronchoconstriction. Also, endotracheal intubation can elicit an increase of the smooth muscle tone of smaller peripheral airways.[59] In contrast, volatile anesthetics, including halothane, isoflurane, sevoflurane, and desflurane, exert bronchodilatory effects.[60]

Patient positioning and the surgical procedure itself may affect the distributions of $\dot{V}_A$ and $\dot{Q}$. During anesthesia in the supine position, a cephalad displacement of the diaphragm with reduction in FRC and impairment of $\dot{V}_A$ in juxtadiaphragmatic zones is commonly observed.[61] Some authors, however, suggest that only the dorsal part of the diaphragm is shifted cranially, while the ventral part is displaced caudally.[31] Such a displacement pattern has been attributed to anesthesia-induced changes in other chest wall structures, like the ribcage, where the diaphragm attaches. On the other hand, surgical procedures requiring the use of the Trendelenburg position and capnoperitoneum, which have more pronounced effects on the respiratory function than the supine position and open abdominal surgery,[62] may lead to a displacement of the whole diaphragm. Interestingly, however, increased pressure in the lung base during the combination of the Trendelenburg position and laparoscopy also shifts $\dot{Q}$ to lung apical zones, resulting in a preserved $\dot{V}_A/\dot{Q}$ matching, despite deterioration in respiratory mechanics.[63] During upper abdominal surgery, the use of retractors also importantly impair lung compliance[64] and their effects on $\dot{V}_A$and $\dot{Q}$ are probably the same as those of laparoscopic surgery.

ONE-LUNG ANESTHESIA AND DISTRIBUTION OF VENTILATION AND PERFUSION

One-lung anesthesia has singular effects on $\dot{V}_A$, $\dot{Q}$, and $\dot{V}_A/\dot{Q}$ matching. Secondary to the collapse of the operated lung, $\dot{V}_A$ is limited to a single lung during such procedures. Gravity, however, slightly favors a shift of $\dot{Q}$ toward the dependent lung,[65] resulting in a better-preserved gas exchange during one-lung anesthesia in the semilateral and lateral decubitus than in the supine position.[66] Furthermore, hypoxic pulmonary vasoconstriction contributes to further redistribute the blood flow toward the ventilated lung. Theoretically, anesthesia has the potential to interfere with hypoxic pulmonary vasoconstriction. In dogs, volatile anesthetics cause pulmonary capillary dilation that may blunt the redistribution of blood flow and worsen oxygenation.[67] The use of volatile anesthetics in patients, however, especially at the minimal alveolar concentration, has not been associated with worsening of oxygenation when compared to intravenous anesthetics.[68–70] On the other hand, the use of epidural anesthesia in combination with intravenous anesthetics seems to result in better oxygenation by mechanisms not related to hypoxic pulmonary vasoconstriction, for instance, reduction of cardiac output.[71]

Assistance of the Respiratory Pump during General Anesthesia

General anesthesia does not necessarily require controlled mechanical ventilation. In fact, for more than a century after its description in 1846, volatile anesthetics have been administered to spontaneously breathing patients.[72] General anesthesia, however, may be associated with a reduction in FRC, tidal volume, changes in breathing pattern, and alterations in the mechanical properties of the respiratory system, resulting in impairment of oxygenation secondary to $\dot{V}_A/\dot{Q}$ mismatching. Furthermore, the need to protect the airways from aspiration by means of endotracheal intubation and the use of neuromuscular blocking agents to facilitate surgery and endotracheal intubation itself led to the regular use of controlled mechanical ventilation to maintain an adequate gas exchange. Nevertheless, certain surgical procedures can be performed without neuromuscular blocking agents, and endotracheal intubation is not always necessary. In this context, facemasks, laryngeal masks, and other supraglottic devices have largely replaced endotracheal tubes. Accordingly, the interest of anesthesiologists in maintaining spontaneous breathing activity during general anesthesia has been increasing.

In view of these facts, anesthesiologists must be able to partially and fully assist the respiratory pump. For this purpose, several assisted spontaneous breathing and controlled mechanical ventilation modes that are present on ICU ventilators are required. Anesthesia ventilators, however, must be able also to deliver inhalation anesthetics in an environmental and economically friendly way, which is not feasible with semiopen systems. Table 24-1 lists the ventilator modes commonly used during anesthesia in the operating room. Obviously, not all anesthesia ventilators offer all of those modes and some of them are not available on anesthesia machines, as they are currently not appropriate for use in combination with volatile anesthetics—for example, modes based on high-frequency ventilation. However, developing technologies may overcome this limitation in the near future.

Ventilator-Associated Lung Injury during Anesthesia

The main goals of mechanical ventilation during general anesthesia are to oxygenate arterial blood and secure adequate CO_2 elimination.[77] To achieve those aims, tidal volumes as high as 12 to 15 mL/kg of predicted body weight for two-lung ventilation, and 8 to 10 mL/kg for one-lung ventilation have been advocated and represent common practice. It was recognized early that the use of high tidal volumes helped in avoiding intraoperative lung atelectasis[40] and decreased FRC. Accordingly, the use of positive end-expiratory pressure (PEEP) has been primarily linked to its potential for increasing FRC and avoiding airway closure, even though PEEP does not necessarily improve oxygenation during general anesthesia.[78,79] Because of the potential

TABLE 24-1: VENTILATOR MODES USED FOR ASSISTING THE RESPIRATORY PUMP DURING GENERAL ANESTHESIA

Mode	Comment	Possible Indications in Anesthesia
CPAP (continuous positive airway pressure)	Increases mean airway pressure and allows spontaneous breathing	Induction of anesthesia to avoid major decrease of FRC; decrease inspiratory effort in the presence of an endotracheal tube; increase tidal volume during decreased inspiratory drive; before extubation to avoid loss of the FRC
PSV (pressure-support ventilation)	Increases the pressure at the airway above the expiratory pressure in response to an inspiratory effort; can be triggered either by flow or pressure	Maintenance of adequate ventilation in presence of reduced inspiratory drive, restrictive lung disease, partial neuromuscular blockade or neuromuscular disease; increased inspiratory effort in presence of a narrow airway device; reduction of atelectasis, improved gas exchange, decreased level of sedation;[73] weaning from controlled ventilation
V- or PACV (volume or pressure assist-control ventilation)	Guarantees that the desired tidal volume or driving pressure is delivered upon an inspiratory effort	Allow patients with respiratory drive to control the respiratory rate and/or tidal volume
SIMV (synchronized intermittent mandatory ventilation; also SIMV-VC and SIMV-PC)	With SIMV, if an inspiratory effort is sensed either by pressure or flow during a sensitive time window, the ventilator applies a preset tidal volume (VC) or pressure (PC); a minimum mandatory ventilation can be set, which will guarantee acceptable gas exchange. SIMV has greater acceptance in the operating room than in the ICU	Maintenance of adequate ventilation in presence of inspiratory effort; emergence from anesthesia
VCV (volume-controlled ventilation)	VCV is time-cycled and volume-targeted; PCV is time-cycled and pressure-limited; corresponds to the default mode on most anesthesia ventilators	Tight control of tidal volume in the absence of inspiratory effort, allows better control of partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$)
PCV (pressure-controlled ventilation)	PCV is time cycled and pressure-limited	Tight control of inspiratory peak pressure; possibly of value in combination with supraglottic airway devices to avoid gastric insufflation[74] and upper airway surgery to avoid anastomose insufficiency. Also useful with uncuffed endotracheal tubes to compensate for leaks
VCV+AutoFlow	Used in the volume-controlled ventilation mode, autoflow automatically adjusts the inspiratory flow to achieve the desired tidal volume with lowest possible inspiratory pressure, resulting in an inspiratory decelerating flow pattern. It is also known as pressure-regulated volume-controlled ventilation (PRVCV) and is similar to pressure control with volume guarantee (PC-VG)	In combination with a supraglottic airway or surgery of the upper airways to reduce peak pressures and avoid gastric insufflation and airway anastomose insufficiency
APRV (airway pressure release ventilation)	Time-cycled ventilation with a higher continuous airway pressure that is maintained for longer periods of time (usually >2 s) and periodically released until positive end-expiratory pressure (PEEP) for short periods of time (usually <1 s, typically 0.5 s), resulting in an inverse inspiratory-to-expiratory timing (I:E) ratio. Free (nonassisted) spontaneous breathing activity is possible at any time at the higher airway pressure	Mainly for patients with acute lung injury and/or acute respiratory distress syndrome to increase mean airway pressure and functional residual capacity; may be helpful to limit the pressure in the airways at comparatively higher levels, while allowing spontaneous breathing (e.g., in combination with supraglottic airway devices) and promoting CO_2 washout
BIPAP (biphasic [intermittent] airway pressure ventilation)	Works similarly to APRV, changing the airway pressure between two levels but allowing more time for expiration than inspiration. BIPAP can be used with time windows that sense inspiratory and expiratory efforts and in combination with pressure-supported breaths at the lower airway pressure level. Also known as BiPAP (bi-level positive airway pressure). A variant called Bi-Vent also provides pressure support for spontaneous breaths at the higher airway pressure level	Similar indications as for PCV and PSV; smoother transition from controlled to assisted spontaneous breathing; maintenance of adequate ventilation in presence of reduced inspiratory drive, restrictive lung disease, partial neuromuscular blockade, or neuromuscular disease

(*continued*)

TABLE 24-1: VENTILATOR MODES USED FOR ASSISTING THE RESPIRATORY PUMP DURING GENERAL ANESTHESIA (*CONTINUED*)

Mode	Comment	Possible Indications in Anesthesia
HFJV (high-frequency jet ventilation)	Usually with respiratory frequencies of 100 to 150 breaths/min and pressure of 1.5 to 2.5 bars; useful with infraglottic, supraglottic, transtracheal, and transluminal airway devices	Surgery and diagnostic procedures of the upper respiratory tract, ventilation of the dependent lung during one-lung anesthesia, emergency transtracheal ventilation[75]
HFOV (high-frequency oscillatory ventilation)	Usually with respiratory frequencies of 600 to 900 breaths/min and increased mean airway pressure; active instead of passive expiration; requires higher bias gas-flow rates. The resulting tidal volume is relatively low and, in case of CO_2 retention, can be increased by reducing the respiratory frequency	Ventilation of the dependent lung during one-lung anesthesia, CT-guided percutaneous procedures of the kidneys to reduce movement artifacts, thoracic and abdominal neonatal surgery where an increase of mean airway pressure is indicated (e.g., congenital diaphragmatic hernia, esophageal atresia, correction of abdominal wall defects)[76]

harmful effects of PEEP, however, especially on hemodynamics, its use during anesthesia does not represent the standard of care.

There is unequivocal evidence that mechanical ventilation can worsen injury in previously damaged lungs. On one hand, high tidal volumes may promote overdistension of the alveoli (volutrauma). On the other hand, the lack of PEEP can lead to destabilization of lung units at end-expiration, resulting in repeated collapse and opening during tidal ventilation (atelectrauma). The mechanical stress caused by volutrauma and atelectrauma can be translated into the activation of the inflammatory cascade, culminating in the release of proinflammatory mediators by cells, a phenomenon known as mechanotransduction and that represents the basis of the so-called biotrauma. The exact mechanisms by which mechanical stress is sensed and then transduced into inflammation are not fully elucidated, but activation of stretch-sensitive channels, partial cell membrane disruption, and conformational changes in membrane-associated molecules and cytoskeletal structure have been implicated in the gene expression and production of cytokines.[80] Following, and most probably also simultaneously with the proinflammatory response, the remodeling process can be activated, with upregulation of gene expression and synthesis of collagen types I and III fibers by fibroblasts.[81–83] Furthermore, the mediators involved in repair and remodeling can also trigger the expression of metaloproteinases,[84,85] enzymes that promote the degradation of components of macromolecules of the extracellular matrix, namely proteoglycans and glycosaminoglycans, as well as fibrous (collagen and elastin) and structural or adhesive proteins (fibronectin and laminin).[86] In addition, the mechanical stress generated by high tidal volumes also elicits changes in the expression of some proteoglycan components of the extracellular matrix, possibly changing its mechanical properties.[87] In fact, fragmentation of pulmonary glycosaminoglycans has been detected with tidal volumes as low as 8 mL/kg in healthy rats, resulting in decreased lung compliance and edema.[88]

Although mechanical stress per se is able to activate the proinflammatory and remodeling responses in noninjured lungs, tidal volumes as high as 22 mL/kg do not exceed the threshold of stress and/or strain necessary to cause lung weight gain, systemic inflammation, and multiple organ dysfunction in healthy pigs.[89] In line with these findings, nonprotective mechanical ventilation with high tidal volume and zero PEEP did not increase the release of inflammation mediators in surgical patients without lung disease.[90–92] Such reports support the hypothesis that ventilator-associated lung injury occurs only if the lungs are predisposed to injury by a first hit, that is, an inflammatory process already present in the lungs (the two-hit hypothesis). In this context, inappropriate mechanical ventilation would represent the second hit that elicits lung injury. The two-hit hypothesis, however, has been challenged. In patients undergoing one-lung anesthesia, protective mechanical ventilation with low tidal volume and PEEP decreased the proinflammatory systemic response after esophagectomy.[93] Also during two-lung anesthesia, the use of low tidal volume and PEEP attenuated the levels of interleukin (IL)-8 and myeloperoxidase in bronchoalveolar lavage fluid in patients without preexisting lung injury.[94] Furthermore, in patients admitted to the ICU, large tidal volumes represent a major risk factor for the development of acute lung injury (ALI).[95,96] Possibly, cytokines released by surgical trauma and surgery-related conditions, for instance, ischemia or reperfusion of different organs, as well as subclinical lung inflammation, could function as a first hit, and thus explain those discrepancies.

Whether protective mechanical ventilation strategies during anesthesia in patients without lung injury may avoid the onset of ALI, the acute respiratory distress syndrome, or other forms of pulmonary complications remains to be determined.

Postoperative Pulmonary Complications

Approximately 234 million major surgical procedures are performed every year worldwide, with 2.6 million representing high-risk procedures.[97] About half of the patients undergoing high-risk interventions develop complications and 315,000 die during their hospital stay. Postoperative pulmonary complications are as common as cardiac complications following noncardiac surgery[98] and occur in approximately 5% of all patients undergoing surgery and anesthesia.[99] This number, however, increases importantly in the presence of certain risk factors, including older age, low preoperative oxygen saturation, respiratory infection in the last 30 days preceding surgery, anemia (hemoglobin level <10 g/dL), surgery of the upper abdominal or thorax, surgery lasting longer than 2 hours, and emergency procedures.[99]

The incidence of postoperative pulmonary complications also vary according to their definition,[98,100–102] and the following entities and/or findings have been classified as a postoperative pulmonary complication: respiratory failure from pulmonary or cardiac origin; pneumonia and respiratory infection; pleural effusion and atelectasis; pneumothorax; bronchospasm; and need for noninvasive respiratory support or reintubation. Once a postoperative pulmonary complication occurs, the average hospital stay is prolonged and the risk of in-hospital death increases.[99,103]

Different strategies have been proposed to reduce the incidence of postoperative pulmonary complications, including postoperative lung-expansion maneuvers, preoperative intensive inspiratory muscle training, selective rather than routine use of nasogastric tubes, use of short-acting rather than long-acting neuromuscular blockade, and laparoscopic instead of open bariatric surgery.[98,104,105] Despite the compelling rationale for the use of PEEP (combined or not with lung-recruitment maneuvers) to prevent formation of atelectasis in the intraoperative period, an increase of FRC did not improve outcome following surgery in a nonselected population.[106] The outcome might be different if patients with higher risk for postoperative pulmonary complications were selected. For this purpose, different propensity scores are available, as shown in Table 24-2. The major weakness common to all of those prediction models is that events and interventions in the intraoperative period, for example, bleeding and hemodynamic instability, are not taken into account and may impair their accuracy. Accordingly, the impact of the intraoperative ventilation strategy is not taken into account. In view of these facts, such scores require validation in independent trials.

ANESTHESIA VENTILATORS

General anesthesia was first delivered using an open-inhaler system by John Snow as early as 1846. Because anesthesia itself often resulted in depression of the respiratory motor output, ventilation had to be assisted by bag ventilation. Thus, besides vaporizers, anesthetic circuits, and scavenging systems, mechanical ventilators became a fundamental part of the anesthesia machine as a means to automate ventilation. Mechanical ventilators, however, represent nowadays more than simple bag substitutes. Rather, they play a central role in the anesthesia machine and must match different requirements than their counterparts in the ICU, justifying the use of the term *anesthesia ventilator*.

Most commonly, the anesthesia ventilator is used in combination with the so-called circle system, which is depicted in Figure 24-2. That system includes an adjustable airway-pressure limiting valve that can be set by the anesthesiologist to limit airway pressure during bag ventilation, a bag ventilation valve itself with a respective on/off valve, an entrance for a fresh mixture of respiratory and anesthetic gases, a scavenging system, an absorber for CO_2, and the anesthesia ventilator. During the expiratory phase, the anesthesia ventilator is filled with a gas mixture coming from the patient, which is pressed again into the anesthesia circuit during inspiration. In other words, such system permits exhaled air to be rebreathed by the patient, thus reducing the consumption of anesthetic gas agents. In general terms, the anesthesia ventilator is embedded in a semiclosed system in contrast to ICU ventilators, which represent open or semiopen systems.

Chapter 2 presents a comprehensive scheme for classification of mechanical ventilators, which also applies for devices embedded in anesthesia machines. The classification of anesthesia ventilators, however, according to: power source, driving mechanism, cycling mechanism, and design, that is, bellows, piston, or turbine, is useful for the anesthesiologist, because it allows inference of expected performance and safety aspects of the anesthesia machine.

Power Source

Some anesthesia ventilators are powered by compressed gas, but most modern ventilators are operated either by electricity alone or a combination of electricity and compressed gas. When compressed gas is used, the ventilator can function even in the absence of electricity.

Driving Mechanism

Several anesthesia machines have high-pressure and low-pressure circuits, that is, are a double-circuit. In the low-pressure circuit, the mixture consisting of anesthetic and respiratory gases are contained in a bag or bellows. Gas at higher pressure, usually oxygen (sometimes mixed with air), compresses the bellows to move the anesthetic gas mixture into the lungs.

Cycling Mechanism

The cycling mechanism describes how the ventilator initiates inspiration in the control mode. Most contemporary anesthesia ventilators are time cycled and use solid-state electronics for timing. Older devices may be based on pneumatic and fluidic timers.

TABLE 24-2: STUDIES ON PREDICTION OF POSTOPERATIVE PULMONARY COMPLICATIONS

Ref	Type of PPC	Predictors of PPCs	Type and Number of Patients/Setting
Christenson 1996[107]	ARDS (1%)	Hypertension; Diabetes mellitus Smoking Reoperative surgery NYHA functional class 3 or 4 Low left-ventricular ejection fraction (<40%)	Cardiac surgery with cardiopulmonary bypass ($n = 3848$)
Kutlu 2000[108]	ALI (0.8%) ARDS (3.1%) Mortality (3.5%)	Age Sex Diagnosis (cancer vs. not) Extent of lung resection	Pulmonary resection ($n = 1139$)
Tandon 2001[109]	ARDS (14.5%), pleural effusion(15%), prolonged pneumothoraces (4.1%), hydropneumothoraces (1.8%), empyema (2.4%), chylothorax (2.4%), pneumonia (17.8%), pulmonary embolism (1.8%), laryngeal edema (0.5%)	BMI Smoking Perioperative fluid/transfusion administration Use of inotropes Perioperative hypoxemia Perioperative hypotension Duration of surgery One-lung ventilation Postoperative leak	Elective esophagectomy ($n = 168$)
Milot 2001[110]	ARDS (0.4%) Total mortality (5.6%) Mortality in ARDS (15%)	Prior cardiac surgery Shock Perioperative fluid/transfusion administration	Cardiac surgery with CPB ($n = 3278$)
Licker 2003[111]	Total PPC (18.5%): ALI (4.2%), ARDS (1.5%), atelectasis (7.1%), prolonged chest drainage (5.0%), pneumonia (4.2%), bronchopulmonary fistula (1.8%), pleural effusion (2%), thromboembolism (0.5%) Mortality (3.0%)	Age History of chronic alcohol consumption Diabetes mellitus FEV_1 High-risk ASA status Pneumonectomy Extended resections Duration of surgery One-lung ventilation Barotrauma Amount of fluid infused Pa_{O_2}/FI_{O_2} at arrival in ICU	Thoracic surgery for non–small-cell lung carcinoma ($n = 879$)
Fernandez-Perez 2006[112]	Total PPC (18%): acute lung injury(50%), cardiogenic pulmonary edema (17%), pneumonia (23%), bronchopleural fistula (7%), pulmonary thromboembolism (3%)	Larger intraoperative V_T Perioperative fluid administration	Pneumonectomy ($n = 170$)
Alam 2007[113]	Total PPC (5.3%): ALI or ARDS (3.1%), pneumonitis (2.2%)	Perioperative fluid administration FEV_1 % predicted postoperative	Thoracic surgery. lung resection ($n = 1428$)
Johnson 2007[114]	Total PPC (3%): pneumonia (35.%), systemic sepsis (23.%), and cardiac arrest (13.3%)	Higher ASA classification Emergency operation Preoperative sepsis Elevated creatinine	Major general or vascular procedures ($n = 180,359$)

(*continued*)

TABLE 24-2: STUDIES ON PREDICTION OF POSTOPERATIVE PULMONARY COMPLICATIONS (*CONTINUED*)

Ref	Type of PPC	Predictors of PPCs	Type and Number of Patients/Setting
Canet 2010[99]	Total PPC (5%): respiratory infection (1.6%), respiratory failure (2.6%), bronchospasm (1.8%), atelectasis (1.4%), pleural effusion (1.7%), aspiration pneumonitis (0.4%)	Age Male sex Low preoperative SpO_2 Acute respiratory infection during the month before surgery Preoperative anemia Positive cough test Upper abdominal or intrathoracic surgery Duration of procedure Emergency surgery	Surgical procedures (general, neuraxial, or regional anesthesia) ($n = 2464$)
Sen 2010[115]	ARDS (7.5%), pneumothorax (6.2%), prolonged air leak (2.1%), empyema (4.2%) Mortality (2.7%)	History of chronic alcohol consumption ASA score Fresh-frozen plasma Pulmonary resection type	Pulmonary resection ($n = 143$)
Ferguson 2011[116]	PPC (38%)	Age FEV_1 % predicted DL_{CO} % predicted Performance status Serum creatinine Smoking Transthoracic resection	Esophagectomy ($n = 516$)
Kor 2011[117]	ALI (2.6%)	Cardiac surgery Vascular surgery Thoracic surgery Diabetes mellitus COPD Gastroesophageal reflux Alcohol abuse	High-risk surgery ($n = 4366$)

Abbreviations: ALI, acute lung injury; *ARDS*, acute respiratory distress syndrome; *ASA*, American Society of Anesthesiologists; *BMI*, body mass index; *COPD*, chronic obstructive pulmonary disease; *CPB*, cardiopulmonary bypass; DL_{CO}, diffusing lung capacity for carbon monoxide; FEV_1, forced expiratory volume at 1 second; *ICU*, intensive care unit; *NYHA*, New York Heart Association; *PPC*, postoperative pulmonary complication; SpO_2, arterial oxyhemoglobin saturation; V_T, tidal volume.

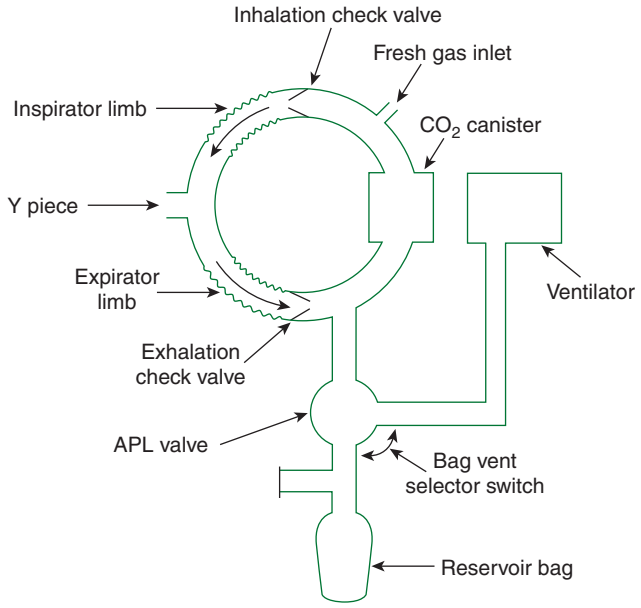

FIGURE 24-2 Schematic of the circle system used in most anesthesia machines. Fresh gas consisting of a mixture of oxygen, nitrogen, and anesthetic gases flows into the circle system between the CO_2 canister, which contains a CO_2 absorber salt, and the inhalation check valve. Gas exhaled by the patient passes an exhalation check valve and refills the anesthesia ventilator and/or reservoir bag. Because the flow rate of fresh gas can be as low as the gas consumption rate, the circle system can recirculate most of the exhaled gas. The anesthesiologist can ventilate the patient manually by bag or using an anesthesia ventilator upon switching of a selector valve. During bag ventilation, the adjustable pressure-limiting (*APL*) valve is set to limit the maximal pressure in the circuit, while, during function of the anesthesia ventilator, the maximal pressure is usually fixed at 70 cm H_2O by an internal pressure-relief valve. (Adapted from Andrews JJ. Inhaled anesthetic delivery systems. In: Miller RD, ed. *Anesthesia.* New York: Churchill Livingstone; 1994.)

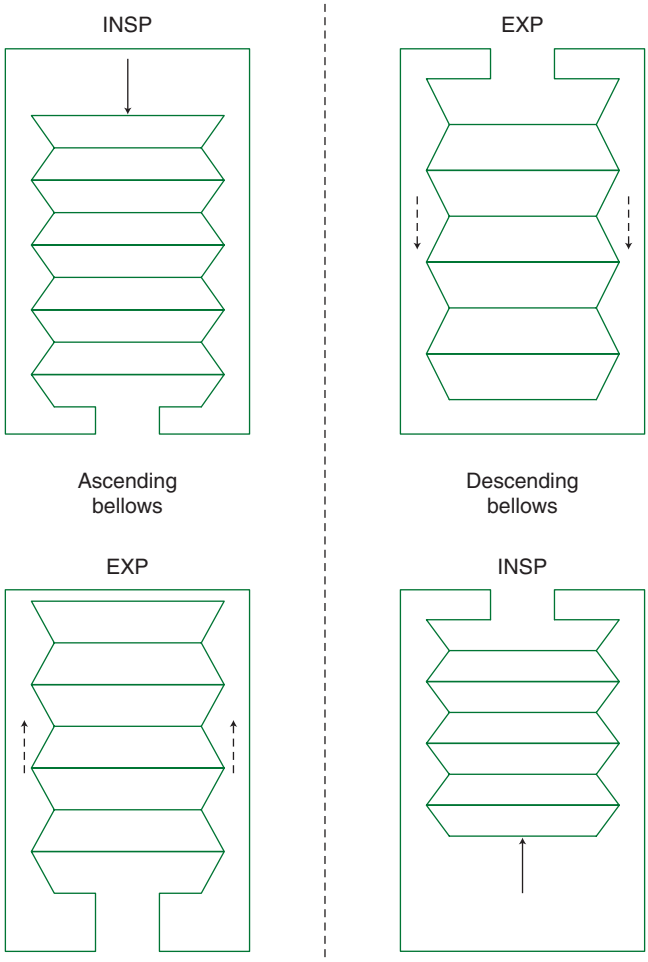

FIGURE 24-3 Schematic of anesthesia machine bellows. *Left:* Ascending type; *right:* descending type. *Straight lined arrows* represent the direction of movement during inspiration; *dashed line arrows* represent the direction of movement during expiration. *Exp*, expiration; Insp, inspiration.

Design

BELLOWS DESIGN

The first anesthesia ventilators were based on the bellows design. Bellows ventilators more or less simply automate bag ventilation, and can be still found in modern anesthesia machines. Bellows are located in a chamber where a driving gas flows in to generate an external pressure that squeezes out their contents. The driving gas mixture, which usually consists of oxygen (sometimes mixed with air), is completely separated from the anesthetic gas mixture delivered to the patient.

Bellows are classified according to their motion during expiration, as shown in Figure 24-3. Accordingly, ascending (standing) bellows move upwards, while descending (hanging) bellows move downwards in the expiratory phase. Alternatively, bellows may be displaced horizontally, minimizing the effect of gravity on bellows movement. In addition, horizontal bellows that have a large surface area offer reduced mechanical resistance to movement.

Given that the weight of a descending bellows promotes its expansion, it may continuously inflate and deflate even in the absence of adequate patient ventilation, for instance during patient disconnection from the anesthesia circuit. Because of this serious safety concern, most bellows ventilators in anesthesia machines are of the ascending type. During inspiration, a driving gas squeezes the bellows downward, pushing its content into the anesthesia circuit. Simultaneously, the driving gas closes a relief valve, avoiding escape of the anesthetic gas mixture into the scavenging gas system. During expiration, the pressure around the bellows is reduced to zero, allowing escape of the driving gas and upward movement of the bellows, which is mainly driven by the pressure in the patient's airways. Because the ventilator relief valve opens first at 2 to 3 cm H_2O during expiration, the bellows are filled first before any gas is scavenged, and a minimal PEEP of 2 to 3 cm H_2O results. Another problem associated with the bellows anesthesia ventilator is that fresh

gas flow is permanently added to the anesthesia circuit during the whole-breath cycle. Accordingly, the effectively delivered tidal volume may differ from the anesthesia ventilator settings depending on inspiration time. Furthermore, the compliance of the breathing circuit may also result in differences between desired and delivered tidal volume.

The problem of fresh gas flow-dependence on tidal volume is not exclusive to bellows anesthesia ventilators and can be fixed by decoupling systems that are present in some anesthesia machines. For instance, the fresh gas can be decoupled from the anesthesia circuit by a valve that closes during inspiration, diverting the fresh gas to the bag reservoir during inspiration. Furthermore, flow and volume sensors placed near the patient–airway interface may be used to compensate for differences between desired and effectively delivered tidal volume (V_T). Such differences may result not only from inappropriate fresh gas flow rates, but also from expansion of the breathing circuit during inspiration. Those sensors, however, are prone to accumulation of moisture, which may impair their accuracy, jeopardizing the performance of the ventilator.

PISTON DESIGN

The use of mechanical ventilators based on piston (Fig. 24-4) instead of bellows design in anesthesia machines is increasing. Anesthesia piston ventilators are able to deal more efficiently with volume compensation secondary to compliance of the breathing circuit because they depend not on measurement of airflow or volume but rather pressure, which is less sensitive to the accumulation of moisture or secretions. Furthermore, control of the piston's displacement allows more accurate volume delivery, especially in situations where low tidal volumes are required, for example, in neonatal anesthesia. In addition, the piston ventilator allows a more rapid increase in flow than a bellows ventilator, which is particularly important for pressure-controlled ventilation (PCV).

Because of the ease and accuracy with which the piston can be controlled, advanced ventilation modes can be implemented through software enhancements to the piston ventilator. The basic piston design has proven itself to be a versatile platform for anesthesia ventilator design, which permits transferring differentiated mechanical ventilation modes from the ICU to the operating room.

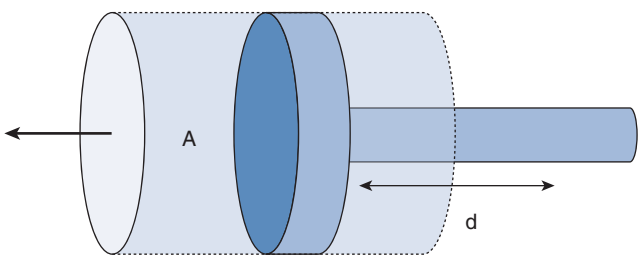

FIGURE 24-4 Schematic of an anesthesia machine piston. *A*, area; *d*, displacement.

TURBINE DESIGN

An innovative anesthesia ventilator design is the electrically driven and controlled compressor turbine. The turbine has a two particularities that make it attractive for anesthesia ventilators:[118] (a) it builds up the breathing pressure and delivers the corresponding flow to the patient during inspiratory time; and (b) it delivers a circuit flow that is required to mix the gas within the breathing system independently of patient inspiratory effort. During the inspiratory phase of controlled ventilation, the turbine transports the breathing gas from the breathing bag reservoir to the patient. During expiration, the gas returns to the bag and is additionally circulated and mixed.[118] This anesthesia ventilator design is particularly important for closed-systems, which allow minimal consumption of anesthetic gases, that is, quantitative anesthesia. Because a turbine-based ventilator performs as well as the best compressed-gas ICU ventilators,[119] it offers a useful platform for implementation of advanced mechanical ventilation modes in anesthesia.

Table 24-3 depicts the basic characteristics of some available anesthesia ventilators. For a complete and comparative description of those devices we recommend the reader to assess the homepage of the nonprofit research agency ECRI Institute at www.ecri.org.

MECHANICAL VENTILATION STRATEGIES DURING GENERAL ANESTHESIA

Current Clinical Practice and Evidence

Mechanical ventilation strategies can influence the development of ventilator-induced lung injury and affect clinical outcome following surgery. Despite a compelling rationale for the use of lower V_T, PEEP, and recruitment maneuvers, the role of protective mechanical ventilation during general anesthesia has not been established. Nevertheless, several clinical trials have addressed the impact of mechanical ventilation on pulmonary function, lung injury, and clinical outcome (Table 24-4).

The clinical practice of mechanical ventilation may vary widely across countries and even within a single department. In fact, anesthesiologists ventilate noninjured lungs with both high and low tidal volumes, as well as high and low levels of PEEP, because definitive evidence supporting the one or the other approach is still missing.

TIDAL VOLUMES

As shown in Table 24-4, the effects of tidal volumes have been investigated during different surgical conditions, including elective abdominal surgery, cardiopulmonary bypass, and thoracic and esophageal surgery, as well as in patients admitted to the ICU after surgery. The lower V_T used in those

TABLE 24-3: BASIC CHARACTERISTICS OF SOME OF COMMERCIALLY AVAILABLE ANESTHESIA VENTILATORS

Fabricant	**Dräger Medical**	**Dräger Medical**	**Dräger Medical**	**Dräger Medical**
Model	*Zeus IE*	*Primus IE*	*Fabius GS Premium, Fabius MRI*	*Cicero EM, Cicero B*
Ventilator design	Turbine	Piston	Piston	Piston
Bellows size	—	—	—	—
Ventilation modes*	Manual/spontaneous, CPAP, VCV, Autoflow, PCV, SIMV-PS, PSV	Manual/spontaneous, CPAP, VCV, Autoflow, PCV, SIMV-PS, PSV	Manual/spontaneous, CPAP, VCV, PCV, SIMV, PSV	Manual/spontaneous, CPAP (APL valve), VCV, PCV, SIMV
Tidal volume (mL)	20 to 1500	20 to 1400	20 to 1400	20 to 1400
Minute volume (L/min)	Up to 40	Up to 50	Up to 50	—
Respiratory rate (breaths/min)	Up to 80	3–100	4–60	6 to 80 (VCV, PCV) 3 to 80 (SIMV)
Inspiratory flow (L/min)	180 maximum	150 maximum	10 to 75 in PCV/10 to 85 in PS and SIMV	5 to 75
I:E ratio	4:1 to 1:4	5:1 to 1:99	4:1 to 1:4	1:3 to 2:1
Inspiratory pause (% of T_I)	20 to 50	0 to 60	0 to 50	0 to 60
Pressure limit (cm H_2O)	Up to 70	Up to 70	Up to 70	Up to 70
PEEP (cm H_2O)	0 to 35	0 to 20 (Pmax-10 hPa in volume mode; Pmax-6 hPa in pressure mode)	0 to 20	0.2 to 15
Control of inspiratory tidal volume	Fresh gas decoupling and compliance compensation	Fresh gas decoupling and compliance compensation	Fresh gas decoupling and compliance compensation	Fresh gas decoupling and compliance compensation

Fabricant	**GE Healthcare**	**MEDEC**	**Spacelabs Healthcare**
Model	*Aisys Carestation, Avance*	*Neptune, Saturn Evo Color, Saturn Evo Standard*	*Blease Focus, Blease Serius*
Ventilator design	Bellows (ascending)	Bellows (horizontal bag-in-bottle)	Bellows (ascending bag-in-bottle)
Bellows size	1500 mL	1 for neonate to adult	Pediatric/adult
Ventilation modes*	Manual/spontaneous, CPAP, VCV, PCV, PCV-VG, SIMV-VC, SIMV-PC, PSVPro, end-tidal control (not in the *Avance*)	Manual/spontaneous, VCV, PCV, SIMV, PSV	Manual/spontaneous, VCV, (Precision) PCV, SIMV-PS
Tidal volume (mL)	20 to 1500	10 to 1600	20 to 1500
Minute volume (L/min)	0.08 to 120	Not specified	0.3 to 25
Respiratory rate (breaths/min)	4 to 100	4 to 80	2 to 99
Inspiratory flow (L/min)	1 to 120	Automatic, decelerating flow pattern	0 to 100, variable
I:E ratio	2:1 to 1:8	4:1, 3:1, 2:1, 1:1, 1:1.5, 1:2, 1:3, 1:4, 1:5, 1:6	2:1 to 1:5
Inspiratory pause (% of T_I)	0 to 60	0 to 50	0 to 50
Pressure limit (cm H_2O)	12 to 100	7 to 99	10 to 70, adult 10 to 50, pediatric
PEEP (cm H_2O)	4 to 30	0 to 20	3 to 20
Control of inspiratory tidal volume	Fresh gas decoupling and compliance compensation	Compliance compensation	Fresh gas decoupling and compliance compensation, tidal volume increased by 10% at every tenth breath (sigh function)

Abbreviations: CPAP, continuation positive airway pressure; *PCV*, pressure-controlled ventilation; *PCV-VG*, pressure controlled with volume guarantee; *PSV*, pressure-support ventilation; *SIMV*, synchronized intermittent mandatory ventilation; *SIMV-PC*, SIMV with pressure control; *SIMV-PS*, SIMV with pressure support; *SIMV-VC*, SIMV with volume control; *VCV*, volume-controlled ventilation.

*Ventilation modes listed may be optional.

The authors and the publisher do not take responsibility for the information contained in this table.

Reference: Healthcare Product Comparison System: Anaesthesia Units at www.ecri.org.

TABLE 24-4: STUDIES ON THE IMPACT OF VENTILATOR SETTINGS DURING GENERAL ANESTHESIA ON PULMONARY FUNCTION, LUNG INFLAMMATION, AND OUTCOME

		Control Group		Protective Group		Inflammation Markers						Intraoperative Outcomes		Postoperative Outcomes			
Ref	Type and Number Patients/Setting	PEEP	V_TmL/kgIBW	PEEP	V_TmL/kgIBW	TNFα	IL-1	IL-2	IL-6	IL-8	IL-10	compl	oxy	oxy	atelect	PPC	Length of Stay
Lee 1990[120]	Postoperative pts (not neurosurgical) ($n = 103$)/ICU	—	12	—	6	NA	NA	NA	NA	NA	NA	NA	↓	NA	NA	↓	↓
Wrigge 2000[90]	Elective surgery ($n = 39$)/OR	0	15	0	6	=	=	NA	=	NA	=	NA	NA	NA	NA	NA	NA
				10	6	=	=		=		=						
Wrigge 2004[91]	Thoracotomy ($n = 35$)/ Laparotomy ($n = 30$)/OR	0	12/15	10	6	=	=	=	=	=	=	=	=	=	NA	NA	=
Koner 2004[121]	Cardiopulmonary bypass ($n = 44$)/OR	0	10	5	10	=	NA	NA	=	NA	NA	NA	↑	↑	NA	↓	=
				5	6								↑	↑			
Wrigge 2005[92]	Cardiopulmonary bypass ($n = 44$)/ICU	—	12	—	6	↓	NA	NA	=	=	NA	NA	NA	NA	NA	NA	NA
Reis Miranda 2005[122]	Cardiopulmonary bypass ($n = 62$)/OR-ICU	5	9	10	4/6	=	NA	NA	=	↓	=	NA	↑	↑	NA	NA	NA
Zupancich 2005[123]	Cardiopulmonary bypass ($n = 40$)/OR	2/3	12	10	8	NA	NA	NA	↓	↓	NA	NA	=	=	NA	=	NA
Michelet 2006[93]	Esophagectomy ($n = 52$)/OR	0	9	5	5	=	↓	NA	↓	↓	NA	NA	↑	↑	NA	=	=
Choi 2006[124]	Surgery for ≥5 h ($n = 40$)/ OR	0	12	10	6	Activation of BALF coagulation (increase in TATc, soluble tissue factor and factor VIIa) in the control group						NA	NA	=	NA	=	=
Cai 2007[125]	Elective excision of intracranial lesion ($n = 16$)/OR	0	10	0	6	NA	NA	NA	NA	NA	NA	NA	NA	NA	=	NA	NA
Wolthuis 2008[94]	Abdominal surgery with duration ≥5 h ($n = 46$)/ OR	0	12	10	6	=	=	=	=	↓	NA	NA	↑	↑	NA	NA	NA
Determann 2008[126]	Abdominal surgery with duration ≥5 h ($n = 40$)/ OR	0	12	10	6	No differences on levels of biomarkers of lung epithelial injury (BALF and systemic levels of SP-A, SP-D, CC16 and sRAGE)						NA	=	=	NA	NA	NA
Determann 2010[127]	Medical-surgical patients admitted to ICU ($n = 150$)/ICU	Best PEEP	10	Best PEEP	6	=	=	NA	↓	NA	NA	=	=	=	NA	↓	=
Sundar 2011[128]	Cardiopulmonary bypass ($n = 149$)/OR	Best PEEP	10	Best PEEP	6	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	↓	↓
Yang 2011[129]	One-lung ventilation in elective lobectomy ($n = 100$)/OR	0	10	5	6	NA	NA	NA	NA	NA	NA	NA	NA	↑	↓	↓	=

Abbreviations: ↑, increased; ↓, decreased; =, unchanged; *atelect*, atelectasis; *BALF*, bronchoalveolar lavage fluid; *CC16*, Clara cell protein; *compl*, compliance; *IBW*, ideal body weight; *ICU*, intensive care unit; *IL*, interleukin; *NA*, not assessed; *OR*, operation room; *oxy*, arterial oxygenation; *PEEP*, positive end-expiratory pressure; *PPC*, postoperative pulmonary complication; *SP*, surfactant protein; *sRAGE*, soluble receptor for advanced glycation end products; *TATc*, thrombin-antithrombin complex; *TNF*, tumor necrosis factor; V_T, tidal volume.

studies was 6 mL/kg (ideal body weight), while the higher V_T ranged from 10 to 15 mL/kg. Furthermore, lower V_T were used in combination with higher PEEP (5 to 10 cm H_2O), while high V_T were used in combination with moderate PEEP (2 to 5 cm H_2O).

Both physiologic and clinical parameters have been investigated in those trials. In elective abdominal surgery, the combination of higher V_T and lower PEEP resulted in no differences in pulmonary biomarkers (inflammatory mediators), in two studies,[90,91] whereas IL-8 in was higher in one study[94] and bronchoalveolar coagulation was more pronounced in another trial.[124] In patients undergoing cardiopulmonary bypass, higher V_T were associated with increased lung inflammation in three trials,[121–123] although one study could not confirm such detrimental effect.[92] High V_T resulted in elevation of plasma levels of inflammatory mediators in one study on thoracic-esophageal surgery,[93] but that finding has been disputed.[91] In postoperative patients recovering in the ICU, lower V_T was associated with decreased plasma levels of IL-6.[127]

With respect to gas exchange, the combination of lower V_T and higher PEEP resulted in improved oxygenation in different trials,[94,121,122] but also increased Pa_{CO_2} and lowered arterial pH in two investigations.[94,124]

The number of hospital-free days could be reduced by protective mechanical ventilation with lower tidal volume and higher PEEP in a postoperative mixed medical surgical patients in one study,[120] but several trials failed to show such a beneficial effect.[91,93,121,124,127,129] In cardiac surgery patients, the use of a ventilation strategy with V_T of 6 mL/kg resulted in a higher proportion of patients extubated 6 hours after surgery and a lower reintubation rate as compared with a nonprotective strategy of V_T 10 mL/kg.[128]

POSITIVE END-EXPIRATORY PRESSURE

Table 24-5 depicts selected prospective randomized trials that adjusted the level of PEEP while maintaining V_T approximately constant during open abdominal,[130–132] laparoscopic,[133–135] bariatric,[136–138] and neurosurgery.[139] Except for

TABLE 24-5: STUDIES EMPLOYING RANDOMIZED-DESIGN COMPARISONS OF DIFFERENT POSITIVE END-EXPIRATORY PRESSURE STRATEGIES DURING GENERAL ANESTHESIA

		Control Group		Protective Group		Intraoperative Outcomes		Postoperative Outcomes			
Ref	**Type and Number Patients/Setting**	**PEEP**	**V_T mL/kg IBW**	**PEEP**	**V_T mL/kg IBW**	**compl**	**oxy**	**oxy**	**atelect**	**PPC**	**Length of Stay**
Berthelsen 1979[130]	Abdominal surgery ($n = 40$)/OR	0	—	10	—	NA	NA	=	NA	NA	NA
Neumann 1999[139]	Neurosurgery or eye surgery ($n = 13$)/OR	0	—	10	—	NA	NA	NA	↓	NA	NA
Tusman 1999[131]	Abdominal surgery ($n = 30$)/OR	0	7/9	5	7/9	=	=	=	NA	=	NA
				5 + R	7/9	↑	↑	↑	NA	=	NA
Wetterslev 2001[132]	Abdominal surgery ($n = 40$)/OR	0	—	Best PEEP	—	NA	↑	=	NA	NA	NA
Pang 2003[133]	Laparoscopic cholecystectomy ($n = 24$)/OR	0	10	5 + R	10	NA	↑	=	NA	NA	NA
Meininger 2005[134]	Laparoscopic surgery ($n = 20$)/OR	0	—	5	-	NA	↑	=	NA	NA	NA
Whalen 2006[137]	Laparoscopic bariatric surgery ($n = 20$)/OR	4	8	12 + R	8	↑	↑	=	NA	=	=
Talab 2009[138]	Laparoscopic bariatric surgery ($n = 66$)/OR	0	8 to 10	5	8 to 10	NA	=	=	↓	↓	=
				10	8 to 10		↑	↑	↓↓	↓↓	↓
Reinius 2009[136]	Bariatric surgery ($n = 30$)/OR	0 + R	10	10	10	↑	=	=	=	NA	NA
				10 + R	10	↑	↑	=	↓		
Kim 2010[135]	Laparoscopic cholecystectomy ($n = 30$)/OR	0	8	5	8	=	↑	↑	NA	NA	NA

Abbreviations: ↑, increased; ↓, decreased; =, unchanged; *atelect*, atelectasis; *compl*, compliance; *IBW*, ideal body weight; *ICU*, intensive care unit; *NA*, not assessed; *OR*, operation room; *oxy*, arterial oxygenation; *PAW*, airway pressure; *PEEP*, positive end-expiratory pressure; *PPC*, postoperative pulmonary complication; *R*, recruitment maneuver; V_T, tidal volume.

one study,[137] the lower level of PEEP was zero in those trials, while the highest levels varied between 5 and 12 cm H_2O. In four studies, a recruitment maneuver was performed before setting high PEEP.[131,133,136,137] In most studies in Table 24-5, higher PEEP was associated with better intraoperative oxygenation, with no major changes in pulmonary inflammation. In three studies, a reduction in atelectasis was also observed in the postoperative period.[136,138,139] The use of higher PEEP during surgery improved oxygenation in the postoperative period in two studies,[131,138] while the other four trials observed no benefit.[132–134,136]

There is also uncertainty with regard to the effects of PEEP on outcome of surgical patients. Higher PEEP levels contributed to prevent postoperative pulmonary complications in one study,[138] but two trials reported no effect.[131,137]

RECRUITMENT MANEUVERS

The use of recruitment maneuvers in patients with ALI and/or acute respiratory distress syndrome is controversial. Moreover, alveolar flooding and consolidation of lung parenchyma are common findings in injured lungs, which challenge the rationale for the use of recruitment maneuver. In contrast, the presence of atelectasis has been well documented during general anesthesia and is found in as many as 90% of patients,[42] beginning during the induction period.[140] Thus, unlike ALI or acute respiratory distress syndrome, there is a strong physiologic rationale supporting the use of recruitment maneuvers for reversing lung collapse during general anesthesia.

Recruitment maneuvers in anesthesia are most commonly performed by "bag squeezing," that is, as sustained inflation, using the airway-pressure limiting valve of the anesthesia machine (see Fig. 24-2). Although simple, this maneuver has some drawbacks. First, the airway pressure is not kept constant, changing with the pressure applied on the bag by the anesthesiologist and the fresh gas flow from the anesthesia machine. Second, switching from manual to controlled ventilation usually leads to a loss of pressure in the anesthesia circuit, and the PEEP valve may require a couple of cycles to achieve the desired level. Thus, depending on the time constant of lungs and breathing circuit, derecruitment can occur with this kind of maneuver. Third, if the anesthesia ventilator initiates an inspiration immediately after switching and the airway pressure is still high, pressure overshoot with barotrauma may result.

Such limitations can be overcome by applying sustained inflations by means of continuous positive airway pressure (CPAP). Unfortunately, CPAP is not available on all anesthesia ventilators (see Table 24-1). Alternatively, the limitations of manual recruitment maneuvers can be avoided if airway pressure is increased during tidal ventilation (so-called cycling maneuver [141]), for example, with a stepwise increase of PEEP during volume-controlled ventilation (VCV), or even PCV, if this latter mode is available on the anesthesia ventilator.

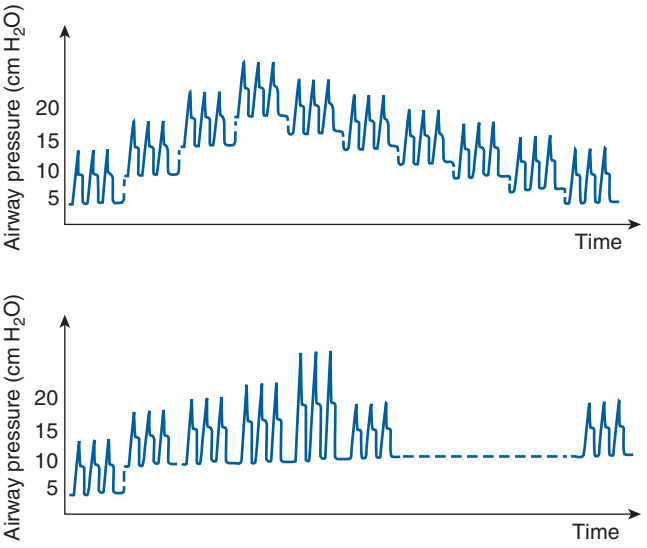

FIGURE 24-5 Schematic of airway pressure during two-lung recruitment maneuvers that can be performed in the volume-controlled ventilation mode on most anesthesia machines. *Top*: in the ascending part, a stepwise change of positive end-expiratory pressure (PEEP) by 5 cm H_2O at constant tidal volume is performed until the desired inspiratory plateau pressure; in the descending part, PEEP is decreased by steps of 2 to 3 cm H_2O and the respiratory system elastance measured at each step; a second recruitment maneuver must follow before the PEEP of minimal elastance is set. *Bottom*: stepwise change of tidal volume at constant PEEP until the desired inspiratory plateau pressure, as described in reference 142.

Figure 24-5 illustrates two possible ways of recruiting the lungs with cycling maneuvers in the VCV mode. Initially, the intravascular volume is expanded to achieve normovolemia, and the fractional inspired oxygen concentration (FI_{O_2}) is increased to 1. Tidal volume is set at 8 to 12 mL/kg and the inspiratory pause at 20% to 50% of inspiration. In the first variant, PEEP is increased in steps of 5 cm H_2O up to 20 cm H_2O every three to five breaths. Then, the PEEP is reduced in steps of 2 to 3 cm H_2O and static elastance of the respiratory system measured at each step (decremental PEEP trial). In the second variant, the PEEP is increased to 10 to 12 cm H_2O and maintained constant thereafter. V_T is increased in steps of 2 to 4 mL/kg until an inspiratory plateau pressure of 30 to 40 cm H_2O is achieved. Finally, V_T is again set at the initial value. This maneuver has been proposed recently for recruitment of noninjured lungs within a multicenter randomized clinical trial on the use of PEEP intraoperatively.[142]

In PCV, the driving pressure is kept constant at 15 to 20 cm H_2O and the stepwise increase and decrease of PEEP is performed as for VCV. Also with this mode, the goal is to achieve an inspiratory plateau pressure of approximately 30 to 40 cm H_2O during three to five breaths.

If the anesthesia ventilator does not enable higher levels of PEEP, V_T or driving pressures may be changed to achieve the desired opening-pressure target. Obviously, this target must be adapted according to a patient's condition, for example,

increased elastance of the chest wall, which will reduce the effective transpulmonary pressure. In patients with normal lungs and chest wall elastance, airway pressure of 40 cm H_2O is sufficient to recruit the lungs,[131] but morbidly obese patients may require up to 60 cm H_2O.[136]

Table 24-6 depicts some of the clinical studies that have addressed the effects of recruitment maneuvers during general anesthesia, including the type of maneuver used. Oxygenation was effectively improved in all but one study, mainly when combined with higher levels of PEEP. In patients undergoing cardiac surgery, Pa_{O_2} was still higher 24 hours after surgery. In some of the trials, moreover, the FRC was increased and respiratory system mechanics improved, while a decrease in atelectasis was documented in children undergoing magnetic resonance imaging (MRI),[143] coronary artery bypass,[144] and bariatric[137] surgery. Recruitment maneuvers after cardiac surgery resulted in a decrease of cardiac output.[145] Recruitment maneuvers, however, performed during elective cardiac surgery did not lead to hemodynamic instability in another study.[146]

As can be inferred from those trials, recruitment maneuvers are effective in reversing atelectasis, increasing FRC and improving oxygenation in general anesthesia, with little or no effect on hemodynamics. Their impact on clinical outcome, however, is not established and, therefore, their routine use cannot be recommended for unselected patient populations.

Spontaneous and Assisted Spontaneous Breathing

Most anesthetic agents are depressants of the respiratory center and some have additional muscle relaxant properties, most notably the volatile anesthetics. Because induction of general anesthesia is conducted with comparatively high dosages of anesthetic drugs, apnea usually develops. Furthermore, endotracheal intubation is frequently needed during general anesthesia to protect the airways from aspiration of gastric contents. To facilitate laryngoscopy and placement of an endotracheal tube, muscle paralytic agents are used. In view of these facts, spontaneous breathing activity is frequently abolished following induction of general anesthesia, and controlled mechanical ventilation is required in order to maintain an adequate gas exchange.

Nevertheless, endotracheal intubation itself can result in different complications, including injuries of the teeth, vocal cords, and arytenoids, which may be avoided if the patient is not at risk of aspiration. For example, supraglottic devices, and more specifically laryngeal masks, can maintain the patency of the upper airways and facilitate ventilation by spontaneous breathing or positive pressure ventilation. Furthermore, short anesthesia procedures may be conducted with a facemask, with or without placement of a Guedel tube, in a spontaneously breathing patient. Even if the use of an endotracheal tube is necessary, general anesthesia can be titrated to allow spontaneous breathing activity, mainly when combined with regional anesthesia techniques. Thus, maintenance of adequate gas exchange during general anesthesia may be possible by spontaneous breathing alone or, alternatively, with assisted ventilation, if tidal volume has to be increased or the work of breathing reduced.

POSSIBLE ADVANTAGES

General anesthesia leads to a decrease in FRC and development of atelectasis in dependent lung zones, which may, in turn, impair gas exchange. Spontaneous breathing activity can counteract such effects if enough transpulmonary pressure is generated in dependent lung zones.[150] Even in the absence of alveolar lung recruitment, spontaneous breathing activity may improve gas exchange by facilitating the redistribution of perfusion towards better aerated and ventilated ventral areas.[151] Also, inspiratory efforts may reduce the mean intrathoracic pressure, contributing to an increase in venous return to the heart and the perfusion of different organs.[152] Furthermore, the maintenance of spontaneous breathing during anesthesia may also have beneficial effects on the lung tissue. In healthy rats under general anesthesia, controlled mechanical ventilation elicits a degradation of glycosaminoglycans of the extracellular matrix and promotes edema formation, which can be prevented by spontaneous breathing.[88]

The presence of spontaneous breathing during general anesthesia is usually associated with a reduction in the use of anesthetic drugs and obviates the need for neuromuscular blocking agents, which may speed the recovery from anesthesia and contribute to avoid complications from inadvertent residual sedation and/or muscle paralysis.[153] Furthermore, a reduction in the use of anesthetic agents will increase the levels of stress hormones, for example, adrenaline, noradrenaline, adrenocorticotrophic hormone, and cortisol, decreasing the requirements for exogenous vasoactive drugs.

POSSIBLE DISADVANTAGES

Some anesthesiologists fear that the decrease in depth of anesthesia for maintaining spontaneous breathing activity may result in intraoperative awareness and recall. Indeed, anesthesia depth requirements may vary according to the surgical stimulus and maintenance of adequate analgesia while avoiding respiratory depression can be challenging. Also, spontaneous breathing activity may be insufficient to generate adequate alveolar ventilation or result in increased work of breathing secondary to a relatively low diameter of the airway assist device, requiring assistance by positive pressure. When pressure-support ventilation, which is the most common mode of assisted mechanical ventilation in anesthesia ventilators, is used for assisting spontaneous breathing, not enough transpulmonary pressure is generated in dependent zones to recruit the lungs.[154] Furthermore, other modes of assisted ventilation also available on anesthesia machines, for example, synchronized intermittent mandatory ventilation, may result in patient–ventilator asynchrony, leading to patient discomfort and even arousal.

TABLE 24-6: RANDOMIZED CLINICAL TRIALS ON THE USE OF RECRUITMENT MANEUVERS DURING GENERAL ANESTHESIA

		Control Group		Protective Group			Intraoperative Outcomes			Postoperative Outcomes		
Ref	Type and Number Patients/Setting	PEEP	V_TmL/kg IBW	PEEP	V_TmL/kg IBW	Type of Recruitment Maneuver	compl	oxy	oxy	atelect	PPC	Length of Stay
Tusman 1999[131]	Abdominal surgery ($n = 30$)/OR	0	7/9	5	7/9	Increase in PEEP and V_T until PEEP = 15 cm H_2O, V_T = 18 mL/kg or Paw_{PEAK} = 40 cm H_2O	=	=	=	NA	=	NA
				5+R	7/9		↑	↑	↑	NA	=	NA
Dyhr 2002[144]	Coronary artery bypass surgery ($n = 16$)/ICU	0+R	6	Best PEEP+R	6	20-s inflations to Paw = 45 cm H_2O twice	=	↑	↑	=	NA	NA
Pang 2003[133]	Laparoscopic cholecystectomy ($n = 24$)/OR	0	10	5+R	10	Manually ventilated with Paw = 40 cm H_2O for 10 breaths (1 min)	NA	↑	=	NA	NA	NA
Tusman 2003[143]	Children (age 6 mo to 6 y) undergoing MRI in general anesthesia ($n = 24$)	0	Spont breath	5	Spont breath	Manually ventilating with Paw_{PEAK} = 40 cm H_2O and PEEP = 15 cm H_2O for 10 breaths	NA	NA	NA	=	NA	NA
				5+R	Spont breath					↓		
Whalen 2006[137]	Laparoscopic bariatric surgery ($n = 20$)/OR	4	8	12+R	8	Increasing PEEP in a stepwise fashion: 10 (3 breaths), then 15 (3 breaths), finally 20 (10 breaths); Paw_{PEAK} ≥50 cm H_2O	↑	↑	=	NA	=	=
Celebi 2008[147]	Coronary artery bypass surgery ($n = 60$)/ICU	5	7	5+R	7	R with CPAP: 30 s with Paw = 40 cm H_2O; R+PEEP: ↑PEEP = 20 cm H_2O and ↑ V_T until Paw = 40 cm H_2O for 2 min; after R	↑	↑	↑	↓(evaluated on atelect score)	↓	↓
				5+RR	7	in both groups PEEP↓ in 1 to 2 cm H_2O every 5 min until the lowest PEEP (>5 cm H_2O) providing best Pa_{O_2}	↑	↑	↑	↓(evaluated on atelect score)	↓	↓
Chalhoub 2007[148]	Bariatric surgery ($n = 52$)/OR	8	10	8+R	10	Paw = 40 cm H_2O for 15 s	NA	↑	↑	NA	NA	NA
Minkovich 2007[146]	Elective cardiac surgery ($n = 95$)/OR-ICU	5	8/10	5+R	8/10	Paw = 35 cm H_2O for 15 s before cardiopulmonary bypass and Paw = 30 cm H_2O for 5 s before ICU admission; R repeated after 20 to 30 min ICU admission	NA	↑	↑	NA	NA	=
Almarakbi 2009[149]	Laparoscopic bariatric surgery ($n = 60$)/OR	10	10	10+R	10	R with Paw = 40 cm H_2O for 15 s; in RR+PEEP groups Paw = 40 cm H_2O for 15 s repeated every 10 min	↑	↑	↑	NA	=	↓
		0+R	10	10+RR	10		↑↑	↑↑	↑↑		=	↓↓
Reinius 2009[136]	Bariatric surgery ($n = 30$)/OR	0+R	10	10	10	Paw increased to 55 cm H_2O, and an inspiratory hold was kept for 10 s	↑	↑	=	=	NA	NA

Abbreviations: ↑, increased; ↓, decreased; =, unchanged; *atelect*, atelectasis; *compl*, compliance; *IBW*, ideal body weight; *ICU*, intensive care unit; *MRI*, magnetic resonance imaging; *NA*, not assessed; *OR*, operation room; *oxy*, arterial oxygenation; Pa_{O_2}, partial pressure of arterial oxygen; *Paw*, airway pressure; Paw_{PEAK}, peak airway pressure; *PEEP*, positive end-expiratory pressure; *PPC*, postoperative pulmonary complication; *R*, recruitment maneuver; *RR*, respiratory rate; V_T, tidal volume.

Nonconventional Modes of Mechanical Ventilation during Anesthesia

In contrast to the ICU, where nonconventional modes of mechanical ventilation are used for severe impairment of gas exchange, respiratory system mechanics, or both, patients under general anesthesia may require differentiated ventilator strategies as a means to facilitate the surgical approach or diagnostic procedures. High-frequency ventilation modes, especially high-frequency jet ventilation (HFJV) and high-frequency oscillatory ventilation (HFOV), are particularly interesting for the anesthesiologist, because they achieve adequate gas exchange while limiting lung and chest excursion, or saving space in the larynx for placement of surgical and diagnostic tools. HFJV is also helpful in emergency situations where supraglottic obstruction is present and percutaneous transtracheal ventilation through a small-bore catheter becomes necessary.

The devices used for high-frequency ventilation during general anesthesia are virtually the same as those found in the ICU. Obviously, those systems do not support use of volatile anesthetics and anesthesia is performed with intravenous drugs.

HIGH-FREQUENCY JET VENTILATION

The possible indications for HFJV include: (a) surgery and diagnostic procedures of the larynx and trachea (e.g., endoscopy, placement of tracheal stents, laser surgery); (b) improvement of oxygenation during one-lung anesthesia; and (c) transtracheal oxygenation in emergency situations. This ventilation mode, however, is contraindicated in patients who are at risk for aspiration and with upper airway obstruction.

HFJV can be delivered either through a tube or cannula placed supraglottically or subglottically. With the supraglottic approach, the jet ventilator can be attached to an endoscope; with the subglottic approach, either a transtracheal or a transglottic route can be used. In the transtracheal variant, a 13-gauge to 14-gauge (adults) or 18-gauge (children younger than age 3 years) catheter is introduced through the cricothyroid membrane into the trachea using the Seldinger method or under endoscopic control. The catheter tip is then advanced and placed 2 to 4 cm above the carina.[155] In the transglottic variant, a catheter with an internal diameter of 1.5 to 3.0 mm and up to 30 cm length is introduced transnasally or transorally and its multipore tip is advanced into the trachea under direct visualization by laryngoscopy using intubation-assist devices.

Jet ventilators apply pressures in the range of 1.5 to 2.5 bars with a respiratory frequency of 100 to 150 breaths/min and inspiration time of 50% (30% to 70%) on the jet catheter.[75] These settings result in airway pressures lower than those obtained with conventional mechanical ventilation, provided there is no stenosis or obstruction of the upper airways. Also, those settings result in tidal volumes of 1 to 3 mL/kg, which can be increased by augmenting the pressure, reducing the respiratory frequency, and increasing the duration of inspiration. Accordingly, if the tidal volume has to be reduced, for example, during arousal from anesthesia, so as to stimulate spontaneous breathing, the respiratory frequency is increased up to 300 breaths/min. Inspiratory oxygen fractions during HFJV are in the range of 50% to 100%, but the effective oxygen fraction in the trachea is usually lower because of air entrainment,[156] that is, mixing of oxygen from the ventilator with air surrounding the jet catheter by means of the Venturi effect.

Although adequacy of oxygenation can be monitored by usual means, for example, noninvasive pulse oximetry, capnography is not suitable for accessing the efficiency of ventilation during HFJV. Thus, transcutaneous or partial pressure of arterial carbon dioxide (P_{CO_2}) measurement may be required for appropriate titration of HFJV. Furthermore, the measurement of the effectively delivered tidal volume during HFJV is not possible in clinical practice, although it can be performed by body plethysmography in the lab. In contrast, airway pressure can be monitored by some jet ventilators through an accessory route in double-lumen jet catheters, or during end-expiratory pauses in conventional single-lumen jet catheters.

Serious complications from HFJV are rare.[155] Pneumothorax and pneumomediastinum have been reported in less than 1% of patients,[155,157] while subcutaneous emphysema has been observed in approximately 8% of patients.[155] Such complications result from pulmonary hyperinflation in presence of obstruction to expiratory flow and may occur even with devices that control tracheal pressure. Newer jet ventilators offer active expiratory assistance that could minimize such events. Supraglottic devices can theoretically promote transport of particles and liquid into the trachea, including tumor tissue, and also cause gastric inflation and rupture.[158] Also, when gas from the jet ventilator is not humidified, drying of the trachea mucosa and tracheobronchitis may occur.[159]

HIGH-FREQUENCY OSCILLATORY VENTILATION

Chapter 19 explains the principles of HFOV in detail. In brief, during HFOV a diaphragm or piston pump generates quasisinusoidal oscillations in airway pressure. This technique has been described originally with oscillation frequencies as high as 50 Hz,[160] but nowadays frequencies of 5 to 15 Hz are used clinically. To remove CO_2 from the respiratory circuit, an inspiratory bias flow of humidified and warmed air is used. The inspiratory bias flow and a gas outflow valve, which regulates the resistance of the expiratory limb, determine the mean airway pressure (mPaw).[161] The amplitude of pressure oscillation (ΔP), which is usually in the range of 60 to 90 cm H_2O, determines the effectively applied V_T, and an inspiratory-to-expiratory timing (I:E) ratio of 1:2 to 1:1 is set separately. Although the ΔP in the HFOV is high, the downstream pressure in the airways is obviously much lower,[162] and the resulting V_T is only a fraction of that obtained with

conventional mechanical ventilation, in the range of 1 to 3 mL/kg. The major factors that determine the V_T during HFOV are the diameter and length of the endotracheal tube, ΔP itself, inspiratory time, impedance of the respiratory system and the oscillation frequency, whereby higher frequencies result in lower V_T.[163]

The possibility of combining the lowest possible V_T with relatively high mPaw, and thereby reduce volutrauma and atelectrauma, respectively, makes HFOV particularly attractive for lung-protective ventilation. HFOV has become popular for the ventilator management of acute pulmonary dysfunction in infants, even if there is no clear evidence that it is superior to conventional ventilation.[164,165] In the operating room, HFOV may be a valuable alternative to limit the tidal excursion of the lungs, while allowing expansion and counteracting increases in abdominal pressure that would otherwise lead to shrinkage of the lungs. Accordingly, possible indications of HFOV in pediatric anesthesia include surgery for[76] congenital diaphragmatic hernia, congenital cystic adenomatoid malformation, esophageal atresia, patent ductus arteriosus, abdominal wall defect, and enterocolitis.

The use of HFOV during general anesthesia of adult patients is practically restricted to cases where HFOV has been initiated in the ICU and continued in the operating room. Possible reasons for that restriction are the time required for stabilization of lung recruitment and gas exchange after beginning of HFOV, lack of experience of anesthesiologists with this mode, and the fact that HFOV is currently not available on anesthesia machines, precluding its use with volatile anesthetics.

Special Situations

MECHANICAL VENTILATION DURING LAPAROSCOPY

Laparoscopy is widely used in the surgical treatment of a number of diseases. Its advantages are generally believed to lie with its minimal invasiveness, better cosmetic outcome, and shorter length of hospital stay based on surgical expertise and state-of-the-art equipment. The insufflation of the abdomen, however, might cause derangements of respiratory mechanics, lung volumes, and hemodynamics. Furthermore, laparoscopy may be associated with longer operation times.

Most patients tolerate mechanical ventilation during laparoscopy without major problems. Pneumoperitoneum, however, with increased intraabdominal pressure may pose difficulties for mechanical ventilation in patients with underlying lung disease and higher-than-normal body mass index.[166]

Abdominal insufflation of gas during laparoscopy, usually within the range of 10 to 15 mm Hg, greatly affects the respiratory mechanics, promoting an upward shift of the diaphragm and reducing lung volume.

Lung Volumes at End Expiration. The reduction in lung volume depends not only on intraabdominal pressure but also on the position of the patient. It is expected the Trendelenburg position will result in further reduction in lung volume, reducing FRC.

Lung and Chest Wall Mechanics. Insufflation of gas into the abdomen causes a rightward shift of the pressure-volume curve of the respiratory system. Such changes reflect the increase in both the lung and chest wall components of elastance. Also, the decrease in lung volume narrows the airways, increasing lung resistance. These effects have profound impact on the correct interpretation of the pressures displayed on the ventilator.

Contemporary anesthesia ventilators assess peak and plateau airway pressures, thus allowing discrimination between dissipation of pressure secondary to airway resistance (difference between peak and inspiratory plateau pressure) and the elastic properties of the respiratory system (inspiratory plateau pressure minus PEEP).

In the presence of abnormal chest wall mechanics, however, airway pressure does not adequately represent the transpulmonary pressure. Thus, it is necessary to closely monitor airway pressure before initiation of pneumoperitoneum, so as to set a new reference point of airway pressures that takes into consideration changes of lung and chest wall elastance, airway narrowing, and lung distortion.

Setting the Mechanical Ventilator for Laparoscopy. During laparoscopic surgery, CO_2 is absorbed from pneumoperitoneum, increasing CO_2 content in blood. Thus, to keep a normal Pa_{CO_2}, an increase in minute ventilation of approximately 30% is needed, which can be accomplished by increasing tidal volume, respiratory rate, or both. An increase in respiratory rate, however, in patients with expiratory flow limitation can worsen the auto-PEEP, whose monitoring may be difficult with ventilators that do not allow an end-expiratory hold or do not display flow-versus-time curves.

Arterial oxygenation is barely impaired during general anesthesia for laparoscopic surgery, even in morbidly obese patients.[167] Nonetheless, tissue oxygenation during laparoscopic surgery is lower than during open surgery.[168] The use of PEEP during laparoscopy increases Pa_{O_2} but such effect is only marginal, independently of body weight.[134] In obese patients in beach-chair position, however, the improvement in arterial oxygenation induced by PEEP may be significant,[169] but higher V_T does not seem to be useful for increasing Pa_{O_2} in such patients.[170]

Table 24-7 shows a list of randomized controlled trials on PEEP during laparoscopy. In most studies, the effects of zero end-expiratory pressure versus PEEP of 6 to 10 cm H_2O, with[133,137,149] or without[134,135,138] recruitment maneuvers, and V_T of 8 to 10 mL/kg were compared. All studies showed an increase in Pa_{O_2} intraoperatively, while two investigations reported an increase in respiratory compliance.[137,149] In one study,[137] there were no significant differences in Pa_{O_2} postoperatively, length of stay, and postoperative pulmonary

TABLE 24-7: RANDOMIZED CLINICAL TRIAL COMPARISONS OF DIFFERENT VENTILATOR STRATEGIES DURING LAPAROSCOPY

		Control Group		Protective Group			Intraoperative Outcomes		Postoperative Outcomes			
Ref	**Type and Number Patients/Setting**	**PEEP**	**V_TmL/kg IBW**	**PEEP**	**V_TmL/kg IBW**	**Type of Recruitment Maneuver**	**compl**	**oxy**	**oxy**	**atelect**	**PPC**	**Length of Stay**
Pang 2003[133]	Laparoscopic cholecystectomy ($n = 24$)/OR	0	10	5+R	10	Manually ventilated with Paw = 40 cm H_2O for 10 breaths (1 min)	NA	↑	=	NA	NA	NA
Meininger 2005[134]	Laparoscopic surgery ($n = 20$)/OR	0	—	5	—		NA	↑	=	NA	NA	NA
Whalen 2006[137]	Laparoscopic bariatric surgery ($n = 20$)/OR	4	8	12+R	8	Increasing PEEP in a stepwise fashion: 10 (3 breaths), then 15 (3 breaths), finally 20 (10 breaths); Paw_{PEAK} ≥50 cm H_2O	↑	↑	=	NA	=	=
Talab 2009[138]	Laparoscopic bariatric surgery ($n = 66$)/OR	0	8 to 10	5 10	8 to 10 8 to 10		NA	= ↑	= ↑	↓ ↓↓	↓ ↓↓	= ↓
Almarakbi 2009[149]	Laparoscopic bariatric surgery ($n = 60$)/OR	10 0+R	10 10	10+R 10+R	10 10	R with Paw = 40 cm H_2O for 15 s; in R+PEEP groups Paw = 40 cm H_2O for 15 s repeated every 10 min	↑ ↑↑	↑ ↑↑	↑ ↑↑	NA	= =	↓ ↓↓
Park 2009[173]	Laparoscopic hysterectomy ($n = 50$)/OR	0	10	15+R	10	10 manual breaths with Paw_{PEAK} = 40 cm H_2O	=	↑	↑	NA	NA	NA
Kim 2010[135]	Laparoscopic cholecystectomy ($n = 30$)/OR	0	8	5	8		=	↑	↑	NA	NA	NA

Abbreviations: ↑, increased; ↓, decreased; =, unchanged; *atelect*, atelectasis; *compl*, compliance; *IBW*, ideal body weight; *ICU*, intensive care unit; *NA*, not assessed; OR, operation room; oxy, arterial oxygenation; *Paw*, airway pressure; Paw_{PEAK}, peak airway pressure; *PEEP*, positive end-expiratory pressure; *PPC*, postoperative pulmonary complication; *R*, recruitment maneuver; RR, respiratory rate; V_T, tidal volume.

complications when comparing low versus high PEEP combined recruitment maneuvers. Some investigators, however, reported a reduction in postoperative atelectasis and postoperative pulmonary complications with high, compared to low, PEEP.[138] With regard to hemodynamic side effects, use of PEEP during pneumoperitoneum has produced conflicting results. Although some authors found that cardiac output was decreased during pneumoperitoneum combined with high PEEP,[137,171] others did not observe such deterioration.[134,172]

Mechanical Ventilation Mode and Laparoscopy. Because pneumoperitoneum can markedly affect compliance and resistance, it can also adversely affect tidal volume, minute ventilation, and alveolar ventilation during PCV. Thus, VCV is a valid choice to keep alveolar ventilation constant in the presence of changing lung mechanics. Most interest in the use of PCV during pneumoperitoneum is related to its potential for reducing peak airway pressures at similar levels of alveolar ventilation. In VCV, if end-inspiratory airway pressure does not equilibrate with alveolar pressure, transpulmonary pressure will be considerably less that the set value. Accordingly, for a given inspiratory time and peak target pressure, PCV applies greater cumulative pressure to the respiratory system than VCV, theoretically providing better oxygenation. Despite these theoretical advantages, however, PCV and VCV resulted in comparable oxygenation and respiratory mechanics during laparoscopy,[174,175] but CO_2 elimination was more effective with VCV than PCV in the morbidly obese patients.[175]

Patient Positioning and Laparoscopy. Patient positioning is extremely important during mechanical ventilation and laparoscopy. In morbidly obese patients under laparoscopy,[169] reverse Trendelenburg improved end-expiratory lung volume both before and after pneumoperitoneum induction and was associated with improved arterial oxygenation. Most importantly, head-up positioning alone or the application of PEEP in a supine position produced similar effects on lung volume and oxygenation. Airway pressures, however, were much lower during the beach-chair position. These data suggest that the combination of beach-chair position with PEEP, when feasible, improves oxygenation and favors a protective lung strategy.

MECHANICAL VENTILATION OF OBESE PATIENTS

The prevalence of adult obesity has increased in the last decade in most countries,[176] reaching up to 35% in North America and 15% to 20% in Europe.[177] Because these patients show several systemic pathophysiologic alterations, intraoperative mechanical ventilation and perioperative respiratory care may be challenging to the anesthesiologist.

After induction of anesthesia in obese patients, FRC decreases to approximately 50% of preanesthesia values,[136,178] and such change correlates well with body mass index.[179] The mechanism leading to reduction in FRC, with consequent development of atelectasis, is enhanced in obese patients, secondary to a possible increase in intraabdominal pressure.[38] Because of gravity, increased intraabdominal pressure is mainly directed toward the most dependent lung regions, leading to further reduction in diaphragmatic excursion and/or cranial displacement. Such changes in the obese patient favor the development of pulmonary atelectasis and ventilation–perfusion mismatching, which combined with anesthesia and muscle paralysis worsens arterial oxygenation.[179]

The loss in FRC also promotes an increase in lung elastance, while increased intraabdominal pressure promotes a further increase in chest wall elastance, resulting in higher elastance of the total respiratory system. Additionally, the lung resistance is increased in obesity,[179] mainly secondary to the reduction in lung volume, although specific resistance remains relatively normal.[62]

Preoperative Measures. It is beyond the scope of this chapter to describe the innumerable particularities concerning the induction of anesthesia in the obese patient, especially those concerning difficult intubation and risk of aspiration. Some aspects, however, are relevant for mechanical ventilation following induction.

In morbidly obese patients, the time to desaturate following standard preoxygenation with pure oxygen at barometric pressure conditions is reduced. The use of CPAP or noninvasive positive pressure ventilation during induction of anesthesia can minimize the loss in FRC, preventing formation of atelectasis and increasing the duration of non-hypoxic apnea.[180,181] In fact, use of noninvasive positive pressure ventilation before intubation improves oxygenation in obese patients undergoing different kinds of surgical approaches,[79,182] and contributes to better preservation of FRC during laparoscopic surgery.[183] Furthermore, induction of anesthesia in obese patients in the Trendelenburg position may additionally contribute to increase the FRC.

Intraoperative Mechanical Ventilation. In the intraoperative period, the following strategies should be considered for mechanical ventilation of the obese patient: (a) the lowest possible inspiratory oxygen fraction to achieve peripheral oxygenation saturation greater than 92%;[52] (b) tidal volumes less than 13 mL/kg (ideal body weight);[184] (c) a recruitment maneuver;[50,136] and (d) PEEP equal to or greater than 10 cm H_2O. Additionally, the use of large, manually or automatically periodically lung inflations (sighs) can be useful.[52]

Inspired oxygen fractions greater than 0.8 should be avoided in obese patients, because they favor the formation of progressive reabsorption atelectasis in the presence of zones with a low ventilation–perfusion ratio. The use high tidal volumes (>13 mL/kg ideal body weight) does not result in further improvements in oxygenation, although it can induce hypocapnia if the respiratory rate does not decrease. Moreover, the continuous use of high tidal volumes even during anaesthesia can promote ventilator-induced lung injury and negative effects on hemodynamics.

Adequate opening pressures can be applied by periodic lung inflations (recruitment maneuvers).[136] Airway pressures up to 60 cm H_2O, however, may be necessary to achieve a transpulmonary pressure that reopens collapsed lung areas. In fact, obese patients have an increased abdominal load secondary to increased intraabdominal pressure as well as thoracic fat mass, with resulting in an increase in chest wall elastance. In these circumstances, transpulmonary pressure is reduced, making the recruitment maneuver less effective. The duration of a recruitment maneuver should be limited to a maximum of 10 seconds so as to minimize as much as possible the negative effects on hemodynamics. Importantly, recruitment maneuvers should be performed only in patients who have stable volume and hemodynamic conditions. In the absence of PEEP, recruitment maneuvers can be repeated every 30 minutes to reopen atelectasis. PEEP levels 10 cm H_2O after a recruitment maneuver, however, may prevent small airways from collapsing. Obviously, excessive PEEP may lead to negative effects, like compression of lung capillaries with increased ventilation–perfusion ratios, alveolar overdistension and reduction of cardiac output. Recruitment maneuver and higher PEEP have also proven effective to improving respiratory function during laparoscopy.[79]

Postoperative Measures. The respiratory function of obese patients is considerably impaired in the postoperative period.[185] Such impairment is mainly related to the postoperative pulmonary restrictive syndrome, which can lead to secondary hypoxemia.[186,187]

A number of measures to reduce postoperative pulmonary complications have been proposed, including chest physiotherapy, patient positioning (30 to 45 degrees semirecumbent position), incentive spirometry, and noninvasive respiratory support.[187–191] The main goal is to restore lung volumes to the preoperative values, improving oxygenation and reducing work of breathing.[192] In this context, CPAP may be useful, especially when it is used before important deterioration of oxygenation.

MECHANICAL VENTILATION OF PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND ASTHMA

Bronchial asthma and COPD are the most common obstructive disorders of the lung. The prevalence of asthma is increasing worldwide, but improvements in medical care have led to a progressive decrease in morbidity and mortality.[193] Conversely, the prevalence of COPD is widely variable among the different regions of the world, and although different medical treatments of COPD have been developed, mortality is high and expected to occupy the second or third place among all causes of deaths within the next decade.[194]

The common feature of bronchial asthma and COPD is an increase of airway resistance, which represents a challenge for anesthesiologists. In addition to basic drug therapy, patients with asthma or COPD require different ventilation strategies for perioperative management.[195,196]

Various pathophysiologic mechanisms may contribute differently to airway narrowing in bronchial asthma and COPD. In asthma, acute episodes of bronchoconstriction are mainly secondary to an exaggerated response of airway smooth muscle to constrictor stimuli; in COPD, persistent airway narrowing is believed to be the result of airway wall thickening secondary to chronic bronchitis, and loss of lung elastic recoil secondary to emphysema.[197]

Airway narrowing has three major consequences, especially during acute exacerbations of bronchial asthma or COPD, that are relevant for the management of mechanical ventilation: dynamic hyperinflation, inefficient gas exchange, and cardiovascular abnormalities.

Mechanical ventilation may affect each of these features, though significant interactions exist between them.[198]

Dynamic Hyperinflation. Lung hyperinflation indicates an increase of any absolute lung volume, for example, FRC, above its predicted value. This may have two main causes: first, an increase of the relaxation volume of the respiratory system (static hyperinflation); second, failure to reach relaxation volume at end-expiration (dynamic hyperinflation). The former is caused by loss of elastic recoil (emphysema) and is not amenable to current pharmacologic treatments. The latter is the consequence of increased expiratory resistance and is mechanically characterized by an elastic threshold load, so-called intrinsic positive end-expiratory pressure (PEEPi), which must be overcome before inspiratory flow can be generated.

During mechanical ventilation, the occurrence of PEEPi can be caused by several mechanisms including (a) increased time-constant (product of resistance and compliance), (b) increase in breathing frequency or decrease in expiratory time, (c) an increase in V_T, and (d) airflow limitation during tidal expiration. In cases *a* to *c*, the airways remain open during the whole breathing cycle, although their diameter may be decreased; in case *d*, the airways collapse at end-expiration. The latter can be easily inferred from flow-time, pressure-time, and flow-volumes curves. On flow-time curves, flow at end-expiration does not equal zero, even when the pressure-time curve indicates that airway pressure has reached the level of set external PEEP. On the flow-volume curve, the expiratory limb of the loop shows a curvilinear shape, and it appears truncated when expiratory flow persists at end-expiration. It is worth noting that: (a) in the case of airway narrowing without achieving flow limitation, one should expect to see the following: (i) flow at end-expiration on the flow-time curve, (ii) increased pressure at end-expiratory occlusion on the pressure–time curve, (iii) a linear flow-volume curve, with a truncated flow-volume loop; and (b) in the case of airflow-limitation, the only difference is the presence of a curvilinear (convex toward the volume axis) flow-volume curve.

When PEEPi occurs secondary to mechanisms other than expiratory flow limitation, application of external PEEP produces a further increase in PEEPi and a plateau pressure of the respiratory system, with possible negative hemodynamic

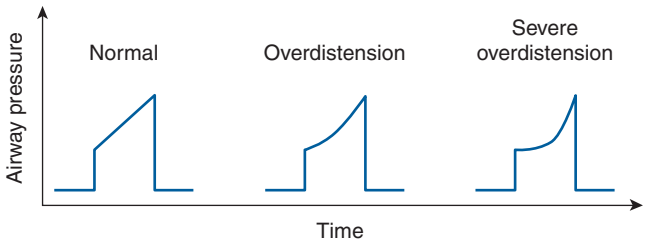

FIGURE 24-6 Schematic of airway pressure versus time curves in a normal subject and in patients with lung overdistension and severe overdistension. The degree of curvature can be related to the severity of overdistension, but is not always present.

effects. Conversely, application of external PEEP in the presence of flow limitation will not affect plateau pressure and hemodynamics, provided it is limited to equal to or less than 75% of PEEPi.

For practical purposes, continuous displays of ventilator waveforms can assist the clinician in detecting and monitoring pathophysiologic changes, optimize ventilator settings and treatment, determine effectiveness of ventilator settings, and minimize the risk of ventilator-induced complications. Flow and volume waveforms can be employed to directly estimate end-expiratory volume above passive FRC. The volume expired during a prolonged apnea (up to 40 seconds) may be used to determine the volume of gas above FRC. The total exhaled volume is measured from the end of inspiration until there is no visually detectable change in volume.

Monitoring of pressure–time curves can also be helpful in avoiding excessive hyperinflation (Fig. 24-6). In the case of normal inflation, the pressure–time curve during inflation at constant flow in VCV is linear (i.e., pressure increases in proportion to an increase in volume); in the case of overdistension, a convexity toward the time axis appears (i.e., a progressive increase in pressure that is not proportional to increase in volume).

In summary, the monitoring of pressure, flow, and volume over time associated with end-inspiratory and end-expiratory occlusion maneuvers is essential to better define the presence and causes of dynamic hyperinflation.

Gas Exchange. Inefficient gas exchange is signaled by $\dot{V}_A/\dot{Q}$ hypercapnia or hypoxemia. Hypoxemia of variable degree, caused mainly by mismatching (mainly venous admixture), is almost invariably present in COPD and during asthma attacks. Hypercapnia reflects both $\dot{V}_A/\dot{Q}$ mismatching and alveolar hypoventilation, the latter resulting from both respiratory muscle dysfunction and increased ventilatory requirements. During asthma attacks, hypoxia is generally associated with hypocapnia, and increasing values of Pa_{CO_2} are a warning sign of potential fatality secondary to respiratory arrest.

Cardiovascular Abnormalities. Cardiovascular dysfunction is usually related to acute and chronic blood-gas derangement, dynamic hyperinflation, and increased right-ventricular afterload. Increases in pulmonary artery pressures may result from hypoxic pulmonary vasoconstriction mainly in hypoxemic patients with COPD, and also from low-grade systemic inflammation as evidenced by elevated levels of serum C-reactive protein and tumor necrosis factor. Left-heart failure may also develop in hyperinflated patients with COPD because of an altered mechanical interaction between heart and lung. Nevertheless, the association between COPD and left-ventricular dysfunction may be simply reflect old age and exposure to common risk factors, such as smoking habit.

Postoperative Pulmonary Complications. Patients with COPD are at increased risk for postoperative atelectasis, pneumonia, and even death.[199] In patients with severe COPD undergoing noncardiothoracic surgery, the incidence of postoperative pulmonary complications is approximately 37% (excluding atelectasis) and the 2-year mortality is approximately 47%. A recent study, however, in cardiothoracic surgery reported that COPD is not a major independent risk factor for postoperative pulmonary complications.[200]

Risk Stratification. In a general surgical population, independent risk factors for postoperative pulmonary complications in adults with respiratory disease include advanced age, preexisting pulmonary disease, cigarette smoking, congestive heart failure, functional dependence (e.g., the inability to perform activities of daily living), and site of surgery (with highest risks for thoracic and abdominal surgery).[102] Epstein et al[201] developed a cardiopulmonary risk index that is a combination of the modified Goldman cardiac index and pulmonary risk factors [obesity, productive cough, wheezing, tobacco use, forced expiratory volume in 1 second (FEV_1)-to-forced vital capacity (FVC) ratio of Pa_{CO_2} >45 mm Hg]. Those with a cardiopulmonary risk index of equal to or greater than 4 were twenty-two times more likely to develop a complication following major thoracic surgery.

In patients with severe COPD, Wong et al. [199] estimated the incidence of five different postoperative complications: death, pneumonia, prolonged intubation, refractory bronchospasm, and prolonged ICU stay. From multivariate analysis, they concluded that American Society for Anesthetists (ASA) physical status equal to or greater than IV, Shapiro score equal to or greater than 5, and FEV_1 were preoperative risk factors, and emergency operation, abdominal incision, anesthesia duration longer than 2 hours, and general anesthesia were intraoperative risk factors. Risk stratification of COPD patients by ASA physical status was associated with higher incidence of postoperative pneumonia, prolonged postoperative intubation, and higher mortality. Additional risk factors include the severity of COPD, assessed by spirometry and 6-minute walk distance results, and body mass index.

More recently the use of dedicated scores has been proposed. A surgical lung injury prediction model to predict risk of postoperative ALI based on readily available preoperative risk factors has been developed. It includes

high-risk cardiac, vascular, or thoracic surgery, diabetes mellitus, COPD, gastroesophageal reflux disease, and alcohol abuse.[117]

Other investigators[99] did not identify COPD or bronchial asthma as individual risk factors for postoperative pulmonary complications after general anesthesia for thoracic or nonthoracic surgery. Seven independent risk factors were identified: low preoperative arterial oxygen saturation (SaO_2), acute respiratory infection during the previous month, age, preoperative anemia, upper abdominal or intrathoracic surgery, surgical duration of at least 2 hours, and emergency surgery. The factor capturing a low preoperative SaO_2 likely included patients with severe COPD.

We believe that the use of scores for better predicting postoperative pulmonary complications should be further developed to better identify patients at risk for complication in the intraoperative and postoperative period.[202]

Preoperative Preparation. Preoperative management involves assessment of general physical status (pulmonary, cardiac, neurologic diseases) and treatment of any reversible signs or symptoms. As a general principle, pulmonary function should be optimized preoperatively by standard treatments. In asthmatic patients, good preoperative control of symptoms and lung function should be achieved by bronchodilator and anti-inflammatory treatment (combination treatment with long-acting β_2-agonists and inhaled corticosteroids), also including leukotriene-receptor antagonists, to reduce the incidence of life-threatening perioperative complications possibly linked to airway hyperresponsiveness.[198] Additional preoperative management includes adequate control of secretions and infection and sound control of anesthesia.

Spirometry is generally used as a guide for both diagnosis and treatments of asthma and COPD, although a chest radiograph may be occasionally necessary for diagnosis.[203] Arterial blood-gas measurements are performed as needed. Indicators for arterial blood-gas analysis include spirometric values of FEV_1 and FVC less than 50% of predicted, FEV_1 less than 1 L, or FVC less than 1.5 L. Pa_{CO_2} greater than 45 mm Hg is a strong risk factor for postoperative pulmonary complications in patients with COPD; Pa_{CO_2} values greater than 50 mm Hg are likely to require postoperative mechanical ventilation following major surgery, whereas preoperative values equal to or less than 45 mm Hg can be usually managed by controlled oxygen therapy and careful monitoring of arterial blood gases.[204,205] Postponing elective surgery should be considered if improvement of pulmonary function can be expected to occur over extended time periods. Preoperative education regarding postoperative deep breathing, incentive spirometry, or CPAP may improve the final outcome.

General Anesthesia in Patients with Chronic Obstructive Pulmonary Disease. Patients with chronic lung hyperinflation may actually be less prone to develop computed tomography scan evidence of dependent atelectasis during anesthesia and paralysis. In awake patients with COPD, the $\dot{V}_A/\dot{Q}$ distribution is more heterogeneous than in healthy subjects, showing zones of relatively low $\dot{V}_A$, although with the amount of intrapulmonary shunt is negligible. In addition, computed tomography scanning shows significantly larger cross-sectional thoracic areas than in subjects with healthy lungs. During anaesthesia and paralysis, patients with COPD suffer a further worsening of $\dot{V}_A/\dot{Q}$ mismatch without increase in intrapulmonary shunt. Furthermore, FRC is only minimally reduced,[36] which is in contrast to findings in patients with healthy lungs.[206]

Therefore, general anesthesia with controlled ventilation should be avoided whenever possible in patients with COPD, and regional anesthesia techniques are preferred if there are no contraindications.

Targets for Controlled Mechanical Ventilation. In COPD or bronchial asthma, mechanical ventilation may be difficult for the following reasons: high level of lung hyperinflation; high risk of barotrauma and volutrauma; and hemodynamic instability. Thus, minimizing the magnitude of dynamic hyperinflation during mechanical ventilation is central to the management of asthma and COPD and the following are some strategies that can be adopted:

1. Decreasing minute ventilation by reducing tidal volume, respiratory frequency, with permitted hypercapnia and mild respiratory acidosis.
2. Increasing expiratory time. In patients with asthma or COPD the time required for a complete expiration often requires 3 seconds or more, and ventilator settings that do not allow adequate time for exhalation can lead to or worsen dynamic hyperinflation.[207] An increase in expiratory time can be achieved by increasing inspiratory flows, at the expense of increasing peak dynamic pressures, and avoiding end-inspiratory pause.
3. Reducing expiratory flow resistance through use of bronchodilators or low-density gas mixtures (e.g., 80% helium and 20% O_2), which may help reduce dynamic hyperinflation.

We recommend, whenever possible, to simultaneously apply all of these strategies. As a starting point for ventilating patients with COPD or severe asthma, we recommend that the ventilator be used in the PCV mode, setting the pressure to achieve a tidal volume of 6 to 8 mL/kg, respiratory rate of 11 to 14 breaths/min, and PEEP at 0 to 5 cm H_2O. We recommend the use of these settings with a goal of obtaining a pH generally greater than 7.2 and an inspiratory plateau pressure less than 30 cm H_2O. If plateau pressure is less than 30 cm H_2O cannot be maintained, then the patient must be evaluated for causes of decreased respiratory system compliance or increased resistance (i.e., pneumothorax, misplaced endotracheal tube, pulmonary edema). In absence of one of these findings, efforts to further limit gas trapping must be considered. Administration of sodium bicarbonate to maintain a pH of 7.2 during controlled hypoventilation has been investigated in patients with COPD and/or status asthmaticus; however, no studies have demonstrated any benefit associated with bicarbonate infusion.

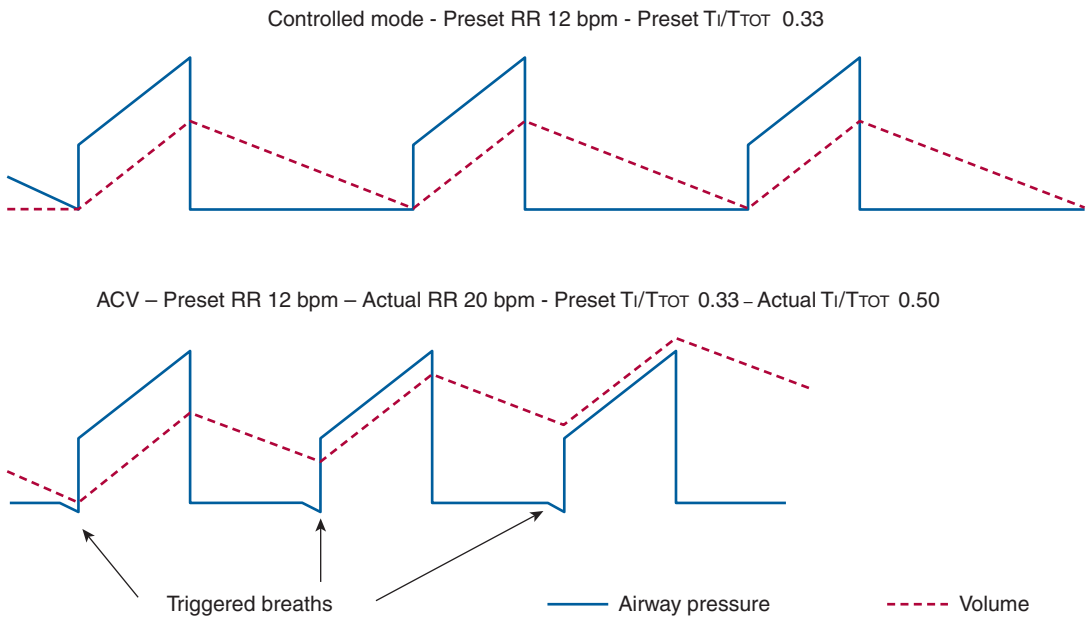

FIGURE 24-7 Schematic of airway pressure and volume versus time curves during mechanical ventilation with controlled (*top*) and assist-control ventilation (*ACV*) in a patient with expiratory flow limitation. Because of the short expiratory time in ACV, dynamic hyperinflation is exacerbated (dashed red line). *ACV*, assist-control ventilation; *RR*, respiratory rate; T_I/T_{TOT}, inspiratory to total respiratory time.

Lung recruitment maneuvers should be cautiously applied in presence of asthma or COPD. Furthermore, particular care should be given to avoid excessive spontaneous breathing during time-cycled ventilation, because the reduction of expiratory time may lead to an increased hyperinflation and PEEPi, as shown schematically in Figure 24-7. For these reasons, ACV should not be routinely used in asthma or COPD patients in the awakening phase from general anaesthesia, while pressure-support ventilation and others modes of mechanical ventilation not cycled by time may be useful.

THE IMPORTANT UNKNOWNS

Approximately 234 million major surgical procedures per year are performed under general anesthesia worldwide, and 1.3 million patients develop complications that result in up to 315,000 in-hospital deaths.[97] The incidence of pulmonary complications following surgery seems to be situated between 2.7%[98] and 56%,[101] depending on individual predisposing factors, as well as type and duration of surgery.[99] Once a patient presents with a pulmonary complication, the length of hospital stay and probability of death increases significantly. It is unknown, however, whether mechanical ventilation management during general anesthesia influences patient outcome, and current data on this issue are conflicting. Given that most patients undergoing general anesthesia have no significant lung disease, it is important to identify by appropriate scores patients who will be at higher at risk of developing pulmonary complications.[202] The importance of selecting appropriate settings of mechanical ventilation in the intraoperative phase is unclear, and argumentation is based on physiologic and pathophysiologic conjectures and laboratory experience, rather than outcome evidence.

THE FUTURE

As discussed above, there is an increased interest in different modes of mechanical ventilation during general anesthesia. We believe that ventilator modes and strategies that have been available only for critically ill patients will become available in the operating room, including modes of assisted spontaneous breathing and high-frequency ventilation. Moreover, strategies to ventilate the lungs during general anesthesia in different conditions, including open-abdominal surgery, one-lung anesthesia, patients with obesity, asthma, COPD or in combination, and laparoscopic surgery, among others, will be investigated and their importance in the development of pulmonary complications better defined. For this purpose, multicenter clinical trials on intraoperative mechanical ventilation will be necessary.

SUMMARY AND CONCLUSIONS

Mechanical ventilation is becoming increasingly complex not only in the intraoperative phase, but throughout the whole perioperative period. Accordingly, ventilator modes that have been used almost exclusively in the ICU can now be found on anesthesia ventilators. Such development is guided by the needs to provide adequate ventilator support

in a variety of situations, including open and laparoscopic surgery, diagnostic procedures of the airways, one-lung anesthesia, presence of expiratory flow limitation (e.g., asthma, COPD), and also morbid obesity. Also, strategies of protective ventilation with low V_T and higher levels of PEEP combined with lung-recruitment maneuvers, as well as invasive and noninvasive assisted spontaneous ventilation, are becoming more popular in general anesthesia, even in the absence of ALI. Whether such protective ventilation or the use of advanced modes of ventilator support during general anesthesia will contribute to reduce the incidence of pulmonary complications has yet to be determined.

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25

INDEPENDENT LUNG VENTILATION

David V. Tuxen

Independent lung ventilation (ILV) was first used in thoracic surgery and the intubation devices were developed for this purpose. Gale and Waters first reported ILV in 1931, by passing a single-lumen endobronchial tube into the main bronchus of the dependent nonoperative lung for ventilation and exclusion of purulent secretion (if present) from the operative lung. In 1936, Magill[1] reported endobronchial placement of a suction catheter with a balloon to occlude the operative bronchus and tracheal placement of an ETT to ventilate the nonoperative lung. In 1947, Moody[2] encased the endobronchial balloon with metal studs to reduce the risk of balloon dislodgment.

The first double-lumen tube (DLT), enabling independent ventilation of both lungs, was reported by Carlens[3] in 1949. Thus, tube was similar to current left DLTs, but had a rubber "hook" to engage the carina for accurate placement. Although a major advance, this tube caused trauma and was unsuitable for left pneumonectomy. The first right DLT, which did not occlude the right upper lobe bronchus, was not reported until 1960 by White.[4] In 1962, Robertshaw[5] reported right and left DLTs, which served as the prototype of today's DLTs. Current DLTs have replaced red rubber with polyvinyl chloride (PVC) to reduce mucosal injury and improve malleability and airflow (Fig. 25-1).

For many years, DLTs and ILV were used entirely for thoracic surgery.[2,5,6] In 1976, Glass and Trew[7,8] and their coworkers reported ILV for nonsurgical purposes: respiratory insufficiency from unilateral lung disease. Since then, application of ILV has broadened to a wide range of conditions (Table 25-1) employing a variety of techniques. Institutions specializing in conditions commonly requiring ILV (such as single lung transplantation or alveolar proteinosis), ILV may be used in approximately 0.5% of all mechanically ventilated patients.[9,10] Although most intensive care units use ILV in fewer than one in 1000 patients requiring mechanical ventilation, it can be a lifesaving measure in specific conditions, making maintenance of suitable equipment and knowledge of its use required.

ILV is infrequently and often urgently required when conventional mechanical ventilation is not a viable alternative. As a result, there have been no randomized controlled trials of ILV in patients and current evidence is based almost entirely on animal models, case reports, and case series with before and after analyses.

BASIC PRINCIPLES OF INDEPENDENT LUNG VENTILATION

All the indications for ILV (see Table 25-1) are based on one or two fundamental requirements.

1. *The need to protect one lung from harmful effects of fluid in the other lung* (blood, purulent or malignant secretions, lavage fluid). Placing the fluid-filled lung in the dependent position (lateral decubitus) minimizes the risk of unwanted fluid entering the other lung but also maximizes hypoxia[11] by maximizing blood diversion to the less-functional lung. Placing the fluid-filled lung in the nondependent position improves oxygen saturation

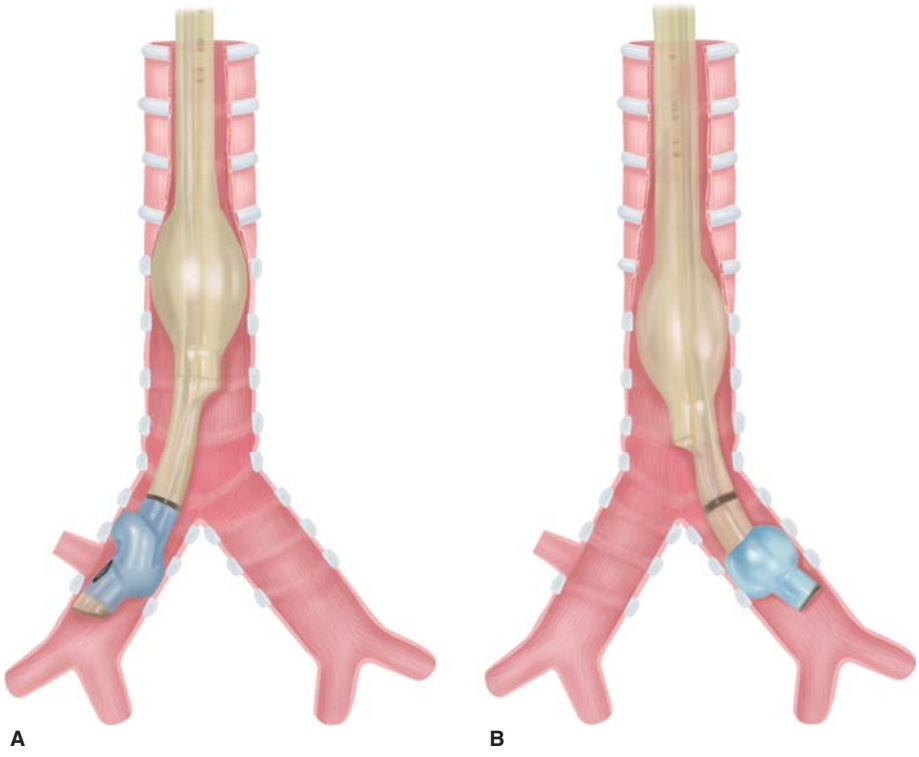

FIGURE 25-1 (**A**) Right and (**B**) left polyvinyl chloride (PVC) (Mallinckrodt) double-lumen tubes (DLT) shown against a schematic of the trachea and major airways.

(SaO_2), but the risk from fluid spillage in this position is unacceptably high.[11] The supine position is usually the best compromise, except during thoracic surgery, where the operative lung must be in the uppermost position.

2. *The need to isolate the ventilatory patterns to each lung.* In each case, the ventilatory pattern for one lung has disadvantageous effects if applied to both lungs. This includes one-lung ventilation (OLV; e.g., thoracic surgery, whole-lung lavage), ventilation to each lung differing in only a single variable (e.g., positive end-expiratory pressure [PEEP]), or ventilation requirements differing in every variable (e.g., single-lung transplant for obstructive airways diseases), or the need to prevent air loss from one lung (e.g., massive air leak).

If OLV is required, a bronchial blocker and endobronchial tube or a DLT may be used. If ILV is required, then a DLT is usually used, although some bronchial blockers can allow limited ventilation such as continuous positive airway pressure (CPAP) or jet ventilation.

TABLE 25-1: POLYVINYL CHLORIDE DOUBLE-LUMEN TUBES: CHOICE OF SIZE

Size (French)	OD (mm)	Tracheal ID (mm)	Bronchial ID (mm)	Use	Manufacturer[a]
26	8.7	3.5	3.5		Rüsch
28	9.3	3.1	3.2	Children weighing <40 kg	Mallinckrodt
32	10.7	3.5	3.4		Sheridan
35	11.7	4.5	4.3	Children weighing >40 kg	Mallinckrodt
37	12.3	4.7	4.5	Small adult	Mallinckrodt
39	13.0	4.9	4.9	Medium adults, usual female size	Mallinckrodt
41	13.7	5.4	5.4	Large adult, usual male size	Mallinckrodt

Abbreviations: *ID*, internal diameter; *OD*, outside diameter.

[a]Rüsch: Duluth, GA; Sheridan: Argyle, NY; Mallinckrodt: St. Louis, MO.

Adapted, with permission, from Campos JH.[267]

Irrespective of technique, tube or blocker position is usually checked using fiberoptic bronchoscopy immediately after instigation, and lung isolation is leak tested. This is important for all indications for ILV but is most critical where protection from secretions is required.

INDEPENDENT LUNG VENTILATION TECHNIQUES

Lung Separation

ILV must be preceded by the placement of a DLT or alternate lung isolation device. These must be introduced, correctly positioned, and then tested to ensure isolation of lung ventilation.

Compared with red-rubber DLTs,[3,4,12] PVC-type DLTs (see Fig. 25-1, e.g., Mallinckrodt, Sheridan, Rusch, Concord, Portex, Marraro) are more flexible, have better internal–external diameter[10] ratios, better gas-flow characteristics, easier suction and bronchoscopy access,[13] allow airway seal with lower cuff pressures,[14] are less irritating to respiratory mucosa, have a lower risk of trauma, and are easier and quicker to position.[15] These characteristics make PVC types the DLTs of choice, although airway injury from PVC DLTs may still occur.[16,17]

For most indications, a left DLT (see Fig. 25-1) should be used because placement is easier than for a right DLT, which has a high risk of right upper-lobe occlusion.[18] A right DLT (see Fig. 25-1) is required for thoracic surgical procedures that include the left main bronchus (left pneumonectomy, left main bronchial lesions, stenosis, or rupture), thoracic aortic aneurysm repair, or anatomic abnormalities that prevent satisfactory access to the left main bronchus.[19–21] A right DLT is also required for ILV with a recent left single lung transplantation to avoid injury to the anastomosis and distal airway. To minimize airflow resistance and maximize endobronchial access, the largest DLT that will not cause laryngeal or airway injury should be chosen (see Table 25-1).

PVC DLTs are usually introduced with the endobronchial curvature angled anteriorly and a rigid stylet in situ to facilitate the passage of the tip through the vocal cords. Once through the cords, the stylet is usually removed and the DLT is rotated through 90 degrees so that the endobronchial curvature is directed toward the appropriate side. The tube is then advanced until an increase in resistance is detected. In a randomized trial of sixty patients receiving a DLT for thoracic surgery, Lieberman et al[22] compared removal of the stylet (as above) and leaving the stylet in situ until placement was complete; the latter increased the correct placement rate from 17% to 60%.

DLT tube position and function must then be confirmed by one or more of three techniques:

1. **Auscultation.** Following cuff inflation, the tracheal port should be clamped and the bronchial port ventilated.[19] Bilateral or contralateral breath sounds indicate placement is too proximal and a need to reposition the DLT (Fig. 25-2A), whereas breath sounds heard only on the correct side indicate correct placement (see Fig. 25-1). Difficulty with ventilation should be resolved by deflating the bronchial cuff: bilateral breath sounds indicate that placement is too proximal, whereas breath sounds heard only on the side of the endobronchial tube indicate that placement is too distal (Fig. 25-2B). Lung auscultation should always include both upper and lower lobes, to ensure correct placement of the endobronchial port within the bronchus, especially with a right DLT where the right upper lobe is easily occluded.
2. **Bronchoscopy.** Following DLT insertion, a small fiberoptic bronchoscope may be passed through the tracheal lumen to confirm position of the tracheal port and that the endobronchial tube is in the correct position.[19,23] The endobronchial cuff should be visible just distal to the carina. Subsequent insertion of the bronchoscope down the endobronchial lumen may be used to confirm that endobronchial placement is not too distal and that, with right DLTs, the right upper-lobe bronchus is over the corresponding fenestration. Although not essential for DLT placement, bronchoscopy reliably confirms accurate placement and should be used routinely. It has an advantage with anatomic variations and in detecting partial airway occlusions.[17]
3. **Leak test.** While ventilating one lung, a connection to the second airway can be placed under water. Any bubbling indicates air leak from the ventilated lung to the opposite side. Such leaks may not be detected by auscultation or bronchoscopy and may be important, particularly when one of the goals is to protect one lung against fluid (whole-lung lavage, blood, or purulent secretions) from the other lung. Bubbling may indicate the need for tube repositioning or higher bronchial-cuff inflation.

Chest radiography may be used to visualize DLT position, but is insufficient to verify critical tube placement or functional isolation.

DLTs may be connected to a single ventilator (e.g., for hemoptysis or at the beginning and end of whole-lung lavage; Fig. 25-3A) or connected to two separate ventilators (see Fig. 25-3B).

Bronchial blocking techniques and selective endobronchial intubation are alternatives to a DLT. The right or left main bronchus may be blocked by placement of a balloon-tipped catheter into that bronchus. This allows OLV and is suitable for thoracic surgery, bleeding, or fistula control. The catheter (Arndt endobronchial blocker, Magill blocker, Cohen Flexitip Endobronchial Blocker, Fogarty or Foley catheter)[24–28] may be placed outside or within a standard cuffed endotracheal tube (ETT) lumen or passed down a specially designed second small lumen in the ETT (Univent tube).[29–31] A Univent tube (Fig. 25-4) has a coudé-tipped bronchial blocker that allows blind guidance of the blocker into the desired bronchus with auscultatory confirmation of correct positioning. Bronchoscopic confirmation of best

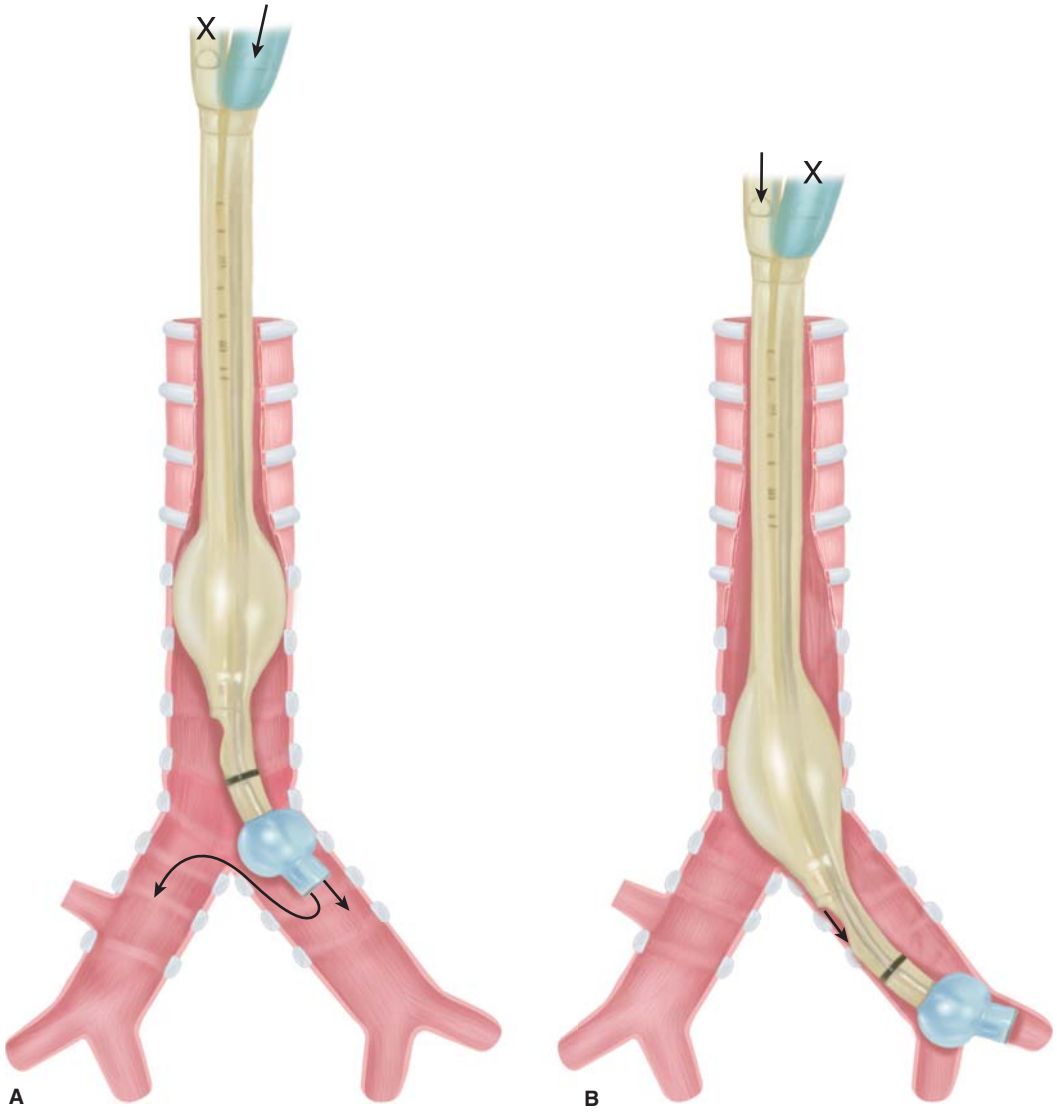

FIGURE 25-2 Flow patterns that may occur during auscultatory verification of a left DLT position (**A**) when DLT is insufficiently inserted and the left lumen is ventilated (right lumen clamped) and (**B**) when DLT is inserted too far and the right lumen is ventilated (left lumen clamped).

position within the airway, however, is still recommended. In addition, the Univent's axial-blocker shaft has a lumen that allows irrigation, suction, O_2 insufflation, CPAP, and high-frequency ventilation.[29] The Arndt endobronchial blocker[24–26] (Fig. 25-5) requires bronchoscopic guidance for placement. The kit comes with an ETT adaptor that allows access for mechanical ventilation, the blocker, and the bronchoscope through separate ports (Fig. 25-5). The bronchoscope is passed into the airway that requires blocking, and the blocker is then guided into that airway via a snare over the bronchoscope (Fig. 25-5A). The bronchoscope then is withdrawn, the balloon is inflated, and its position is confirmed by bronchoscopy before withdrawal (Fig. 25-5B). This has the advantage of being performed via the ETT in situ, thereby avoiding reintubation, provided that the ETT is sufficiently large to admit both the blocker and the available bronchoscope. The Cohen Flexitip Endobronchial Blocker[28] has a flexible tip that can be guided under bronchoscopy but independently of the bronchoscope (Fig. 25-6).

Techniques for Independent Lung Ventilation

A variety of techniques have been reported.

SYNCHRONIZED INDEPENDENT LUNG VENTILATION

Synchronized independent lung ventilation (SILV) consists of synchronous initiation of inspiration into each lung. Each lung must necessarily have the same respiratory

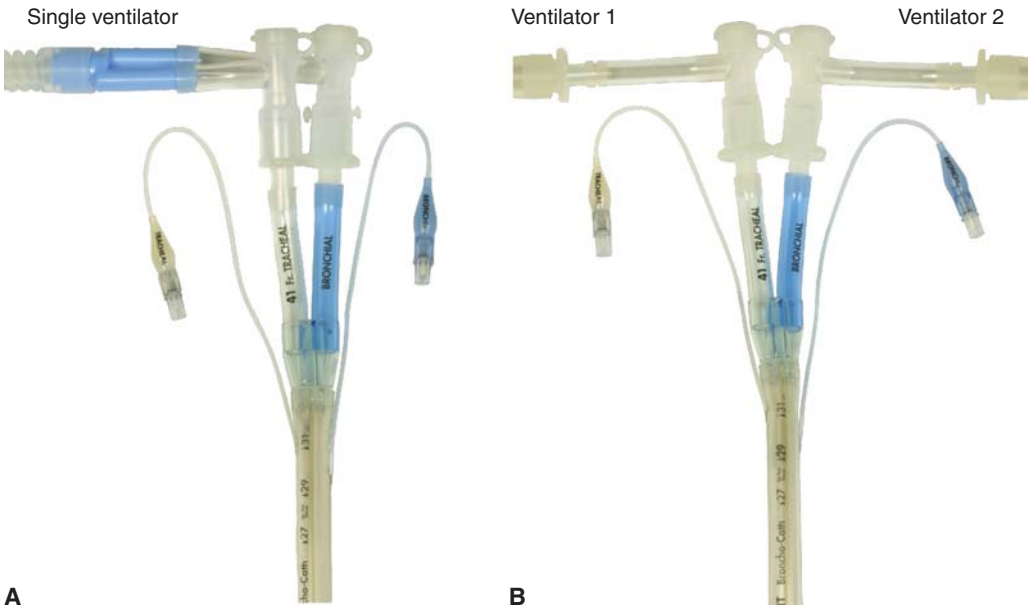

FIGURE 25-3 **A.** Both lumens of a double-lumen tube connected to a single ventilator airway. **B.** Each lumen of a double-lumen tube connected to separate ventilators.

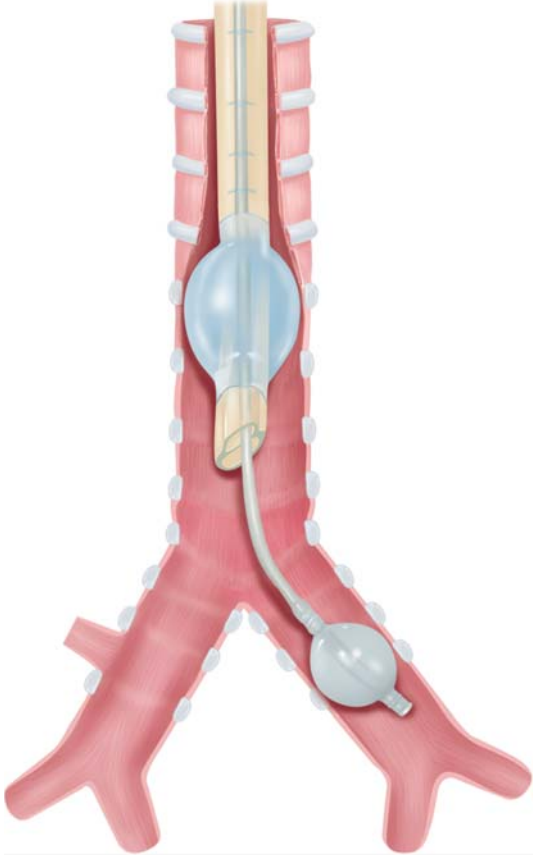

FIGURE 25-4 The Univent tube with the balloon inflated in the left main bronchus.

rate, but may have different tidal volume (V_T), PEEP, and inspiratory flow. SILV may be achieved by a variety of techniques.

1. *Two ventilators of the same type linked to cycle synchronously*. This may be achieved by electronically "slaving" the rate control of a second ventilator to a primary ("master") ventilator,[18,32–40] by electronically synchronizing both to an external control device,[41,42] or by simultaneously resetting the respiratory cycle on paired ventilators and relying on accurate internal timing to maintain synchronization.[43,44] These forms of SILV allow difference in all variables apart from rate—different V_T, PEEP, and inspiratory flow, and hence different inspiratory-to-expiratory time (T_I/T_E) combinations. SILV with two ventilators synchronized 180 degrees out of phase[45,46] has been successful in animals, but appears to have no advantages over other forms of ILV and has not been reported in humans.
2. *A single ventilator linked to a twin circuit with variable resistances in each inspiratory line*[47–49] can create different flows to each lung. The V_T received by each lung will then be determined by both the resistance in the circuit and the impedance in the lung and must be independently measured in each circuit and resistance adjusted accordingly. An alternative to this is flow controllers in both inspiratory lines[50,51] resulting in a fixed V_T to each lung determined by the set flow and inspiratory time and independent of lung impedance. Separate PEEP in each circuit was achieved by expiratory flow controllers. This method allows different V_T and PEEP to each lung, but necessarily must have the same T_I, T_E, and rate.

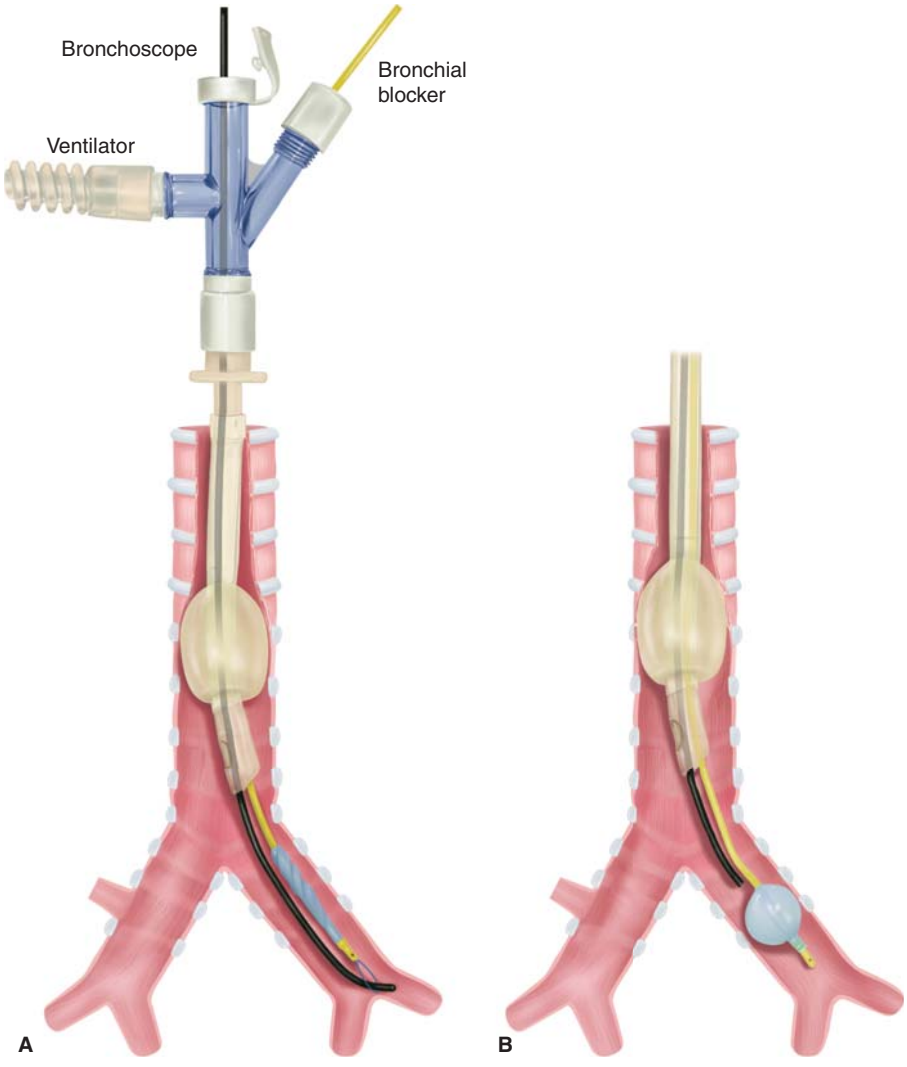

FIGURE 25-5 The Arndt endobronchial blocker shown (**A**) during bronchoscope guidance into the left main bronchus and (**B**) after partial bronchoscope withdrawal and balloon inflation, with the bronchoscope remaining to check balloon position.

3. *A single ventilator linked to two circuits, each with a separate PEEP valve or other PEEP-generating device.*[52,53] This arrangement allows different PEEP to each lung. The division of V_T between the lungs is not controlled independently, being determined by both the relative inherent impedance of each lung and the effect of PEEP on that impedance.
4. *A single ventilator linked to two circuits with no attempt to influence the distribution of ventilation.*[13] This method generally is used during selective airway protection. The division of V_T between the two lungs is determined solely by their relative impedance.

While many indications for ILV are suited to having the same ventilator rate to each lung, there is usually no particular benefit for exact coordination of two ventilators. The only exception may be the uncommon circumstance where patient-triggered ventilation is attempted.

ASYNCHRONOUS INDEPENDENT LUNG VENTILATION

Asynchronous independent lung ventilation (AILV) consists of completely independent ventilator techniques applied to each lung. It requires two separate ventilation devices. Options include:

1. *Controlled* (CMV) *or intermittent mechanical ventilation to both lungs.*[9,54–62]
2. *CMV or intermittent mechanical ventilation to one lung and high-frequency jet ventilation* (HFJV) *to the other.*[57,63–66]
3. *CMV or intermittent mechanical ventilation to one lung and CPAP to the other.*[7,57,58,67]
4. *High-frequency oscillatory ventilation to both lungs.*[68]

AILV permits different rate, V_T, inspiratory flow, and PEEP to each lung. Lack of synchronization between the two lungs offers the greatest flexibility and appears to hold

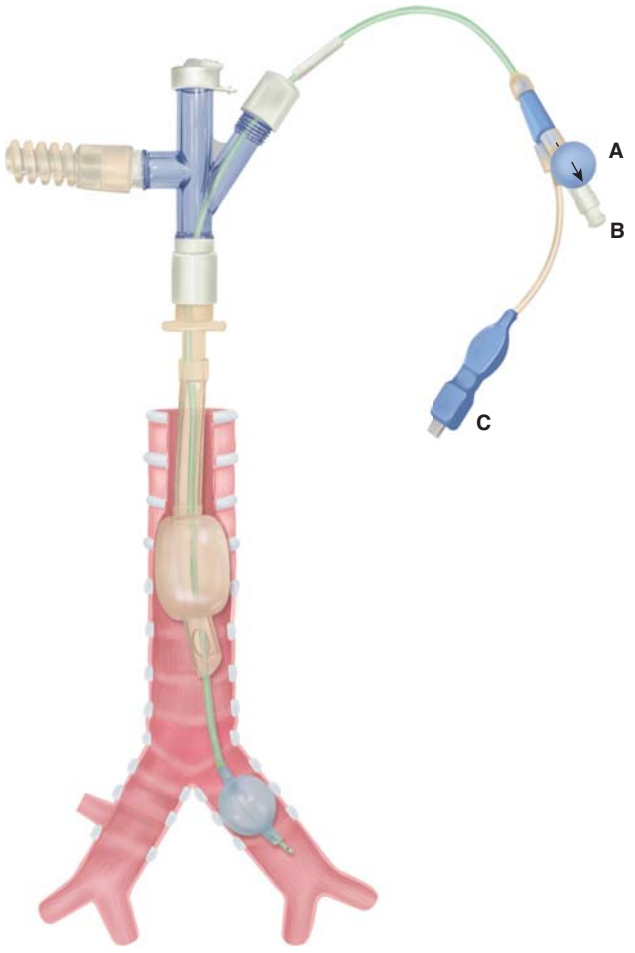

FIGURE 26-6 The Cohen Flexitip Endobronchial Blocker shown with its endotracheal tube attachment. **A** is the knob that controls and locks the tip flexion. **B** is a Luer lock port to the lumen of the Cohen blocker. **C** is the valved insufflation port for the blocker balloon.

no disadvantage and a number of advantages compared with SILV.[55,61]

ONE-LUNG VENTILATION

With OLV, one lung is ventilated mechanically while the other is either occluded or open to atmosphere with an option of spontaneous ventilation. OLV is used mainly in thoracic surgery to keep the lung collapsed and immobile. It also may be used in bronchopleural fistula (BPF) to prevent air leak or for selective airway protection if secretions from the affected lung prevent any useful ventilation (e.g., massive hemoptysis). Options include:

1. *DLT intubation*[11,20,21,69–71] or in infants, two separate uncuffed tracheal tubes of different lengths attached longitudinally (Marraro DLT)[69] with CMV applied to only one lumen.
2. *Endotracheal intubation with a bronchial blocker inserted into one of the major bronchi.* The occlusive balloon excludes that lung from mechanical ventilation and the blocker lumen allows deflation (and inflation) of that lung.[1,21,24–26,30]
3. *Endobronchial intubation with a single lumen tube* (e.g., Mackintosh-Leatherdale left endobronchial tube and Gordon Green right endobronchial tube).[21]

SPONTANEOUS VENTILATION

Spontaneous ventilation with a DLT and differential CPAP applied to each lung was first reported by Venus et al.[72] It has been used in spontaneously breathing patients with unilateral pulmonary contusion and atelectasis with good results.[72,73] It is not recommended because of increased work of breathing through a long narrow tube.

APPLICATIONS OF INDEPENDENT LUNG VENTILATION

Applications of ILV (Table 25-2) fall into five categories.

TABLE 25-2: INDICATIONS FOR INDEPENDENT LUNG VENTILATION

Thoracic Surgery
Pneumonectomy
Some lobectomies
Thoracic aortic surgery
Thoracoscopy
Some esophageal surgery and diaphragmatic surgery
Selective airway protection
Secretions (tuberculosis, bronchiectasis, abscess)
Whole-lung lavage
Massive hemoptysis
Bronchial repair protection
Bronchopleural fistula
Asymmetrical lung disease
Unilateral parenchymal injury
Aspiration
Pulmonary contusion
Pneumonia
Massive pulmonary embolism
Reperfusion edema
Asymmetrical acute respiratory distress syndrome
Asymmetrical pulmonary edema
Atelectasis
Unilateral airflow obstruction
Single lung transplantation for chronic airway obstruction
Unilateral bronchospasm
Severe bilateral lung disease
Acute respiratory distress syndrome
Aspiration
Pneumonia

Thoracic Surgery

A number of thoracic surgical procedures require OLV, usually in the lateral position. Table 25-1 lists the common thoracic surgical indications for OLV.[19,21,69] Although OLV is required during surgery, ILV may be required before, and sometimes after, the surgical procedure.[69,74]

OLV may be achieved with a DLT, bronchial blocker, or endobronchial tube. A DLT has the advantage of enabling ILV, which may be important in alleviating hypoxia, but has the disadvantage of high-resistance airways with more difficult suctioning. An ETT with a bronchial blocker has the advantage of a wide-bore, low-resistance endotracheal lumen with better bronchoscopic and suction access, through which either OLV (bronchial blocker inflated) or double-lung ventilation (bronchial blocker deflated) can be delivered.[30] The narrow lumen in some bronchial blockers can enable lung inflation, deflation, CPAP, or HFJV, but does not allow conventional ILV. OLV may be delivered to either lung, but repositioning of the bronchial blocker is required.[30] When the blocker is an integral part of the ETT (Univent tube, see Fig. 25-4),[29–31] it is easier to insert and it maintains a more stable position compared with an intraluminal or extraluminal blocker that is more subject to movement and dislodgment, especially during suctioning, bronchoscopy, or patient movement.[30] With any bronchial blocker, bronchoscopy is easier and required less frequently.[19,30] A disadvantage is that the inflated blocking balloon near the site of intended bronchial surgery (e.g., pneumonectomy, single lung transplantation) may hamper that procedure, and a DLT placed in the opposite lung may be technically easier.

EFFECTS OF INDEPENDENT LUNG VENTILATION IN THE LATERAL DECUBITUS POSITION

Irrespective of patient position, gravity-induced differences in ventilation and perfusion occur vertically within each lung: between the bases and apices in the erect position, and between the dependent and nondependent lung regions in the supine position.

When a patient is in the erect or supine position, gravitational differences in ventilation and perfusion occur vertically within each lung. In the lateral decubitus position, these gravitational differences occur between the two lungs.[71,75] Up to two-thirds of perfusion shifts to the dependent lung.[75–77] During *spontaneous ventilation,* a smaller increase in ventilation also occurs in the dependent lung in the lateral position, thereby reducing ventilation–perfusion mismatch.[71,75] When the patient is anesthetized and *mechanically ventilated* in the lateral decubitus position, however, reduced diaphragmatic activity allows the weight of abdominal contents to retard expansion of the dependent lung,[71,75] and most ventilation is diverted to the nondependent lung. In this situation, the nondependent lung may receive up to two-thirds of ventilation.[36,40,76] Opening the nondependent thorax further reduces ventilation to the dependent lung by facilitating expansion of the nondependent lung.[77,78] The net effect of these changes is overperfusion relative to ventilation (or shunting) in the dependent lung and overventilation relative to perfusion (or dead space ventilation) in the nondependent lung with adverse effects on gas exchange.

Left thoracotomy achieves a higher partial pressure of arterial oxygen (Pa_{O_2}) during OLV than does right thoracotomy because the left lung normally receives 10% less cardiac output than the right lung.[70] The presence of chronic airway obstruction (CAO) is associated with better Pa_{O_2} during OLV possibly because of dynamic hyperinflation in the dependent lung.[70] Pa_{O_2} during double-lung ventilation is also predictive of Pa_{O_2} during OLV.

Some forms of ILV cannot be applied when the nondependent lung is immobile, deflated, or removed, yet ILV has been shown to improve many of these abnormalities. Application of PEEP to both lungs improves dependent-lung ventilation and oxygenation.[76] SILV (see "Techniques for Independent Lung Ventilation" above) with delivery of equal V_T to both lungs,[39] or PEEP to the dependent lung,[37,38,40,79,80] or both,[38] improves oxygenation when compared with double-lung ventilation or generalized PEEP.

When OLV is undertaken and the nondependent lung is excluded from ventilation, the reduction in ventilation to the dependent lung is eliminated, but all perfusion through the nondependent lung constitutes a shunt. In this situation, the amount of perfusion of the nondependent lung is a major determinant of hypoxia. Hypoxic vasoconstriction (not opposed by anesthetic agents), lung collapse, and surgical occlusion of blood flow (pneumonectomy) to the nondependent lung all have the potential to reduce shunt and improve Pa_{O_2} in OLV.

PEEP in the dependent lung may be beneficial by increasing functional residual capacity and improving distribution of ventilation or be detrimental by increasing alveolar pressure and diverting blood flow to the nonventilated lung.[71,81–86] Consequently, PEEP to the dependent lung during OLV may improve Pa_{O_2},[81,86] decrease Pa_{O_2},[81,82,86] or cause no change.[84–86] During OLV, Cohen et al[79] compared PEEP (10 cm H_2O) to the dependent lung, CPAP (10 cm H_2O) to the nondependent lung, and both. All three maneuvers increased Pa_{O_2} compared with OLV alone. PEEP caused the smallest (nonsignificant) increase in Pa_{O_2}. CPAP and PEEP + CPAP caused larger (significant) increases in Pa_{O_2}, whereas PEEP + CPAP reduced cardiac output and oxygen (O_2) delivery significantly, which CPAP alone did not. Cohen et al[28] concluded that CPAP alone (to the nondependent lung) had the most beneficial effect by diverting blood flow to the dependent lung without reducing cardiac output. More recently, PEEP has been shown to benefit oxygenation during OLV to the dependent lung during thoracotomy.[87]

Because of these variable effects, it has been recommended that CPAP (5 to 10 cm H_2O) be applied to the nondependent lung, combined with no, low, or high PEEP (5 to 15 cm H_2O) to the dependent lung, depending on patient response.

Although function of the two lungs commonly differs after thoracotomy, conventional mechanical ventilation or spontaneous ventilation are usually resumed after surgery. ILV is required occasionally in the postoperative period for marked asymmetry of lung function with hypoxia,[7,8,55] BPF,[47,58,63,66,88] or following esophagectomy.[74] Pawar et al[69] reported successful use of the Marraro pediatric double-lumen tube[89] (two separate uncuffed tracheal tubes of different lengths attached longitudinally) in seventeen children, ages 1 day to 3 years (2.7 to 12 kg) who required OLV during cardiothoracic surgery. Of these, six children required ILV up to 48 hours postoperatively. All children survived. Ito et al[90] reported ILV with a separate bronchial cannula in each main bronchus, combined with bilateral HFJV, the repair of tracheal stenosis in a 2-year-old infant.

Selective Airway Protection

WHOLE-LUNG LAVAGE

Pulmonary alveolar proteinosis is the most common indication for whole-lung lavage. This condition was first described in 1958,[91] and soon after, bronchopulmonary lavage became established as the main treatment.[92–100]

Pulmonary alveolar proteinosis is most often acquired (90%) but may be congenital or secondary to conditions such as acute silicosis and other inhalational syndromes, immunodeficiency disorders, malignancies, hematopoietic disorders, and lysinuric protein intolerance.[101] It has also been reported following prolonged cotton dust exposure.[102] Recent studies suggest that acquired pulmonary alveolar proteinosis may be caused by deficiency of granulocyte-macrophage colony-stimulating factor,[101,103] and administration of this factor is of value in approximately 50% of patients. Despite these advances, lavage remains the most effective therapy.[101,103]

The clinical course is variable: increasing dyspnea progressing to respiratory insufficiency, static disease with minimal symptoms, asymptomatic disease, and spontaneous resolution in some patients.[101,104] Because the course is variable, the decision to undertake bronchopulmonary lavage is based on disease progression and symptoms.

Whole-lung lavage has been used for asthma,[105,106] chronic bronchitis, and cystic fibrosis,[11,98,105–111] but with doubtful benefit; it is no longer recommended. Radioactive dust inhalation is another indication.[112]

Procedure for Whole-Lung Lavage. To minimize hypoxia during the procedure, the worst lung should be lavaged first. The worst lung can be identified by chest radiograph, ventilation–perfusion scan, or oxygenation[3,113,114] during OLV to each lung before the procedure.

The procedure usually is performed with anesthesia, neuromuscular paralysis,[11,105,115] and a left DLT in the supine position. The supine position is chosen to balance the risk between hypoxia and fluid spillage[11] (see "Basic Principles of Independent Lung Ventilation" above).

Complete lung isolation to prevent spillage of fluid from the lavaged lung into the ventilated lung is essential. Correct DLT position should be established using both bronchoscopy and leak testing (as above) up to plateau pressures of 40 to 50 cm H_2O.[11,19] Both lungs should be preoxygenated with 100% O_2 to maximize gas exchange and eliminate nitrogen, which may prevent full access of lavage fluid to the lung to be lavaged.

Isotonic saline, warmed to body temperature, then should be infused through wide-bore tubing into the lung to be lavaged from a gravitational height 30 cm above the midaxillary line.[11] This infusion pressure of 30 cm H_2O usually results in infusion volumes of 500 to 1000 mL depending on the compliance of the lung. Efflux of fluid may be commenced as soon as fluid influx is complete; the drainage tube is placed below the patient, assisted by head-down posturing, and percussion and vibration of the hemithorax.[11,115] Fluid flow may be achieved using separate clamped inlet and outlet lines or a single line that is elevated for fluid influx and lowered for fluid efflux. Total fluid exchange may range from 10 to 50 L and should be continued until efflux fluid is relatively clear.

When fluid influx into the lavaged lung is complete, the alveolar pressure usually exceeds the pulmonary capillary pressure, minimizing shunt through this lung and maximizing arterial oxygenation at this stage of the procedure.[105,115–118] When the lavaged lung is emptied of fluid, blood flow returns, and significant hypoxemia can occur (Fig. 25-7).[11,105,115–117]

On conclusion of the lavage, double-lung ventilation should be recommenced with the DLT in situ using a single ventilator and a bifurcated circuit. If oxygenation is satisfactory, the patient may be weaned and extubated or reintubated with a regular ETT and later weaned. If oxygenation is unsatisfactory, ILV may need to be recommenced. Up to 1000 mL of saline may be retained in the lavaged lung;[115] although this is absorbed rapidly, lung function may not improve for hours or days. The procedure is repeated on the second lung after an interval of 1 to 3 days.

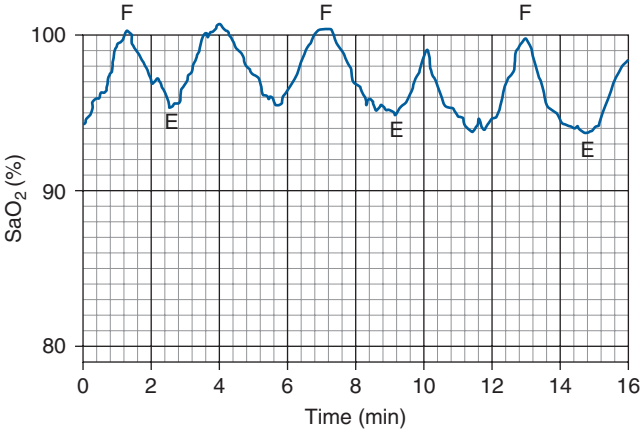

FIGURE 25-7 Variations in arterial oxygen saturation (SaO_2) during the influx (**F**) and efflux (**E**) phases of whole-lung lavage. (Modified, with permission, from Claypool et al.[115])

Leakage of fluid into the ventilated lung may be recognized by desaturation, crepitations, and rhonchi in the ventilated lung; fluid in the tubing to the ventilated lung; or air bubbles in the fluid from the lavaged lung.[11] If this occurs, lavage should be ceased, and the patient should be placed in the lateral decubitus position with the lavaged lung dependent and the head down to facilitate drainage from both lungs. Active suctioning of both lungs should be undertaken. If the leak is only minor and adequate oxygenation is restored, the correct DLT position may be reestablished, lung isolation rechecked, and the procedure continued. With a major leak and failure to restore adequate oxygenation once fluid removal is complete, double-lung ventilation with PEEP should be resumed and further lavage delayed until hypoxia has improved.

Hypoxemia during the procedure is common. Some patients with severe lung disease are too hypoxemic before the procedure to tolerate OLV. Several options exist for such patients. Extracorporeal membrane oxygenation (ECMO) may be instituted before lavaging the first lung.[11,119–123] ECMO may or may not be required for lavage of the second lung, depending on the effect of the first lung lavage on subsequent oxygenation. Cohen et al[121] reported successful lavage of both lungs with ECMO during a single session, avoiding the need for a second procedure. Because of the complexity and limited availability of ECMO, an alternative is to perform limited bronchoalveolar lavage using a fiberoptic bronchoscope,[124,125] with or without an inflatable cuff on the bronchoscope, under local anesthesia. This may be undertaken in a spontaneously breathing patient or during CMV through a single-lumen ETT. Limiting lavage to a lobe or several subsegments necessitates multiple procedures but minimizes hypoxemia. Nadeau et al[126] reported that the combination of inhaled nitric oxide and inflation of a balloon in the right pulmonary artery during right whole-lung lavage improved oxygenation sufficiently to avoid ECMO.

Randomized studies of whole-lung lavage for pulmonary alveolar proteinosis have not been undertaken. Seymour and Presneill[101] analyzed survival of 231 patients in multiple reports; 5-year actuarial survival from diagnosis was 94% ± 2% in patients who underwent whole-lung lavage ($n = 146$) compared with 85% ± 5% for patients who did not ($n = 85$). In fifty-five patients in whom duration of benefit was reported,[101] median duration of benefit from lavage was 15 months; fewer than 20% of patients followed beyond 3 years remained symptom-free. In a series of twenty-one patients followed prospectively after whole-lung lavage, Beccaria et al[127] found that more than 70% remained free from recurrent pulmonary alveolar proteinosis at 7 years. Although whole-lung lavage is labor-intensive, these data suggest that it is worthwhile.

MASSIVE HEMOPTYSIS

Massive hemoptysis carries a high mortality[128–130] and requires prompt intervention. Common causes include tuberculosis, bronchiectasis, lung abscess, mycetoma, pulmonary carcinoma, cystic fibrosis, arteriovenous malformations, and trauma.[104,128,131–133] The source of bleeding is the bronchial arterial system in 90% of patients.[134] Iatrogenic causes are uncommon but include pulmonary artery rupture by a pulmonary artery catheter[128,135,136] and transbronchial lung biopsy. Death results from acute asphyxia and is related to the rate and volume of blood loss and the underlying condition.[13,128,129,137,138] Factors increasing mortality include preexisting pulmonary insufficiency, obtundation from any cause, poor cough, and coagulopathy.[129,137,139,140]

Management consists of general measures, diagnosing the site of bleeding, isolating the bleeding lung, and controlling the bleeding. The patient should be given 100% O_2, placed in the head-down lateral-decubitus position, bleeding side down, clotting studies performed, blood typed, wide-bore intravenous access established, and cough suppressed with an opiate, and resuscitation and suction equipment should be in close proximity. Chest radiography and computed tomography scanning should be done when appropriate.

A number of alternatives exist for the localization, isolation, and control of the bleeding:

1. Fiberoptic bronchoscopy and placement of an endobronchial blocker (Fogarty catheter or Arndt endobronchial blocker) in the bleeding lung or segment should be done.[25,26,141–143] This can be performed in a patient who is not intubated but is easier in one who is. Fiberoptic bronchoscopy is limited by the narrow suction channel and rapid visual loss secondary to occlusion of the lens by blood.[140] Fiberoptic bronchoscopy, however, can allow accurate localization of bleeding,[104,128,140,144,145] catheter placement in a bronchial segment,[128,141,146] and lavage with iced isotonic saline or epinephrine.[128,146]
2. Rigid bronchoscopy has advantages over fiberoptic bronchoscopy when blood loss is massive because of better suction, visual access, and airway control.[137,139,140,144,147,148] It allows easier placement of endobronchial blockers and iced saline or epinephrine lavage. It also allows diathermy, laser therapy, and cryotherapy,[130] as well as placement of endobronchial tampons soaked in vasoconstrictor drugs.[137] As use of embolization increases, rigid bronchoscopy is required less, although it still has a place.[144,147]
3. Endotracheal intubation may be required where bleeding is sufficient to compromise oxygenation, particularly if mentation is depressed or cough is inadequate. If bleeding is so rapid that acute asphyxia arrest is imminent despite intubation,[128] the ETT can be advanced beyond the carina (usually into the right main bronchus) and OLV commenced.[128,149] If blood does not flow out of the ETT (implying blood loss from the contralateral side), the cuff is inflated and the ETT left in situ. If bleeding continues through the ETT, a Fogarty or Foley catheter is passed, the main bronchus is occluded, and the ETT is withdrawn to the trachea to ventilate the contralateral side.
4. Selective intubation is performed with a small (6 to 7 mm) ETT, with or without fiberoptic bronchoscope guidance, or a selective left or right endobronchial tube.[128,137] Selective intubation must be preceded by accurate bronchoscopic localization of bleeding because it excludes one lung from ventilation. Selective intubation has the

advantage of reliable protection of the nonbleeding lung[137,140] but the disadvantage of permitting OLV only and excluding the bleeding lung from endobronchial procedures and suctioning. Bleeding then must be controlled by tamponade, bronchial angiography, and embolization or surgery.

5. DLT insertion is an alternative that isolates the lungs but preserves access to both. In the past, DLTs were not recommended as an early alternative[128,137] to control bleeding. Problems included difficulties with insertion under adverse circumstances, requirement for an experienced operator, difficulties with suction and bronchoscopy access, and easy blockage of DLT lumen with clot. More recently, use of PVC DLTs has been successful.[13,131,150] DLT enables lateralizing of the bleeding, protects the nonbleeding lung, allows ILV, and allows therapeutic procedures to address the bleeding lung without compromise of the healthy lung.[13,150] A left DLT is the tube of choice.[13,131,137,150] Most commonly, a single ventilator with a Y connection to the DLT lumens is used[13] with distribution of ventilation according to the relative impedance of the two lungs (see "Lung Separation" above). If there is risk of blood overflowing to the nonbleeding lung, or if differential ventilation is required, a second ventilator with AILV should be used. OLV must be present during bronchial blockade or endobronchial intubation and may be required during iced saline lavage or massive blood loss.
6. Embolization. Because 90% of major hemoptyses arise from bronchial arteries,[134] once bleeding has been localized, bronchial artery embolization has a high success rate.[104,134,145,151–153] Once the bleeding lung or segment has been isolated, the bleeding must be controlled.
7. Emergency surgery. Urgent surgical resection is undertaken if bleeding overwhelms airway control or fails to respond to other measures. Resection is associated with a low mortality in many series.[104,129,140,144,152,154] It should not be unduly delayed if bleeding is not readily controlled.

The choice of these alternatives depends on the intubation status of the patient, the rate of bleeding, and whether the site of bleeding is known (Table 25-3). The choice is also affected by the availability of the technique and the skills of the personnel involved. In an unintubated patient who remains stable despite moderate hemoptysis, bleeding may settle with correction of clotting abnormalities and general measures (above) or angiographic embolization (Table 25-3). An obtunded patient with a decompensating respiratory or circulatory state requires intubation combined with a plan to confine the bleeding to one lung (Table 25-3). This can include a primary choice of specialized tubes, such as the Univent or a DLT. A patient who is already intubated will usually have control attempted primarily by a blocker or manipulation of the ETT in situ (Table 25-3).

In reported series of patients with major hemoptysis, localization of bleeding is usually achieved by history, fiberoptic bronchoscopy, or radiology (chest radiograph, computed tomography scan, or angiography). Bleeding is controlled by conservative measures, embolization, or surgery.[104,145,152] The relative requirement for these three treatments varies widely,[104,145,152] depending on cause, amount of bleeding, and local expertise. Supportive care, correction of coagulopathy, and time as the only measure ranged from 13% to 87% of patients with major hemoptysis. Embolization was used in 7% to 51% with success rates of more than 80%. Surgery was required in 6% to 50%.

LUNG PROTECTION FROM SECRETIONS

Spread of purulent secretions from a lung abscess, empyema, bronchiectasis, cavitating tuberculosis, or cavitating malignant disease to the dependent normal lung during chest

TABLE 25-3: FACTORS INFLUENCING CHOICE OF PROCEDURES IN PATIENTS WITH MODERATE TO MASSIVE HEMOPTYSIS

	Intubation	Severity	Side of Bleed	Management Options
A	Not required	Moderate		Conservative only Angiogram and embolization Elective intubation and blocker
B	Required	Moderate or massive Massive Massive	 Known Known left Unknown	ETT + blocker[a] ± bronchoscopic guidance Univent tube ± bronchoscopic guidance or DLT ETT advanced into R main bronchus DLT or ETT to right main ± blocker[a] and withdraw ETT[b]
C	Already present	Moderate Massive		Blocker[a] ± bronchoscopic guidance ETT to right main ± blocker and withdraw ETT[b]

[a]In an emergency, the blocker may be any suitable device with and inflatable balloon—Arndt, Cohen, Swan-Ganz catheter, balloon-tipped cardiac pacing wire, Fogarty catheter.

[b]If the site of bleeding is known, directed balloon placement can be done before bronchoscopy. If the site of bleeding is unknown, bronchoscopy may be required first to guide blocker placement.

surgery is associated with considerable risk.[1,2,5,6,155] A DLT not only allowed thoracic surgery but provided an important protective role for the dependent normal lung[1,66,155] and allowed perioperative ILV if required.[1,66,155]

Although these conditions have become less common, the requirement for ILV for lung protection, during or outside thoracic surgery, occurs occasionally.[156] Essential during thoracic surgery, it is problematic outside that setting because viscous or tenacious secretions drain poorly through the narrower lumen of a DLT. Appropriate antibiotic therapy, postural drainage, and a standard ETT may be preferable.

BRONCHIAL REPAIR PROTECTION

Mainstem bronchi and lower trachea (near the carina) can be ruptured by severe blunt chest trauma, resulting in tension pneumothoraces, massive air leak, and the need for urgent surgical repair. Selective airway intubation usually is required for the repair and ILV has been used postoperatively to protect the anastomoses.[157–160] Pizov et al[160] used one-lung high-frequency ventilation in the management of traumatic tear of the bronchus in a child. After a right mainstem bronchial rupture, Moerer et al[157] used a left DLT with bilevel ventilation to the left lung and CPAP alone to the right lung for 48 hours before switching to CMV. In three patients with lower tracheal rupture (near the carina), Wichert[158] reported that standard DLTs position the cuff too close to the site of carinal injury and used bronchoscopy-guided selective endobronchial intubation with two tubes to undertake the repairs. After repair, the tubes were reintroduced via tracheostomy, and ILV was performed for 9 to 14 days to allow recovery from respiratory and other complications.

Bronchopleural Fistula

BPFs can result from trauma, necrotizing pneumonia, lung abscess, tuberculosis, acute respiratory distress syndrome (ARDS), thoracic surgery, overinflation from mechanical ventilation, central venous catheter insertion, and intercostal catheters. Persisting BPF often leads to infection of the pleural space.[161] If massive air leak from a BPF occurs during mechanical ventilation, the consequences include respiratory insufficiency and sometimes tension pneumothorax. Persisting failure of lung expansion can occur despite intercostal catheters if the rate of air leak exceeds the rate of drainage through the catheters. BPFs are estimated to occur in 2% of ventilated patients.[162] Mortality depends on the size of the leak[162] and the cause and is reported to be 18% to 67%.[161,162]

Management includes antibiotics, pleural sclerosing agents, surgical control of air leaks at thoracotomy, intercostal catheter insertion, underwater seal drainage with suction, conventional ventilation strategies to reduce air leak, patient positioning,[161] positive pleural pressure during inspiration,[161,163] HFJV, a variety of bronchoscopic occlusion techniques, and ILV. ILV is usually employed when massive air leak persists despite conservative measures and results in respiratory insufficiency. Before instigating ILV, conservative measures should be optimized.

Inadequate drainage can occur despite actively bubbling intercostal catheters and can lead to failure of lung expansion and respiratory insufficiency. Intercostal catheters must be adequate in number and diameter; their patency must be visualized and demonstrated by active bubbling. Underwater-seal drainage systems and wall-suction units must have an adequate maximum flow capacity. Air-filter patency must be checked. High resistances and low maximum flow rates in either the drainage system or wall-suction unit actually can retard thoracic drainage and increase pneumothorax size. Ideally, maximum flow capacity should approximate or exceed the percentage of V_T lost to the BPF multiplied by the inspiratory flow rate. Drainage devices vary widely in maximum flow capacity but rarely exceed a capacity of 35 L/min. Increased bubbling or radiologic improvement after suction disconnection suggests retardation by the device. Persisting negative pressure on a wall-suction unit after disconnection suggests an occluded air filter. With massive air leaks, more than one underwater-seal drainage system may be required.

The conventional ventilator strategy for a BPF has three goals: reduce air-leak rate (to facilitate healing), reduce pneumothorax size, and maintain adequate gas exchange. These goals often have conflicting needs. The usual strategy is directed toward lowering alveolar and airway pressure to reduce air leak. V_T and PEEP should be minimized and the rate reduced, especially if dynamic hyperinflation is present, although these steps may impair gas exchange. Inspiratory flow is controversial. Increasing flow may decrease air leak by decreasing inspiratory time or increase proximal air leak by increasing peak airway pressure. The impact of any change on all three goals must be assessed.

HFJV without ILV appears to benefit patients with a proximal BPF and otherwise relatively normal lungs.[161,164] Reported success of HFJV in patients with parenchymal lung disease, whose BPFs usually are peripheral, is variable.[161] ILV has been used in many patients with a BPF.[35,47,56–58,60,62–64,66,88,162,164–174] Conditions in which ILV has been used for BPF include pneumonia with and without CAO,[174] ARDS,[168] trauma,[57,63,162,166,167] pulmonary contusion or large airway trauma,[62,133,164,166,171] emphysema, asthma,[165] staphylococcal pneumatoceles,[173] and thoracic surgery.[47,58,63,66,88] Most patients had air leaks exceeding 50% of V_T, lung collapse despite multiple intercostal catheter insertions, and hypercapnic acidosis and hypoxia despite attempts at optimizing mechanical ventilation.

The most common form of ILV for BPF is AILV using two ventilators[56–58,60,66] with low V_T, low rates, and low or no PEEP for the lung with the BPF. The BPF lung also has been ventilated with SILV with low V_T, PEEP, and inspiratory flow;[35,88,170–173] HFJV;[63,64] and high-frequency oscillation[168] or excluded from ventilation by a Fogarty catheter passed through a DLT after failing to respond to both CPAP and jet

ventilation.[174] Successful use of a DLT with a single ventilator and a variable-resistance valve in the inspiratory circuit to the BPF lung has been reported in an animal model[48] and in one patient[47] with a large BPF.

Almost all authors report reduction in air leak with improvement in gas exchange. ILV was continued from 2 hours[66] up to 10 days[58] in some patients before CMV could be resumed. Improvement was reported in most patients with ILV. Overall survival was approximately 50%, although a large BPF is as a poor prognostic factor.[161] Outcome mainly was related to the prognosis of the underlying condition.

Asymmetrical Lung Disease

ILV has been used for a variety of unilateral or asymmetric lung diseases (see Table 25-1). Three main indications are unilateral pulmonary parenchymal injury, unilateral atelectasis, and unilateral airflow obstruction.

UNILATERAL PARENCHYMAL INJURY

Patients who receive ILV for asymmetric pulmonary injury have poor compliance on the affected side, hypoxemia refractory to high O_2 concentrations and high levels of PEEP. Under these circumstances, PEEP may cause hyperinflation of the unaffected lung, collapse of the affected lung,[41,50] barotrauma,[41,50,175,176] and worsening of hypoxemia[41] consequent to increased pulmonary vascular resistance in the unaffected lung (diverting blood flow to the injured lung). This hyperinflation also can elevate intrathoracic pressure, reduce arterial pressure and cardiac output,[41,50,169,170] and, combined with arterial desaturation, reduce O_2 delivery.[51,71,169,170,177–181]

The prime objective of ILV under these circumstances is differential PEEP, although different ventilator patterns have been applied to achieve a similar effect and optimize gas exchange and minimize barotrauma. ILV allows lung recruitment maneuvers and high PEEP to the affected lung, permitting maximum benefit to that lung without adverse effects on the contralateral lung, intrathoracic pressure, cardiac output, and the distribution of ventilation between the two lungs. PEEP applied to the diseased lung can improve oxygenation by alveolar recruitment and diverting blood flow to the more normal lung. Low or no PEEP in the more normal lung avoids hyperinflation and the adverse effects of high intrathoracic pressure.

ILV has been used in various unilateral or asymmetric lung diseases (see Table 26-1). The most common indication has been *pulmonary contusion*. Of forty-five patients who received ILV for asymmetric lung injury,[9,41,50,63,73,133,166,175,176,182,183] three received SILV,[41,50] but most received AILV.[9,166,175,176,182,184] Two patients received no mechanical ventilation and breathed spontaneously through a DLT with different levels of CPAP applied to the expired limb of each circuit.[73] All methods improved gas exchange, and overall mortality was only 10%. In twelve trauma patients with unilateral contusion requiring ILV, Cinnella et al[182] monitored end-tidal CO_2 and static compliance in each lung and reverted to conventional ventilation when these became similar in the two lungs.

ILV has been reported in patients with *aspiration*[55,56,169,170] and *pneumonia* or *consolidation*.[9,32,35,43,53,59,68,169,170,184–186] As with contusion, a mixture of AILV and SILV has been used. In one patient, high-frequency oscillatory ventilation was used with a higher mean airway pressure to the affected lung.[68] SILV has been used in patients with unilateral consolidation on a background of congenital heart disease with asymmetric lung blood supply.[32,185] Mortality was 48%.

SILV has been reported in patients with asymmetric ARDS secondary to trauma and sepsis (56% mortality[34]), asymmetric acute pulmonary edema,[32,169,187] and massive pulmonary embolism.[188] In a patient with a single-lung transplant, it enabled weaning from ECMO.[187]

All patients received differential PEEP: 0 to 10 cm H_2O on the unaffected side and 7 to 25 cm H_2O on the affected side. In all cases, higher PEEP was used on the affected side. V_T values to the two lungs were equal in some studies, smaller to the affected lung in some, and larger in one study.[50] In two studies,[34,169] PEEP administered to each affected lung was carefully adjusted to the compliance response of that lung. Carlon et al[169] increased PEEP in the affected lung until its compliance was similar to that of the unaffected lung. Siegal et al[34] found that increasing PEEP in the affected lung initially improved compliance, but then it decreased secondary to overinflation. They set PEEP at the level that achieved maximum compliance. Both methods improved oxygenation, shunt fraction, and cardiac output. The duration of ILV ranged from 1 hour[50] to 12 days.[176]

From these reports, several factors emerge as requirements for ILV:

1. *Differential PEEP* with a higher level applied to the affected lung is a key factor. PEEP may be applied to the affected lung until gas exchange improves, to an inflection point[34] on a compliance curve, until lung compliance is equal on the two sides,[169] or based on CO_2 excretion. PEEP most commonly is 10 to 20 cm H_2O. A recruitment maneuver and PEEP level that maximizes arterial oxygenation can be recommended.[189] PEEP may or may not be required in the contralateral lung.
2. *Equal* V_T to both lungs was used most commonly and was most likely to maximize gas exchange[36,39,40] compared to smaller or larger V_T values to the affected lung. Maintenance of plateau pressure below 30 cm H_2O is an important goal.[190,191]
3. *AILV* or *SILV* is equally acceptable because there is no requirement for a different respiratory rate. AILV holds no disadvantages when compared with SILV[55,61] and is simpler and more flexible.

The primary goal of ILV and differential PEEP or CPAP is improvement in gas exchange and hemodynamics and physical expansion of collapsed lung regions.

UNILATERAL ATELECTASIS

Unilateral atelectasis that has failed to respond to either standard ventilator support, bronchoscopy, or both[7,50,51,55,59,65,67,150,169,170,192–194] is another indication for ILV. High PEEP, CPAP, HFJV, or high-frequency oscillation have been applied to the atelectatic lung for the purpose of reinflation without the risk of overinflating the contralateral lung and generalized elevation of intrathoracic pressure.

In some studies,[42,51,59,67,169,170] high PEEP was applied to the atelectatic lung during AILV or SILV with mechanical ventilation of both lungs. The collapsed lung received 10 to 30 cm H_2O of PEEP, whereas the unaffected side received 0 to 10 cm H_2O of PEEP. In other studies, the collapsed lung received transient CPAP alone[7,65,67,150,193] (20 to 80 cm H_2O) without mechanical ventilation, or 30 cm H_2O CPAP followed by HFJV with 25 cm H_2O PEEP,[65] or 80 cm H_2O CPAP followed by AILV,[67] or unilateral high-frequency oscillation with a mean airway pressures of 28 to 30 cm H_2O.[192,194] Millen et al[193] transiently applied 60 to 70 cm H_2O of CPAP to individual lungs in two nonintubated, spontaneously breathing patients via a cuffed fiberoptic bronchoscope with good results. There was no report of lung injury despite transient application of very high inflation pressures, and there were only two deaths in this group of eighteen patients with atelectasis.[7,42,51,55,59,65,67,150,169,192,194]

These reports demonstrate success with a range of recruitment maneuvers. Application of CPAP up to 50 to 60 cm H_2O to both lungs for a few minutes has no prolonged consequences of raised intrathoracic pressure and is recommended for lung collapse.[189] In unilateral atelectasis, recruitment maneuvers should be undertaken routinely during double-lung ventilation (unless contraindicated by a problem in the nonatelectatic lung) before attempting ILV and may prevent the need for ILV in many patients.

UNILATERAL AIRFLOW OBSTRUCTION

Unilateral airflow obstruction occurs most commonly following single lung transplantation (SLT) but may occur with a mechanical or chemical insult to one lung in a patient with asthma or partial occlusion of a major bronchus. Under these circumstances, standard ventilation can cause dynamic hyperinflation and high intrinsic PEEP in the obstructed lung. This can elevate intrathoracic pressure, reduce cardiac output, and compress the contralateral lung.

To achieve hypoventilation of the obstructed lung, SILV can be used with a much lower V_T to the obstructed lung. It is better achieved with AILV using reduced rate and V_T (or CPAP alone) to the obstructed lung.[54,67]

Single Lung Transplantation. Early reports suggested that SLT was contraindicated in chronic obstructive pulmonary disease because of the risk of dynamic hyperinflation in the native lung with mediastinal shift.[122,195] Initial experience supported these concerns.[196–199] Subsequent series[10,195,200–209] combined with 210 SLTs at our institution[10] result in a total of 733 patients. Overall early mortality is 18% and only 13% when the primary diagnosis is CAO (emphysema, α_1-antitryspin deficiency, lymphangioleiomyomatosis) (Table 25-4). Thirty-day mortality varies widely (0%[203] to 50%[200]). Small series reveal that early mortality[195,200,207,208] ranges from being slightly lower with SLT than with

TABLE 25-4: INCIDENCE OF ACUTE NATIVE LUNG HYPERINFLATION AND INCIDENCE AND MORTALITY WITH INDEPENDENT LUNG VENTILATION IN PATIENTS UNDERGOING SINGLE LUNG TRANSPLANTATION FOR AIRFLOW OBSTRUCTION

	SLT for Airflow Obstruction			Radiologic ANLH		Symptomatic ANLH		ILV		ILV Mortality	
Authors	**No. Pts**	**No. Died**	**Mortality**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Kaiser et al[209]	11	0	0%	—		—		1	9%	0	0%
Patterson et al[195]	7	1	14%	1		1		0			
Egan et al[208]	4	0	0%	—		—		1	25%	0	0%
Marinelli et al[206]	7	1	14%	—		—		0			
Low et al[207]	16	2	13%	—		—		0			
Montoya et al[205]	39	1	3%	—		—		0			
Yonan et al[173]	27	5	19%	12	44%	12	44%	8	30%	2	25%
Weill et al[210]	51	0	0%	16	31%	8	16%	1	2%	0	0%
Mitchell et al[202]	132	34	26%	—		—		13	10%	6	46%
Hansen et al[201]	90	1	1%	—		—		0			
Angles et al[200]	14	7	50%	9	64%	9	64%	6	43%		
Pilcher et al[10]	170	21	12%	78/95	82%	*20*	12%	20	12%	7	35%
Totals	**568**	**73**	**13%**	**116**	**60%**	**50**	**19%**	**50**	**9%**	**15**	**30%**

Abbreviations: ANLH, acute native lung hyperinflation; *ILV*, independent lung ventilation; *SLT*, single lung transplantation.

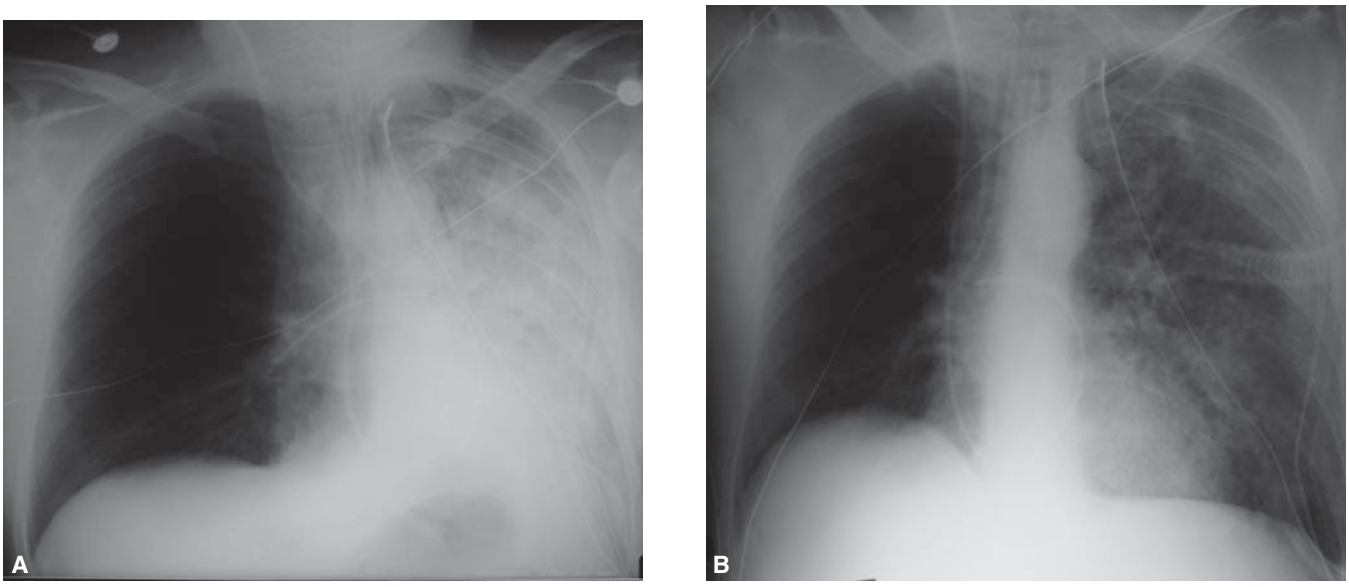

FIGURE 25-8 Chest X-rays of a patient with a right single-lung transplant before (**A**) and (**B**) after insertion of a right double-lumen tube and independent lung ventilation.

bilateral lung transplant[195,207,208] to higher with SLT.[200] Larger series suggest lower mortality with bilateral lung transplantation,[210–213] although selection criteria such as age may have contributed.[210]

Although SLT is becoming less popular, it remains an alternative to bilateral lung transplantation, especially in patients older than 50 years of age with nonsuppurative lung disease. SLT is technically easier than bilateral lung transplantation and benefits more recipients when donor availability is a limiting factor. The most common indication for SLT is some form of CAO, which accounts for 77% of SLTs.[195,200–209] Although lung function is better after bilateral lung transplantation, SLT substantially improves quality of life[195,207] and achieves equivalent maximum work capacity and maximum O_2 consumption.[214]

More than thirty reports[10,27,54,67,187,195–209,215–226] plus experience from our institution provide information on 768 patients receiving SLTs, 601 for CAO. ILV was required almost exclusively in patients who received SLT for CAO.[10,27,54,200,202–204,208,209,215,217–219,221,223] There are few reports of patients requiring ILV after bilateral lung transplantation for any reason, nor after SLT for restrictive lung disease. In one patient,[223] ILV was required for a large, unresolving BPF arising in the native lung after SLT that eventually necessitated pneumonectomy of the native lung. In another patient,[187] ILV was required for reperfusion edema after SLT for primary pulmonary hypertension. Use of ILV in SLT series for CAO (see Table 25-4) varies widely: 0%[195,201,205–207] to 43%,[200] with an overall frequency of 9%.[10,195,200–209]

The phenomenon leading to use of ILV has been termed *acute native lung hyperinflation* (ANLH), which is defined as radiologic mediastinal shift with flattening of the ipsilateral hemidiaphragm (Fig. 25-8A) associated with signs of hemodynamic instability or respiratory dysfunction.[10,200,203,204] Evolution of this phenomenon can be divided into three stages:

1. *Asymptomatic ANLH*. Dynamic hyperinflation of the native lung with mediastinal shift is seen commonly in the postoperative period without transplanted lung collapse, hypoxia, or hypotension, and without the need for ILV.[10,195,225] This phenomenon arises because of asymmetry of lung disease following transplantation. The native lung with severe airflow obstruction undergoes dynamic hyperinflation during CMV, just as both lungs would do during CMV before transplantation.[227] A healthy transplanted lung with normal compliance and airflow resistance will receive most of the blood flow and ventilation, thereby reducing the degree of dynamic hyperinflation that would have occurred if both lungs received the same ventilation. Nevertheless, the transplanted lung does not have a "balancing" degree of dynamic hyperinflation, and mediastinal shift occurs commonly. The occurrence of asymptomatic ANLH is reported infrequently (Table 25-5). Weill et al[203] reported asymptomatic ANLH in sixteen of fifty-one patients (31%), although smaller series have reported symptomatic ANLH in 44%[204] and 64%[200] of SLTs for CAO. In our institution, mediastinal shift (shift of right-heart border relative to the spine by 1 cm or greater toward the transplanted lung) occurred in seventy-eight of ninety-five consecutively evaluated SLTs (82%) for CAO (Table 25-5).[10] The asymmetry usually improves or resolves over time, but it persists indefinitely in some patients. In some patients it can arise weeks or months after transplant.[200]

TABLE 25-5: INCIDENCE OF RADIOLOGIC AND SYMPTOMATIC ACUTE NATIVE LUNG HYPERINFLATION IN LEFT AND RIGHT SINGLE LUNG TRANSPLANTATION FOR AIRFLOW OBSTRUCTION

	Radiologic ANLH						
	Left			Right			
	No.	Total	%	No.	Total	%	*P* value
Weill et al[179]	10	27	37	6	24	25	NS
Pilcher et al[10]	45	54	83	33	41	80	NS
Total	**55**	**81**	**68**	**39**	**65**	**60**	**NS**
	Symptomatic ANLH						
	Left			**Right**			
	No.	**Total**	**%**	**No.**	**Total**	**%**	***P* value**
Weill et al[179]	4	27	15	4	24	17	NS
Angles et al[169]	5	6	83	4	8	50	NS
Pilcher et al[10]	14	82	17	7	88	8	NS
Total	**23**	**115**	**20**	**15**	**120**	**13**	**<0.05**

Abbreviations: ANLH, acute native lung hyperinflation; *NS*, nonsignificant; *SLT*, single lung transplantation.

2. *Transplanted lung dysfunction*. Any dysfunction in the transplanted lung, whether parenchymal (e.g., reperfusion edema, contusion, rejection, pneumonia, or collapse) or airway (e.g., anastomosis narrowing or sputum obstruction), impedes ventilation in the transplanted lung and redistributes ventilation to the native lung, especially during volume-controlled ventilation. This necessarily increases dynamic hyperinflation in the native lung and increases mediastinal shift and collapse and further impairs gas exchange in the transplanted lung. A vicious cycle results, redistributing more ventilation to the native lung with greater dynamic hyperinflation and mediastinal shift. Primary dysfunction of the transplanted lung,[219] severe postimplantation syndrome,[10,218] or ARDS have been identified as major contributors to native lung hyperinflation and mediastinal shift[10,27,208,209,218,219,221] usually resulting in hypotension, collapse of the transplanted lung with hypoxia, or both. Progressive compromise of the transplant lung can lead to refractory hypoxia and hypercapnia, whereas dynamic hyperinflation, mediastinal shift, and pulmonary vessel compression can lead to circulatory compromise with hypotension (see Fig. 25-8A). This has been termed *symptomatic ANLH*[203,204] (see Table 25-5). Almost all such problems have occurred only during mechanical ventilation, in the immediate or early postoperative period.
3. *Mechanical ventilation response*. The typical response to a lung collapse with worsening hypoxemia and hypercapnia includes increasing PEEP, increasing rate, and/or increasing V_T. Each response increases dynamic hyperinflation in the native lung,[227,228] which can worsen gas exchange, precipitate circulatory collapse, and necessitate ILV. Although the requirement for ILV usually is attributed to transplant dysfunction (see previous paragraph), the precipitant often is the failure to improve (or deterioration) with mechanical ventilation. In addition to transplanted lung injury (see previous paragraph), factors that increase the risk of this problem include the severity of airflow obstruction in the native lung, the size of the transplanted lung, and the side of the transplantation (see Table 25-5). Yonan et al[204] found that patients who developed ANLH had higher pulmonary artery pressures, higher residual volumes, and lower forced expiratory volumes in 1 second (FEV_1) than did patients who did not develop symptomatic ANLH. Weill et al[203] suspected more symptomatic ANLH in patients with bullous emphysema, but lung function and pulmonary artery pressure were equivalent among patients with and without symptomatic ANLH. We found that patients who required ILV had a greater degree of preoperative airflow limitation and preoperative hyperinflation, and lower postoperative Pa_{O_2}/FI_{O_2} ratios, more radiologic mediastinal shift, and more transplanted lung infiltrate on the postoperative chest radiograph.[10] Severity of airflow obstruction directly affects the degree of dynamic hyperinflation.[227,228] The size of the donor lung[195,209,218] is an important factor. A donor's predicted vital capacity that approximates[209] or is smaller than[218] the recipient's predicted vital capacity is associated with the need for ILV. A donor-to-recipient predicted vital capacity ratio of 1.4[209] or a donor-lung predicted vital capacity exceeding recipient-lung predicted vital capacity by 2 L[195] is associated with the absence of

mediastinal shift following SLT. Others have found no difference as a consequence donor size.[203]

Several reports have suggested a higher incidence of ANLH with left SLTs (see Table 25-5). Weill et al[203] found radiographic ANLH in 37% of left SLTs and 25% of right SLTs and no difference in symptomatic ANLH (see Table 25-4). Angles et al[200] did not report radiographic ANLH but found symptomatic ANLH in 83% of left SLTs and 50% of right SLTs. We[10] found no difference in mediastinal shift between left and right SLTs for CAO, but ILV was required twice as often with left SLTs (see Table 25-5).

Severe symptomatic ANLH commonly requires urgent intervention. Options include:

1. *Permissive hypercapnia*.[201] Permissive hypercapnia reduces dynamic hyperinflation in the native lung and may improve mild symptomatic ANLH but is unlikely to be adequate for severe ANLH. Although ILV was not used in this study, four patients required ECMO.
2. *ILV*.[27,54,198,200,202–204,208,209,215,217–219,221,223] Although technically complex, ILV commonly results in immediate resolution or improvement in gas exchange and circulatory problems and provides the most rapidly available and chosen solution (see Fig. 25-8).
3. *ECMO*.[201] ECMO is a complex and invasive solution, but provides an alternative to ILV.
4. *Contralateral lung-reduction surgery*.[202–204] This has been reported recently. It has been undertaken concurrently with SLT, during the postoperative period, and late after SLT. It may offer the best long-term solution to ANLH but is less readily applicable in urgent or life-threatening situations.
5. *Contralateral lung transplantation*.[202,204] After primary SLT, this offers a solution but depends on availability of a donor lung and subjects the recipient to two major surgical procedures and two sets of foreign antigens.
6. *Retransplantation of the SLT*.[204] This has been used for early graft dysfunction associated with ANLH.

The choice of DLT for ILV is different following SLT. A left DLT normally is easier to position correctly. With a left SLT, however, this can compromise the anastomosis and airway distal to the anastomosis, which has a tenuous blood supply in the immediate postoperative period. Thus, a DLT opposite to the side of the SLT normally is chosen in the early postoperative period. If ILV is required for more than 2 to 3 weeks after left SLT when the anastomosis is stable, a left DLT may be used, although a smaller size is chosen in case the anastomosis is narrower than the adjacent airway.

ILV after SLT usually consists of CMV to the transplanted lung and AILV,[208,209,218,219] SILV,[221] bronchial blockade,[27,209] CPAP,[223] or spontaneous ventilation[218] to the native lung. All methods are viable options. The ventilatory requirements of each lung differ so much, however, that AILV is the method of choice primarily because of different rate requirements of the two lungs (Table 25-6). AILV was the method of choice in forty-seven patients in four series.[10,200,202,204] The donor lung

TABLE 25-6: VENTILATOR SETTINGS FOR INDEPENDENT VENTILATION AFTER SINGLE LUNG TRANSPLANTATION FOR AIRFLOW OBSTRUCTION

	Native Lung	Transplanted Lung
Ventilator rate (breaths/min)	2 to 4	14 to 20
Tidal volume (mL/kg)	2 to 3	3 to 4
Plateau pressure (cm H_2O)	<25	<30
Inspiratory flow rate (L/min	80	40 to 50
PEEP (cm H_2O)	0	10 to 17
Recruitment maneuver (cm H_2O)	No	±35 to 50[a]

[a]Stability of the anastomosis and the presence of air leak need to be considered before undertaking a recruitment maneuver. Lower-than-normal recruitment pressures may be initially chosen.

commonly requires PEEP at a sufficient level to expand collapsed regions and improve oxygenation, a V_T sufficiently low to avoid pressure injury to the lung, and a rate high enough for adequate CO_2 elimination without causing flow limitation. A recruitment maneuver may maximize the benefit from PEEP, provided that it is safe to undertake.[189,229,230] The native lung should be ventilated with a pattern that maximizes its contribution to gas exchange without excessive dynamic hyperinflation. This necessitates low V_T, high inspiratory flow rate, and a very low rate (Table 25-6).[228] The goals of native-lung ventilation are to maintain a low plateau pressure, restore the mediastinum to the midline (see Fig. 25-8B), and allow restoration of circulatory instability (that caused by dynamic hyperinflation). If this is not achieved, rate should be reduced further (even to 0). The goals of SLT ventilation are a safe plateau pressure (Table 25-7) and restoration of adequate SaO_2 and Pa_{CO_2}. If this is not achieved, further recruitment maneuvers and higher PEEP should be explored. The introduction and stabilization of these different ventilator

TABLE 25-7: COMPLICATIONS ASSOCIATED WITH DOUBLE-LUMEN TUBES AND INDEPENDENT VENTILATION

- Trauma to larynx, trachea, and major bronchi during insertion
- DLT malposition resulting in bronchial occlusion, poor oxygenation, ventilation, and secretion clearance
- Incomplete lung isolation resulting in unwanted lavage fluid, blood, or pus in the protected lung
- Retention of secretions as a result of long narrow airways and difficulty with suction
- Tube dislodgement following routine patient position changes
- Complications from prolonged immobility associated with the need for sedation and controlled ventilation
- Airway injury because of prolonged requirement for high cuff pressures to maintain
- Laryngeal injury from the prolonged presence of large diameter tube

strategies to each lung generally necessitate sedation and paralysis during the early stages of ILV. If SaO_2 or circulation is not satisfactory, ECMO may be needed.

Withdrawal of ILV can be initiated when function of the transplanted lung improves and its ventilatory requirements decrease. This can be assessed with a DLT in situ by ventilating both lungs with a single ventilator and a bifurcated ventilator circuit (see Fig. 25-3). Because spontaneous ventilation is difficult with a DLT, patients usually require reintubation with a single-lumen ETT for weaning before extubation. Others experience recurrent dynamic hyperinflation with double-lung ventilation and must wean with the DLT in situ. ILV has been required for as little as 1 day.[209] In most instances, prolonged ILV has been required; periods exceeding 1 month[218,219,221,223] have been reported with eventual resolution and good functional outcome. Patients who require prolonged ILV should undergo a tracheostomy and receive a double-lumen tracheostomy tube(Fig. 25-9).[218,221,231]

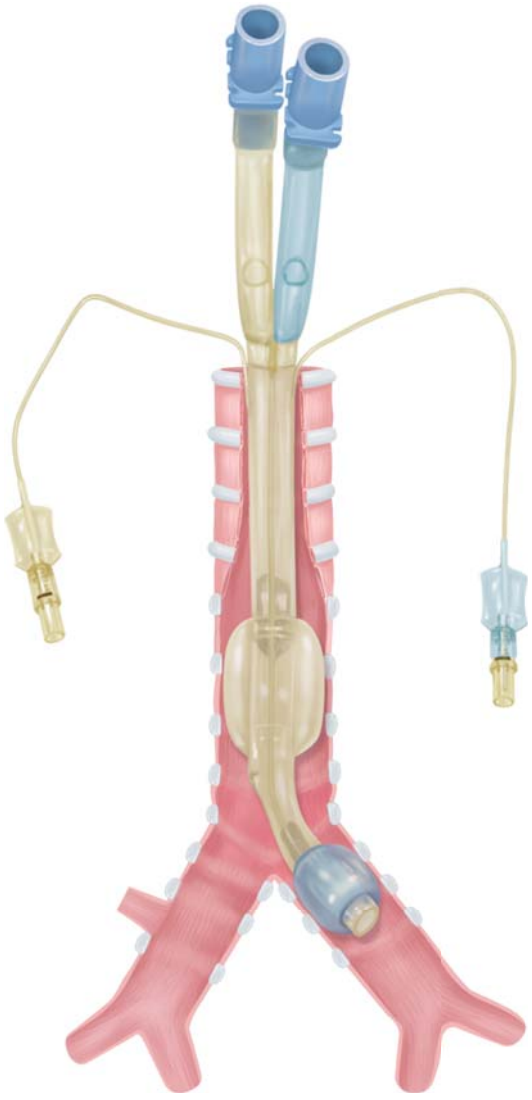

FIGURE 25-9 A double-lumen tracheostomy tube.

Outcome of Acute Native Lung Hyperinflation. Several investigators[10,200,203,204,218,221,231] have reported that patients with symptomatic ANLH have a longer duration of mechanical ventilation, a longer intensive care unit stay and higher mortality: 7% mortality in 213 SLT patients without symptomatic ANLH, and 37% mortality in fifty SLT patients with symptomatic ANLH ($P < 0.05$). Yonan et al[204] reported lower FEV1 values and higher residual volumes after transplantation in ANLH patients, whereas Weill et al,[203] in a larger series, found no differences in long-term lung function.

Outcome of Independent Lung Ventilation. Fifteen papers[10,27,54,198,200,202–204,208,209,215,217–219,221,223] report sixty-three patients with ILV following an SLT for CAO. Overall mortality was 30%. Including only recent case series in which all SLT patients and ILV survival were reported,[10,202–204] ILV patients had higher mortality (fifteen of forty-two patients, or 36% mortality) than non-ILV patients (forty-five of 338 patients, or 13% mortality). This difference is not surprising because ILV patients are sicker and show a higher incidence of graft dysfunction.

In summary, SLT for airflow obstruction poses a risk of ANLH with mediastinal shift. When this is sufficient to compromise gas exchange and/or circulation, ILV is the initial method of choice and may reduce the need for ECMO.

Unilateral Bronchospasm. In patients with asthma, airways respond locally to local stimuli; irritants applied to one lung may create a different degree of bronchospasm in the two lungs.[232] During mechanical ventilation, this can lead to different levels of dynamic hyperinflation and mediastinal shift, and during thoracic surgery, this can lead to difficulty with thoracotomy closure and the need for ILV. Narr et al[67] reported unilateral bronchospasm during unilateral pleurodesis. The pleurodesed lung initially collapsed; following DLT insertion and ILV with 80 cm H_2O of CPAP applied to the collapsed lung, that lung inflated and would not deflate. Low-level CPAP to the affected lung, CMV to the unaffected lung, and aggressive bronchodilator therapy allowed deflation of the affected lung, maintenance of gas exchange, and thoracotomy closure.[67]

Patient Selection for Independent Lung Ventilation in Unilateral Lung Disease. Asymmetric lung disease usually is easy to recognize, but criteria for ILV are not so clear. Not all patients with asymmetric lung disease require ILV. Commonly used criteria are unilateral or clearly asymmetric lung disease, which is evident on chest radiography or known from the patient's condition (e.g., SLT), plus one of the following:

1. Severe hypoxemia despite 100% O_2 and different levels of PEEP.
2. Circulatory failure/hypotension secondary to dynamic hyperinflation.

Factors that suggest that a patient is likely to benefit from ILV include

1. Worsening hypoxemia and/or circulatory status by increasing PEEP, rate, or V_T.
2. Improvement in gas exchange but marked deterioration in circulatory status with increasing PEEP and the opposite when PEEP is reduced.

Bilateral Symmetrical Lung Disease

Acute bilateral lung injury may appear diffuse, uniform, and symmetric on chest radiography but contain significant in homogeneity on computed tomography scan.[233,234] Many of these changes result from a uniformly injured lung collapsing in dependent zones as a result of increased lung weight. Because patients commonly are nursed on their back, collapse occurs in posterior zones and is not apparent on anteroposterior chest radiographs. In this case, no PEEP is required to open alveoli in the least dependent regions, and high PEEP may be required in the most dependent regions. Generalized PEEP may fail to inflate the most dependent regions and may overinflate nondependent regions. There is now increasing evidence that the injury can result from prolonged collapse[235] and repetitive collapse/reexpansion and overexpansion,[236,237] and that lung injury may contribute to multiorgan failure and death.[190,238] Considerable effort has been devoted to ventilator strategies that reduce prolonged collapse, collapse/reexpansion, and overexpansion,[190,191,239] and more recently to reduce prolonged collapse by higher PEEP with or without lung recruitment.[240–243] Although some strategies have been successful, all have the same problem of conflicting pressure requirements within different regions of the same lung.

The application of ILV under these circumstances is based on two principles:

1. Differences in compliance, ventilation–perfusion ratios, and gas exchange between the two lungs may be present and not be suspected from plain X-rays.[34,39,40,169]
2. Placing the patient in the lateral decubitus position will redistribute much of the collapsed (high-PEEP-requiring) lung regions to the dependent lung and the open (low-PEEP-requiring) regions to the nondependent lung.[39,40,244,245]

When a patient with normal lungs is ventilated in the lateral decubitus position, up to two-thirds of perfusion goes to the dependent lung, and up to two-thirds of ventilation goes to the nondependent lung,[36,75] creating significant ventilation–perfusion mismatch and shunt. Application of global PEEP improves distribution of ventilation,[246] but perfusion inequality may be increased and cardiac output reduced[36] with little net benefit.

In acute bilateral lung disease, the changes in ventilation and perfusion and the resulting mismatch in the lateral decubitus position are similar to those seen in patients with normal lungs[37,38] but with redistribution of lung collapse from posterior lung zones to the dependent lung. ILV with equal V_T to each lung and selective PEEP to the dependent lung proved additive in improving shunt fraction, arterial oxygenation, cardiac output, and O_2 delivery compared with CMV in both the supine and lateral positions.[37,38] These maneuvers have been applied on a long-term basis in bilateral lung injury with some early success.[245] Wickerts et al[244] and Diaz-Reganon Valverde et al[33] prospectively studied eleven and forty-five patients, respectively, with severe bilateral ARDS who received ILV. These patients were assessed in the supine position on global PEEP and then reintubated with a DLT and placed in the lateral decubitus position. PEEP was applied to the dependent lung and no PEEP to the nondependent lung. Both groups reported improved oxygenation, and Diaz-Reganon Valverde et al[33] reported a good response in 83% of patients.

ILV is difficult and labor-intensive to apply.[244] Accordingly, it has not gained widespread acceptance for symmetric bilateral lung injury.

COMPLICATIONS WITH INDEPENDENT LUNG VENTILATION

Many of the problems with ILV are related to the DLT. The technique of DLT placement and verifying its correct position is complex, time-consuming, and requires experienced personnel.[15,19,21,23] These considerations can limit the use of DLTs and ILV when required urgently or under adverse circumstances, such as massive hemoptysis.[137,140]

Trauma of the larynx and upper airways was a common problem with red-rubber tubes[19,106] but is uncommon with PVC tubes.[15,247,248] Rare complications have included cardiovascular collapse after a DLT displaced a mediastinal tumor into the mediastinal vessels[249] and exsanguination following inclusion of the DLT in sutures during pneumonectomy with subsequent vessel laceration when the DLT was removed.[250,251]

Placement of right DLTs is critical with respect to right upper-lobe ventilation. Benumof et al[252] estimated a right upper-lobe occlusion rate of 11% with PVC tubes. McKenna et al[18] assessed occlusion of the right upper lobe by bronchoscopy: occlusion was 89% with Mallinckrodt PVC DLTs and only 10% with right Robertshaw red-rubber DLTs. High malposition rates are reported after primary insertion.[22,253] This has become an uncommon problem now that most DLT insertions are assessed routinely by bronchoscopy. Left upper-lobe occlusion also has been reported[254,255] with left PVC DLTs from overinsertion, wedging the tip of the DLT in the left lower-lobe bronchus. Saito et al[256] found 27 ± 6 mm movement of the tip of a left DLT, proximally with neck extension and distally with flexion, with a total potential range of movement of up to 4.5 to 7 cm. This range of movement is sufficient to either occlude the left upper-lobe bronchus or lose lung isolation. Similar problems are more likely with a right DLT, with which tube position is more critical.

High cuff pressures are a significant problem with DLTs. In routinely placed tubes with cuffs inflated to avoid air leak, bronchial cuff pressures were 56 ± 21 mm Hg in left PVC DLTs and 130 ± 41 mm Hg in Carlens tubes.[14,257] This study suggests a considerably lower risk to the airway from PVC tubes, although the pressures required to prevent leaks still were well above safe limits.

Bronchial rupture was reported regularly[248,258–263] and there is one report of bronchial stenosis[183] with red-rubber tubes. Bronchial rupture is uncommon with PVC DLTs, although they are not free of this complication.[248,250,264]

Although lumen diameter has improved considerably with PVC tubes, difficult suction access, retained secretions,[41,43,60,88] and lumen blockage remain a problem and can lead to difficult ventilation, the need for regular bronchoscopic toilet, and the need to change the DLT.[13]

When ILV is continued for some time, several difficulties related to patient care arise. Head movement, patient movement, and routine patient turning all threaten DLT position and can lead to loss of lung isolation and lobe occlusion.[43,60,88,256] Frequent bronchoscopy may be required to maintain DLT position.[43,248] Running two ventilators requires additional space, O_2, air, and suction outlets, and standard patient charts usually are inadequate.[60] There are significant increases in nursing time requirement and workload,[60,265,266] and the patient may find the DLT more uncomfortable and restrictive than normal intubation.[88]

CONCLUSION

ILV has been used in a wide range of conditions (see Table 25-2). Although ILV is infrequently required, it has an established and sometimes lifesaving role for many of conditions and users of mechanical ventilation should be familiar with the complexities of ILV so that it can be instigated promptly and appropriately when the need arises. A ILV can be undertaken with any ventilator and can be used for all indications.

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MECHANICAL VENTILATION DURING RESUSCITATION

Holger Herff
Volker Wenzel

Before the arrival of an emergency medical service unit, ventilation given by bystanders must employ techniques that do not require special equipment. Safar, Elam, and Ruben first showed that obstruction of the upper airway by the tongue and soft palate occurs commonly in victims who lose consciousness or muscle tone and that ventilation with manual techniques is markedly reduced or prevented by such obstruction.[1–3] Subsequently, Safar et al[4,5] developed techniques that prevent obstruction by extending the neck and jaw and applied these in conjunction with mouth-to-mouth ventilation. The "gold standard" today for airway maintenance during resuscitation is intubation of the trachea, which provides a route for ventilation with oxygen, allows suctioning of the upper airway, protects the airway from aspiration of gastric contents, and prevents inflation of the stomach.

SPECTRUM OF EMERGENCY CARE SKILLS

Airway management should be mastered by all properly trained prehospital personnel. This involves both airway assessment and airway control. Compromise of the airway may occur suddenly or slowly and progress over time; therefore, continuous assessment of the airway is vitally important. Pulse oximetry is helpful in identifying hypoxia, although hypoxia may be a relatively late sign of airway compromise. It is therefore important to evaluate breathing pattern, level of consciousness, and shortness of breath continuously.

When endotracheal intubation of children was added to paramedic practice, fifteen of 177 (approximately 8%) children were either intubated esophageally or dislodgment of the endotracheal tube were unrecognized; fourteen of these fifteen children subsequently died.[6] Accordingly, invasive pediatric airway equipment was removed from emergency medical service units in Los Angeles County; instead, bag-valve-mask ventilation was recommended. A similarly alarming experience was seen in Orlando, Florida, when the esophagus was intubated in eighteen of 108 (approximately 16%) patients being managed by the emergency medical services.[7] This suggests that the skills and experience of a rescuer performing basic and advanced airway management may determine if these maneuvers achieve effective oxygenation and carbon dioxide elimination or result in extremely serious complications, such as severe neurologic impairment, or even death.[8]

Endotracheal intubation is the "gold standard" for providing emergency ventilation. Thus, every advanced emergency medical service provider must acquire and, especially, maintain intubation skills. Such a goal may be difficult to guarantee because of the large numbers of individuals who require training and/or the infrequent

performance of intubations. This experience is similar to observations of the emergency medical services in Houston, Texas, where airway device-related complications were associated more with training with the devices than with the devices themselves.[9] This confirms that the success rate of airway management interventions depends on three factors: (a) initial training, (b) continuous quality assurance, and (c) actual frequency of performing the specific intervention. For example, when the actual frequency of performing endotracheal intubation is relatively low, as in the case of the Los Angeles County emergency medical services (e.g., 2584 trained individuals performing 420 actual endotracheal intubations over 33 months), it is not surprising that endotracheal intubation performed by paramedics (who were allowed to perform bag-valve-mask ventilation) did not improve survival or neurologic outcome; instead, it caused some catastrophes.[6] In a recent study in Germany, however, trained emergency medical service physicians intubated the esophagus in approximately 7% of all out-of-hospital intubation scenarios.[10] These high incidences of intubation disasters even by highly trained rescuers actually may tip the scales toward supraglottic airway devices or bag-valve-mask ventilation for emergency ventilation of patients with a respiratory or even cardiac arrest performed by emergency medical services personnel without excellent intubation skills. Thus, teaching emergency medical services personnel a limited number or even a single airway procedure may follow the axiom "the simpler, the better" and ensure adequate oxygenation and avoid airway-related catastrophes.

DISTINCTION BETWEEN AIRWAY PROTECTION AND ASSISTED VENTILATION

Discussion of whether health care professionals or lay bystanders should or should not perform mouth-to-mouth ventilation has emotional connotations. The question of whether satisfactory lung ventilation in an unintubated cardiac arrest patient can be achieved, however, is clearly a scientific issue. If it is possible to identify ventilation strategies that are beneficial to patients and not harmful, then resuscitation outcomes may be improved.

The distribution of ventilation volume between lungs and stomach in a patient with an unprotected airway depends on factors such as lower esophageal sphincter pressure, airway resistance, and respiratory system compliance.[11] Of equal importance are specifics of techniques used for basic or advanced airway support, such as head position, tidal volume, inflation flow rate, and duration, all of which determine upper airway pressure.[12,13] The combination of these variables determines gas distribution between the lungs and the esophagus and, subsequently, the stomach. Several fundamental differences exist between respiratory mechanics in a healthy, awake adult, an anesthetized supine patient, and a victim of a cardiac arrest (Table 26-1).

Lower esophageal sphincter pressure is the pressure that prevents regurgitation of stomach contents into the pharynx and insufflation of air into the gastrointestinal tract during ventilation. Sphincter pressure in a healthy adult is approximately 20 to 25 cm H_2O but may be lower in patients with chronic esophageal reflux disease, during induction of anesthesia, and after insertion of a laryngeal mask airway.[14] It is unclear, however, whether these changes in sphincter pressure result from induction of anesthesia. Animal investigations showed that the lower esophageal sphincter pressure deteriorated rapidly from a baseline level of 20 to 5 cm H_2O within 5 minutes of untreated cardiac arrest.[15,16] This decrease in lower esophageal sphincter pressure was also measured in human subjects following cardiac arrest.[17] In a healthy adult, air flows freely from the lips to the alveoli, and therefore, minimal inspiratory pressure is required to move gas during spontaneous ventilation. In a patient with chronic obstructive lung disease, airflow through the respiratory system may be impaired by mucus or airway spasm.[18] Data from clinical studies showed an airway resistance of 2 to 4 cm H_2O/L/s in healthy volunteers, 8 to 15 cm H_2O/L/s in patients with varying degrees of lung disease, and 17 cm H_2O/L/s with positive-pressure bag-valve-mask ventilation in a patient during induction of anesthesia.[19] In a healthy awake adult, 1 cm H_2O of inspiratory pressure moves approximately 100 mL of air into the lungs; compliance decreases to 50 mL in an anesthetized supine adult and may decrease to approximately 20 to 50 mL in a cardiac arrest patient.[20] Many factors can change lung compliance. Pulmonary vascular

TABLE 26-1: RESCUER AND PATIENT VARIABLES AFFECTING RESPIRATORY MECHANICS DURING MOUTH-TO-MOUTH VENTILATION AND BAG-VALVE-MASK VENTILATION

Rescuer	Patient	Conscious	Anesthetized	Cardiac Arrest
Chin support	LESP (cm H_2O)	~20 to 25	~20	5?
Tidal volume	Crs (mL/cm H_2O)	~100 to 150	~50	~20 to 50
Inflation time	Raw (cm H_2O/L/s)	~2 to 4	~15	?
Ventilator setting				
Bag-valve-mask size				

Abbreviations: Crs, compliance of the respiratory system; *LESP*, lower esophageal sphincter pressure; *Raw*, airway resistance.

congestion during cardiac arrest increases the volume of the parenchymal interstitium and reduces compliance. Chest compressions and pulmonary edema secondary to left-ventricular failure also contribute to a reduction in compliance.[21]

Chin support and backward tilt of the head are the two most important maneuvers during rescue ventilation of paralyzed and nonparalyzed patients with an unprotected airway. Moreover, a slight lateral tilt of the head may reduce upper airway obstruction arising from backward relaxation of the tongue and soft tissues.[22] The settings of an automatic ventilator or the technique of bag-valve-mask ventilation governs inflation flow rate, inflation time, and tidal volume, all of which affect peak inflation pressure, assuming that there is no significant upper airway obstruction.[23] The relationship between peak inflation pressure and lower esophageal sphincter pressure determines gas distribution between the stomach and lungs.[24] For example, when peak inflation pressure exceeds sphincter pressure, some air will flow into the stomach; if sphincter pressure is higher than peak inflation pressure, inspiratory air will flow completely into the lungs. The preceding scenario, however, depends on the assumption that the lower esophageal sphincter pressure acts like a mechanical valve, which may not be the case. For example, Safar[25] stated that stomach inflation in healthy volunteers was self-limiting, but lower esophageal sphincter pressure was not reported. This observation implies that the physiology of respiratory mechanics in human subjects may be more complex than has been considered previously. Until a better understanding of these mechanisms is obtained, the goal of ventilation with an unprotected airway is to keep it permanently patent and to keep peak inflation pressure to a minimum at all times to prevent stomach inflation.

Stomach inflation is a complex problem that may cause regurgitation,[26] aspiration,[27] pneumonia,[28] and possibly death.[29] Stomach inflation will increase intragastric pressure,[30] elevate the diaphragm, restrict lung movements, and so reduce respiratory system compliance.[31] A reduced respiratory compliance may direct even more ventilation volume into the stomach when the airway is unprotected,[10] thereby inducing a *vicious cycle with each breath*.[32] The life-threatening complication of stomach inflation, regurgitation, and subsequent aspiration pneumonia (induced by gastric acid) causes a loss of alveolocapillary integrity and pulmonary surfactant. As a result, fluid and proteins pass into the interstitial spaces, alveoli, and bronchi, causing pulmonary edema, decreased pulmonary compliance, increased lung weight, and significant intrapulmonary shunting or ventilation–perfusion mismatching. Consequently, alveolar gas exchange is impaired markedly. Data from an animal model showed that aspiration of more than 0.8 mL/kg of body weight resulted in 50% mortality. Extrapolation of these results to humans suggest a critical aspiration volume of 50 mL at a pH of 1.[33] The results from recent studies of anesthetic practice, however, suggest that the true morbidity from acid aspiration has been exaggerated greatly.[34]

Cricoid Pressure and the Sellick Maneuver

A maneuver for preventing stomach inflation during ventilation with an unprotected airway is to apply cricoid pressure; this is a simple, effective maneuver to prevent stomach inflation[35] that was first described 200 years ago.[36] In a model of human cadavers, an intraesophageal pressure of 75 cm H_2O was required to overcome cricoid pressure, indicating that the Sellick maneuver may be able to prevent gastric distension even when ventilating with a high peak inflation pressure.[37] One study investigating the efficacy and minimum inflation pressure at which gas entered the stomach in pediatric patients found that appropriately applied cricoid pressure was invariably effective in preventing gas insufflation into the stomach in all children with and without paralysis.[38] The value of cricoid pressure, however, has been established based on case report series and cadaver and animal studies, and has never been validated in a large, controlled prospective study. Because of the lack of prospective studies, some authors regard the level of evidence for cricoid pressure as V (expert opinion) and the level of recommendation as D (levels being A to D, with A being the highest recommendation level).[39] The value of cricoid pressure has been further questioned because of the risk of esophageal rupture when vomiting occurs.[40] A further technical limitation is that applying both cricoid pressure and bag-mask ventilation by a single rescuer is nearly impossible and requires a second person to assist.

Moreover, a possible complication of cricoid pressure is airway obstruction.[40,41] In fifty-two anesthetized patients, airway obstruction did not occur without cricoid pressure, occurred in one patient (2%) with cricoid pressure of 30 N (3 kg or approximately 6.6 lb), in twenty-nine patients (56%) with cricoid pressure of 30 N (3 kg or approximately 6.6 lb) applied in an upward and backward direction, and in eighteen (35%) patients with cricoid pressure of 44 N (4.4 kg or approximately 9.7 lb).[40] These findings were validated in a recent study in children.[42] Furthermore, cricoid pressure deforms the larynx and impedes laryngoscopic visibility for intubation and thus may result in more intubation difficulties.[43] Finally, modern magnetic resonance imaging has questioned whether cricoid pressure truly closes the hypopharyngeal space or upper esophagus secondary to lateral displacement of the esophagus.[44] Thus, in regard of all these limitations it is not surprising that the European Resuscitation Council's 2010 cardiopulmonary resuscitation (CPR) guidelines stated: "The routine use of cricoid pressure in cardiac arrest is not recommended. If cricoid pressure is used during cardiac arrest, the pressure should be adjusted, relaxed or released if it impedes ventilation or intubation."[45]

ROLE IN DIFFERENT SETTINGS

Prehospital Care

Securing the airway by tracheal intubation in the prehospital setting may be very difficult. If airway management is difficult in a prehospital patient, maintenance of oxygenation

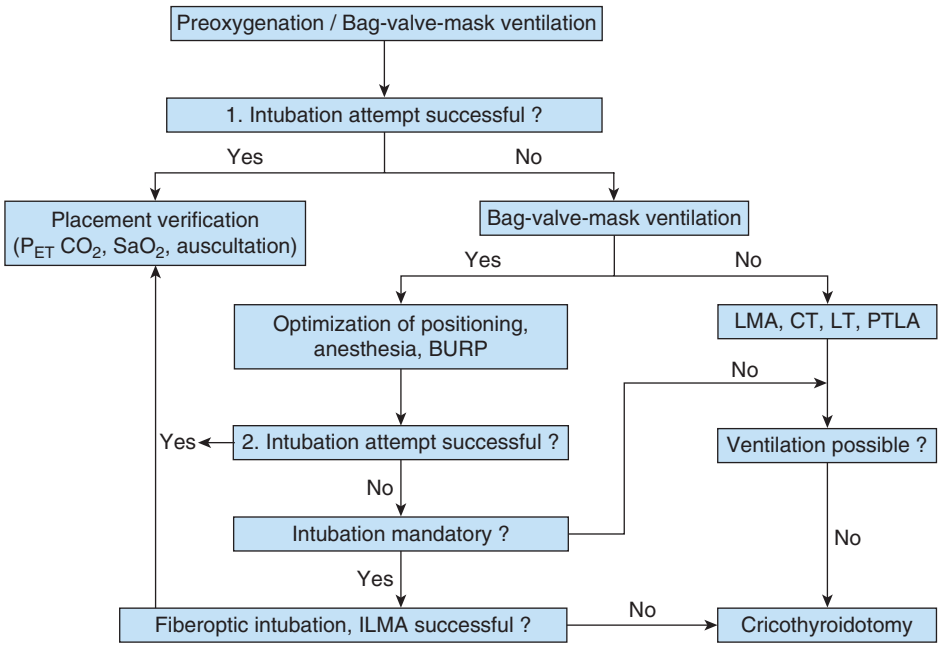

FIGURE 26-1 Algorithm for airway management. *BURP*, backward, upward, rightward pressure maneuver; *CT*, Combitube; *ILMA*, intubating laryngeal mask airway; *LMA*, laryngeal mask airway; *LT*, laryngeal tube; *PTLA*, pharyngotracheal lumen airway; $P_{ET}CO_2$, end-tidal carbon dioxide; SaO_2, arterial oxygen saturation.

can be in doubt despite use of a bag-valve-mask. Definite securing of the airway can be done later in the emergency department with more experienced personnel and equipment. In acute life-threatening situations, however, a standardized procedure, such as an algorithm, may be fast and reliable (Fig. 26-1).

Cardiopulmonary Resuscitation

Outcome after CPR in adults with chest compression alone was similar to that after chest compressions combined with mouth-to-mouth ventilation; Hallstrom et al. concluded that chest compressions alone may be the preferred approach for bystanders inexperienced in CPR.[46] It has been suggested that more lives could be saved if only rapid chest compressions are performed (producing immediate reperfusion of vital organs but with decreased oxygen content) in contrast to the "gold" solution of rapid chest compressions combined with ventilation, which may produce less perfusion but with higher oxygen content.

In a more recent prospective study in Japan, chest-compression-only CPR resulted in increased survival rates in adults.[47] Results, however, have been inconsistent in follow-up studies.[48,49] In a 2011 study, there seemed to be a time-dependent factor with regards to survival rates: The longer CPR was performed by lay rescuers, the more dependent ventilation became. This is rational from a physiologic viewpoint; at the beginning of a cardiac arrest caused by cardiac disease, there is still enough air in the lungs to enable sufficient oxygen uptake as long as chest compressions are able to deliver any circulatory output. Moreover, directly after cardiac arrest gasping may additionally ventilate the patient's lungs if the airway is in a patent state.[50] This reasoning is in accordance with a study in children where compression-only CPR seemed to be less effective. Because pediatric cardiac arrest contrasts with adult cardiac arrest, being more often caused by hypoxemia than cardiac disease, superiority of ventilation CPR is not surprising in pediatric patients.[51] In a metaanalysis, authors detected a potential benefit for compression-only CPR, with a "number needed to treat" of forty-one, based on prospective studies; in contrast, analysis of retrospective studies did not reveal any benefit for chest-compression-only CPR.[52] The 2010 CPR guidelines recommend that trained lay rescuers provide ventilation; untrained or unwilling rescuers should provide chest-compression-only CPR.[53] Chest compressions and ventilation are performed in a 30:2 ratio (thirty compressions to two ventilations) in a cardiac arrest when the airway is not secured.[53] After intubation, ventilation is performed out of synchrony with chest compressions; a respiratory rate of 10 breaths/min is recommended.

One argument that ventilation during CPR could be abandoned is that gasping provides sufficient gas exchange. The value of gasping in human subjects has to be interpreted with caution because fundamental differences in human and animal upper airway anatomy make it difficult to extrapolate results from laboratory studies, where gasping was beneficial. The human upper airway is kinked and is subject to rapid occlusion by the tongue and/or head position in the supine position, whereas the upper airway in swine, dogs, and rats is straight and may not be occluded by the

tongue or head position in the supine position.[54] In addition, animal studies were performed in fasting animals that, as a consequence of fasting, are extremely unlikely to aspirate gastric contents. Furthermore, it is unknown if humans gasp as frequently or as deeply as animals during cardiac arrest. Whether gasping in humans results in effective gas exchange has not been studied, and for ethical reasons, such a study would be extremely difficult to perform. If a patient is gasping and the rescuer is unwilling or unable to perform mouth-to-mouth ventilation during basic life-support CPR, one strategy is to keep the airway open and perform chest compressions alone until emergency medical services arrive so as to provide a minimum of ventilation.[53] In the absence of a dedicated airway, extending the head by placing a pillow under the shoulder or gently tilting it laterally could reduce the acute pharyngeal obstruction from the tongue falling backward over the palate.

Ventilation consumes time during CPR that could be devoted to chest compressions.[53] Because only rapid chest compressions are effective, some argue that time spent for ventilation should be decreased and the time for chest compressions increased. Because cardiac output during CPR is at best approximately 25% of normal, some argue that the low cardiac output does not need to be accompanied with a normal minute ventilation. This argument has yet to be proven in a clinical study. Until evidence is available, assisted ventilation should be performed during CPR whenever possible, although the rate of chest compressions should not be decreased critically by ventilation attempts.

Another method, first being described in the late 1990s, is to decrease intrapulmonary pressure by intermittent airway occlusion during the chest-decompression phase. Therefore, a special impedance-threshold valve was designed that is adjusted to a tracheal tube and occludes the airway in the decompression phase.[55] This occlusion results in decreased intrapulmonary pressure that enhances venous return to the heart and subsequently increases cardiac output with the next chest compression, improving oxygen transport to vital organs in cardiac arrest. The impedance-threshold valve is especially effective when intrapulmonary pressure is further reduced by active chest decompression using special suction cups attached to the sternum.[55] In a clinical study, use of such an impedance-threshold device significantly increased the proportion of patients that "survived to hospital discharge with favorable neurological function" (from 6% to 9%).[56] It should be noted, however, that active ventilation is mandatory using the impedance-threshold device, because continuous airway occlusion may otherwise result in atelectasis compromising pulmonary function.[57]

Trauma

The underlying principle for care of trauma patients is the ABCs (*a*irway, *b*reathing, *c*irculation) of resuscitation. Initial priorities after trauma are the same for the field and the hospital, but field providers usually have only limited equipment and limited assistance. They also provide care in the least-controlled circumstances, such as the roadside. Airway management is the highest priority and should occur as early as possible; in severe cases, it may be necessary in the field. Physical examination may reveal subcutaneous emphysema, absent breath sounds, and unilateral hyperresonance, identifying a tension pneumothorax, which can be decompressed. Progressive clouding of consciousness indicates nearly always a loss of airway protection, risking aspiration; endotracheal intubation is required. Oral intubation is the most common method because adequately sized tubes can be placed under direct vision. Nasal intubation requires significant expertise, especially when performed blind, and may exacerbate agitation; it is contraindicated in patients with midface fractures. Laryngoscopy in an awake patient nearly always worsens agitation; in these instances, rapid-sequence intubation (RSI) is advised.

RSI involves administration of a sedative followed by a short-acting muscle relaxant, typically succinylcholine. If endotracheal intubation fails, however, the patient must be ventilated with a bag-valve-mask device until short-term paralysis resolves. A retrospective analysis of trauma patients revealed that RSI in the field and in hospital were equally successful (97.9% vs. 98.5%) and safe.[58] Other studies reported success rates of 84% to 90.5% for field intubations, suggesting that training and experience are the major determinants of success.[59] Failed intubation was associated mainly with inadequate relaxation and difficult anatomy (i.e., morbid obesity or inability to visualize the vocal cords). Although the length of hospital stay and mortality were comparable, pneumonia occurred more frequently with RSI in the field than in hospital.[60] In a prospective study of severely injured trauma patients who were intubated in the field via RSI or immediately intubated on admission to the hospital, total out-of-hospital times were twice as high for the field group versus the hospital group (26 vs. 13 minutes).[59,61] Patients intubated in the field versus in the hospital had more ventilator, hospital, and intensive care unit days, higher mortality (23% vs. 12.4%), and a 1.5-fold increased risk of nosocomial pneumonia.[62] These data argue against spending extra time in the field with severely or even moderately injured patients (injury severity score 15 to 25).[63] Even in recently published studies, conducted several years after the problems of high failure rates in out-of-hospital emergency airway management had been identified, the rate of failed intubations is still unacceptably high.[64]

The high failure rate may indicate that although proper ventilation and perfect intubation skills in the field had been identified as being of utmost importance, it is not possible to achieve in all cases. Rescue personnel must recognize the importance of skill retention. Thus, before intubation attempts, a risk-to-benefit assessment is needed to prevent harm with multiple failed attempts. For example, if conditions are difficult (morbid obesity or midface fractures), it may be prudent to use a bag-valve-mask device and subsequently intubate immediately after arrival in the emergency

department. Health care personnel, however, must understand that bag-valve-mask ventilation needs to be performed carefully. In laboratory shock models, excessive ventilation with a bag-valve-mask caused increasing positive intrathoracic pressure, inhibition of venous return, decreased coronary perfusion, and thereby decreased survival.[65,66] In contrast, reduced intrapulmonary pressure resulted in better venous return in severe hemorrhagic shock and thus improved blood flow in an animal model comparable to CPR.[67] In contrast to the impedance-threshold device during CPR, however, large prospective studies determining the effect of decreased intrapulmonary pressure in shock patients are still lacking.

Cervical Spine Injury

Cervical spine injuries occur in 2% to 5% of blunt trauma patients,[68] and approximately 10% of these are unstable.[69] The most common fracture was C2, accounting for 24% of fractures. Dislocations are most common at C5-6 and C6-7.[70] Missed cervical spine injury can have disastrous consequences. The incidence of missed or delayed diagnosis is 1% to 5%, and up to 30% of these patients develop secondary neurologic damage.[71] The primary objective when managing the airway of such a patient is to minimize neck movement while the airway is secured rapidly and efficiently. Flight paramedics had only a 52% success rate with blind nasal intubation in spontaneously breathing patients in an out-of-hospital setting but were successful with this procedure in fourteen of fifteen patients in the hospital.[72] Traumatologists working in a prehospital environment used RSI with a success rate of 97% to 99%.[73] When emergency physicians were compared with anesthesiologists using RSI in an out-of-hospital environment, the nonanesthesiologists were twice as likely to fail to intubate and needed to undertake a surgical airway.[74]

During normal direct laryngoscopy and oral intubation, significant extension occurs between the occiput and C1 and between C1 and C2.[75] In an emergency department, the most common approach to intubating the multiple-injury patient with a potential cervical spine injury is RSI while maintaining cricoid pressure and manual inline neck stabilization. Manual inline neck stabilization is provided by an assistant who holds the patient's mastoid processes firmly down, opposing the upward forces generated during laryngoscopy.[76] In anesthetized patients, this maneuver reduced head extension by 50% and should increase the safety of direct laryngoscopy.[77] Axial traction must be avoided because excessive distraction may injure the spinal cord. The view at laryngoscopy is better with manual inline neck stabilization than with rigid-collar immobilization[78]; if a cervical collar is left on during laryngoscopy, the view will be often grade 3 or 4.[79] Once manual inline neck stabilization has been applied, the rigid collar should be removed and then reapplied when successful placement of the tracheal tube has been confirmed. Direct laryngoscopy and oral intubation are the quickest method for securing the airway in a patient with potential cervical spine injury.

Many clinicians advocate awake intubation as the safest approach in a patient with a cervical spine injury. It is thought that preservation of muscle tone provides protection, and spinal integrity can be monitored during airway manipulation.[80] Prolonged hypotension or malposition after intubation is at least as likely to cause neurologic injury as the intubation itself.[81] Awake techniques are particularly favored when the need for intubation is not urgent. Awake intubation is slower than RSI. In the acute trauma patient, it may increase the risk of aspiration and can increase intracranial pressure. Awake techniques, such as blind nasal, blind oral, and fiberoptic intubation, require considerable training and the patient has to be cooperative. Of the awake techniques, fiberoptic intubation is best in the patient with a cervical spine injury. The laryngeal mask airway (LMA), intubating LMA, and ProSeal LMA are useful alternatives if tracheal intubation is not possible. The LMA can be inserted easily in the neutral position and is an option in patients with cervical spine instability.[82] The standard LMA and intubating LMA cause temporary pressures of greater than 250 cm H_2O against the posterior pharyngeal wall during insertion in cadavers. This pressure is sufficient to induce up to 2 mm of displacement of C3.[83] During insertion, the intubating LMA causes some movement of the upper cervical spine, but it is less than that produced during direct laryngoscopy.[84] Neck stabilization methods make insertion of the LMA and intubating LMA more difficult, although the effect on the intubating LMA is less.[85]

Open Penetrating Chest Wounds and Tension Pneumothorax

An open penetrating chest wound is a challenging injury that is potentially associated with life-threatening airway compromise requiring complicated emergency airway management.[86] Intubation is challenging because preoxygenation may be less effective than usual; furthermore, if mask ventilation is attempted, air may be forced into the subcutaneous tissue, further distorting the anatomy.[87] In one study of thoracic trauma, approximately 20% of the patients suffered a pneumothorax and/or hemothorax, injuries were penetrating in approximately 10%, and only approximately 3% required a thoracotomy.[88] Dyspnea, hemoptysis, subcutaneous emphysema, pneumomediastinum, and pneumothorax are found commonly in patients with open, penetrating chest wounds (secondary to blunt trauma). Such a difficult airway needs to be secured; alternative airway techniques have been recommended as first-line approach, in particular, fiberoptic laryngoscopy. Fiberoptic intubation is the "gold standard" whenever the airway is expected to be difficult; direct airway injury can be diagnosed definitively, and an endotracheal tube can be placed into one of the bronchi if there is a major injury of the opposite side.[89] The patient should breathe spontaneously for as long as possible and ideally undergo

a gas induction of anesthesia followed by bronchoscopy; a rigid scope may be useful if there is blood or copious secretions in the pharynx.

Traumatic Brain Injury

Outcome of traumatic brain injury depends heavily on initial and admission Glasgow Coma Scale score and age.[90] Direct trauma-related destruction of brain structures (primary lesion) cannot be saved therapeutically. Secondary brain injury, however, defined as the damage to neurons owing to a systemic physiologic response to the initial injury, can be influenced. Hypotension and hypoxia are major causes of secondary brain injury.[91] One of the first tasks of trauma resuscitation is airway management. Approximately 50% of traumatic brain injury patients are reported to be hypoxic in the field, a finding associated with increased mortality.[92] Indications for intubation include an inability to maintain and to protect the airway but also may include inadequate ventilation, need to hyperventilate, hemodynamic instability, and need for radiographic imaging and subsequent surgery. The common coexistence of cervical spine injury requires vigilance. Early orotracheal intubation is recommended if the Glasgow Coma Scale score is 8 or less, although retrospective studies revealed increased mortality with field intubation.[93,94] Intubation usually can be accomplished without sedation and pharmacologic paralysis. Sedation and neuromuscular blockade can be useful in optimizing transport of the head-injured patient, but they interfere with neurologic examination and influence initial evaluation and management.[95] Hemodynamic stability similarly is ranked as a priority before and after intubation. These priorities should not be compromised in an attempt to prevent an increase in intracranial pressure.

Intracranial hypertension itself is not harmful unless it causes cerebral perfusion pressure to fall below a critical value. Cerebral ischemia leads to neuronal injury and cerebral edema, which further increases intracranial pressure, progressing to irreversible neurologic damage. Proper maintenance of gas exchange is more important than pharmacotherapy aimed at intracranial pressure control. Hyperventilation reduces intracranial pressure by causing cerebral vasoconstriction with a subsequent reduction in cerebral blood flow. Long-term hyperventilation is no longer recommended because outcome is worse than with normocapnia[96,97]; initial target partial pressure of arterial carbon dioxide (Pa_{CO_2}) should be 35 to 40 mm Hg.[98] Short-term hyperventilation, however, may have a role in reducing intracranial pressure in patients who are deteriorating rapidly before other measures can be instituted.[99] The lowest level of positive end-expiratory pressure that maintains adequate oxygenation and prevents end-expiratory alveolar collapse should be used.[92] Hemodynamic stability has particular importance in serious traumatic brain injury patients because outcome is worse with systolic pressures of less than 90 mm Hg[100] and cerebral perfusion pressures of less than 70 mm Hg. Thus, anaesthesia for intubation has to be performed as cautiously as possible maintaining a stable blood pressure.[101]

Burns

In a burn patient, airway and respiratory complications remain a common cause of morbidity and mortality. Multiple variables have an impact on resuscitation, including delay in its initiation, inhalation injury, and the depth and vapor-transmission characteristics of the wound itself. Inaccurate volume administration causes substantial airway, respiratory, and other morbidity; thus, burn resuscitations must be guided by hourly evaluation of resuscitation end points.[102] Constricting circumferential or near-circumferential torso wounds can reduce chest wall compliance as soft tissues swell beneath the inelastic eschar. Improvement in ventilation is common after escharotomy of the chest and abdomen.

In the initial evaluation and resuscitation phase, the key point of airway management is assessment of airway patency and inhalation injury. The latter results from aspiration of superheated gases, steam, or noxious products of incomplete combustion. Inhalation injury adversely affects gas exchange and hemodynamics. It also profoundly influences mortality from that predicted by age and burn size.[103] Physical signs of particular importance are singed nasal hair, facial burns, and soot in the mouth and between the teeth. Stridor mandates rapid intubation. In questionable cases, direct laryngoscopy and fiberoptic bronchoscopy can be very helpful; the bronchoscope can serve as a stylet for intubation. Patients at risk for progressive edema should be observed closely and intubated early. After securing the airway, the following require close attention: bronchospasm, small airway obstruction, carbon monoxide poisoning, and respiratory failure. If massive edema is associated with burn resuscitation, reintubation after unplanned extubation can be especially difficult; prevention by endotracheal tube security is the best approach, such as securing the endotracheal tube with an umbilical tie harness. Adjunctive techniques in case of difficult intubation, such as laryngeal mask airway or a needle or open cricothyroidotomy, can be lifesaving.

Drowning

Worldwide, 3.5 deaths per 100,000 population are caused by drowning accidents. Death by submersion is the second most common cause of accidental death in children.[104] Victims of drowning accidents usually show an initial phase of panic and swimming movements. Apnea and breath holding often are followed by swallowing of large amounts of fluid with subsequent vomiting, gasping, and fluid aspiration. Ultimately, severe hypoxia leads to unconsciousness, loss of airway reflexes, and further movement of water into the lungs. Aspirated hypotonic or hypertonic fluids result in

bronchospasm, leading to an increase in relative shunt and alveolar edema.[105] These events cause hypoxemia, decreased lung compliance, and increased work of breathing. Up to 70% of drowning victims aspirate foreign material such as mud, algae, and vomitus. Patients usually develop acute lung injury followed by acute respiratory distress syndrome within a very short time. Because hypoxia is the major cause of death, the primary goal is to restore oxygen delivery. Immediate rescue out of the water is critical. After initial resuscitation, continuing heat loss must be prevented by adequate insulation against the environment.[106] Patients presenting awake or somnolent but with clinical signs of respiratory distress should receive oxygen at a high concentration using a tight-fitting mask and a reservoir bag. In the case of progressive deterioration of respiratory or neurologic function, RSI has to be performed and ventilation with positive end-expiratory pressure and 100% oxygen initiated without delay. A nasogastric tube will decompress a full stomach and aid ventilation in these patients. Asystole and ventricular fibrillation warrant aggressive CPR because the prognosis is dismal; unfortunately, CPR is underused in drowning victims.[107] In an investigation of unwitnessed out-of-hospital cardiac arrest, near-drowning was an independent predictor of survival.[108]

ADJUNCTS FOR OXYGENATION, VENTILATION, AND AIRWAY CONTROL

Use of Oxygen

During resuscitation, 100% inspired oxygen ($FI_{O_2} = 1$) should be used as soon as possible. Exhaled air contains approximately 17% oxygen and approximately 4% carbon dioxide.[109,110] Ventilation with such a gas mixture of 17% oxygen and 4% carbon dioxide in animals[111] and healthy, conscious volunteers resulted in insufficient oxygenation and ventilation.[112] Short-term therapy with pure oxygen is beneficial and not toxic. Oxygen toxicity occurs only during prolonged therapy with a high FI_{O_2}. During bag-valve-mask ventilation using room air (21% oxygen) and a normal cardiac output, tidal volumes of 700 to 1000 mL (approximately 8.5 mL/kg) were required to maintain adequate oxygenation.[113,114]

Careful preoxygenation is essential to increase safety before induction of anesthesia and intubation in emergency settings such as trauma victims. Completely preoxygenated lungs can provide a supply of oxygen for up to 10 minutes by resorption of oxygen out of functional residual capacity.[115] This time can be further extended secondary to diffusion respiration.[116] Hemoglobin streaming through the pulmonary vessels continuously absorbs oxygen out of the functional residual capacity of the lungs (approximately 200 mL/min), whereas carbon dioxide remains (because of its high solubility) mainly in the bloodstream and only a small amount diffuses into the lungs (approximately 40 mL/min). Because the balance constitutes a negative amount of approximately 160 mL of gas per minute in the lungs, a subatmospheric pressure develops, which suctions gas into the lungs from the upper airways. If oxygen is administered continuously, for example, over a nasopharyngeal tube, partial alveolar oxygen pressure may be maintained at levels sufficient for arterial oxygenation; hypercarbia is generally well tolerated (unless brain injury or pulmonary hypertension).[115] Thus, oxygenation of the body had been maintained for up to 1 hour in animal settings and, in clinical settings, apnea times of up to 15 minutes have been reported.[115,117] Of note, in acute shock states in animal experiments, apnea times were dramatically shorter until oxygen saturation in the blood dropped[118]; nevertheless, the better preoxygenated are the lungs of a patient, the more reserve is available for apnea time.[115,118]

Ventilation Devices

BAG-VALVE-MASK VENTILATION

A simple, portable bag-valve-mask device usually is available in hospital wards and in every emergency medical service. Proper bag-valve-mask ventilation is a fundamental skill of resuscitation and should receive a high priority in training. Unfortunately, these skills are poorly performed even after retraining, and inadvertent hyperventilation is detrimental to morbidity and mortality. With an unprotected airway, the risk of stomach inflation and aspiration is high using standard bag-valve-mask resuscitators. Short inspiratory times, high flow rates, and high airway pressures, caused by squeezing the bag too hard and too fast, are the main causes of stomach inflation. Reduced expiratory times produced by inadvertent hyperventilation stacks air in the lungs, creating decreased cardiac refill and decreased coronary perfusion pressure. A small self-inflatable bag was advantageous over a large one when paramedics undertook bag-valve-mask ventilation with a pediatric versus an adult-sized self-inflatable bag using an in vitro model of ventilation with an unprotected airway. Pulmonary ventilation was similar with both bags, but stomach inflation was much less with the pediatric bag.[119,120]

Depending on lung compliance, different tidal volumes caused stomach inflation in patients, but most often at a peak inflation pressure of greater than 20 cm H_2O. Data from an in vitro model of an unprotected airway confirmed that longer inflation times produced increased lung ventilation and reduced stomach inflation, especially when intrapulmonary airway resistance was high. Although the bag-valve mask is the simplest and most-cost-effective ventilation device available, its efficacy is diminished by lack of skill of the user, the "incident stress" associated with treating a patient in cardiac arrest, and the subsequent inadvertent hyperventilation that these issues cause. A relatively new bag-valve-mask technology exists that assists rescuers in ventilating correctly by responding to squeeze and release of the bag and controlling the flow of gas from the bag, reducing airway pressure, increasing inspiratory times, and reducing the risk of stomach insufflations even in the hand of less-well-trained rescue personnel.[121]

AUTOMATIC TRANSPORT VENTILATORS

In prehospital care, mechanically powered devices are as effective as other devices for ventilating intubated patients. In unintubated patients, it depends on the mode of power; that is, in pressure-cycled devices, because these device must achieve a relatively high airway pressure (usually greater than the reported lower esophageal sphincter pressure) to turn off the flow and cycle to an exhalation, they create large amounts of stomach inflation, especially as the airway resistance increases or lung compliance decreases. The guidelines for resuscitation recommend avoiding these devices. On the other hand, tidal volume should be restricted in volume- and time-cycled ventilators. In an in vitro model of an unprotected airway, significantly less stomach inflation was found when applying a tidal volume of approximately 500 mL versus approximately 1000 mL.[122] Controlling inflation time, flow rate, and flow waveform with a mechanical ventilator may be the best solution to control and limit peak inflation pressure for a given tidal volume, but these variables are not controlled easily during manual ventilation.

Airway Control Devices

OROPHARYNGEAL AND NASOPHARYNGEAL AIRWAYS

These airway adjuncts can be used in unintubated patients requiring ventilation. The oropharyngeal airway should be inserted only in unconscious patients; otherwise, gagging and vomiting can be evoked. The nasopharyngeal airway is better tolerated in somnolent patients. The devices should be inserted carefully by trained personnel; lubricants ease insertion.

ENDOTRACHEAL TUBE

As early as possible during resuscitation, trained personnel should intubate the trachea. Before commencing intubation, the patient should be preoxygenated either by spontaneously breathing pure oxygen or by controlled bag-valve-mask ventilation with a high inspired concentration of oxygen. Preoxygenation increases the alveolar pressure of oxygen; elimination of nitrogen increases the reservoir of oxygen fivefold and generates a grace period of several minutes before a patient becomes hypoxic. The grace period depends on the alveolar volume, shunts, oxygen consumption, and oxygen-carrying capacity. The interruption of ventilation should be as brief as possible, and adequate ventilation and oxygenation must be provided if more than one intubation attempt is necessary. To facilitate intubation, the sniffing position and hyperextension of the head at the atlantooccipital joint is beneficial. A stylet, which should not extend over the distal end, can be used to provide some stiffness to the tube and makes control during insertion easier. When the cuff of the tracheal tube is inflated and the airway thus secured, cricoid pressure can be removed. Tube placement is confirmed by chest excursion and auscultation; over the epigastrium, no stomach gurgling should be heard during inspiration. These clinical signs are not always reliable[123]; unrecognized misplacement of the endotracheal tube occurred in up to 25% of intubated patients in the field.[6,7] Verification by direct visualization of the tube passing through the vocal cords and use of end-tidal carbon dioxide monitoring also are recommended.[124,125] Clinical assessment and esophageal detector devices may be used but are not reliable in all patients.

LARYNGEAL MASK AIRWAY

The LMA is now used widely for managing failed intubations or difficult airways.[126,127] It should be considered first among the alternative airway devices. Placement and use of an LMA are simpler than tracheal intubation because laryngoscopy and visualization of the vocal cords are unnecessary. The LMA is introduced into the hypopharynx, and the cuff seals the larynx after inflation. While the arrow is positioned at the upper esophageal sphincter without sealing it, the distal opening of the tube is just above the glottis, providing ventilation and oxygenation. The main limitation of the LMA is a lack of protection against aspiration,[128] although regurgitation is less likely than with bag-valve-mask ventilation.[129]

A recently developed ProSeal LMA has an additional lumen to introduce a nasogastric tube to drain the stomach or regurgitated fluids[130] away from the respiratory tract.[131] The bowl of the mask is deeper than that of a standard LMA, with an additional cuff on the dorsal side. Because of these modifications, the airway sealing pressures achievable with the ProSeal LMA are at least 10 cm H_2O higher than with the standard LMA. As with the standard LMA, the ProSeal LMA can be inserted in the neutral position, making it attractive in potential cervical spine injury. Another limitation of the LMA is the relatively low leak pressure, 19 to 22 cm H_2O,[132] which may decrease tidal volume and increase stomach inflation.[133]

The intubating LMA is a modified conventional LMA; once inserted, it allows passage of a tracheal tube, either blindly or by fiberoptic bronchoscopy. Standard insertion requires a neutral position; manipulation of the head and neck is not needed. In a recent study in Bordeaux, France, "senior emergency physicians" achieved a nearly 100% success rate in advanced out-of-hospital airway management applying the intubating LMA as a first-choice alternative to conventional intubation.[134] Again, this study indicates that it is not only a question of which airway device is applied but which airway device is applied by which rescuer.

COMBITUBE

The Combitube is essentially a double-lumen tube that is inserted blindly through the mouth and is more likely to pass into the esophagus (approximately 95%) than into the trachea (approximately 5%). The esophageal lumen is closed distally and perforated at the hypopharyngeal level with several small openings; the tracheal lumen is open distally. First, the proximal large pharyngeal balloon is inflated, thereby

filling the space between the base of the tongue and the soft palate. Second, the distal cuff is inflated. These cuffs provide a good seal of the hypopharynx from the oropharynx and stability in the trachea or esophagus, respectively. The most common reason for failure to ventilate is placing the Combitube too deeply; the entire perforated pharyngeal section enters the esophagus. Pulling the Combitube back 3 to 4 cm usually resolves the problem. The success of insertion and ventilation with the Combitube is comparable with that of other upper airway devices[135] and is 100% in an urban environment where trauma patients receive care.[136] The Combitube, however, is not well tolerated by patients with a persistent, strong gag reflex. It should be exchanged to an alternative airway as early as possible. Advantageously, the Combitube can be a routine device in emergency medicine[137] and in "cannot ventilate, cannot intubate" situations.[138] The Combitube has the same limitations as the LMA. Thus, it may be unsuitable in patients with hypopharyngeal pathology or preexisting esophageal pathology, such as a malignancy or esophageal varices.[139]

LARYNGEAL TUBE

The recently introduced single-lumen laryngeal tube can be inserted orally without additional equipment and is effective for ventilating and oxygenating patients who experience a respiratory arrest during induction of anesthesia.[140] Thus, the laryngeal tube may be used as an alternative airway device during routine or emergency airway management. Handling of the laryngeal tube has been simplified by blocking two cuffs with one instead of two catheters; the first secures inflation of the oropharyngeal cuff, and the second secures inflation of the esophageal cuff because of different resistance characteristics of the connected tubing. Given its design, the laryngeal tube may not be the best device for spontaneously breathing patients.[141] The blind ending in the esophageal inlet also may cause esophageal rupture in the case of vomiting.[142] Accordingly, the laryngeal tube has been fitted with a second lumen for suctioning and free stomach drainage (laryngeal tube S) but not for ventilation, as with the Combitube. In contrast to the Combitube, the laryngeal tube S has only one adapter, which may be connected with a ventilation device, whereas the remaining connector can only be connected to a suction adapter. This may achieve additional patient safety; it prevents an inexperienced user from inadvertently attaching a ventilator or bag-valve-mask device to the esophageal tubing, which could result in stomach inflation and subsequent ventilation-related complications.

VIDEOLARYNGOSCOPY

In the past, patients' tracheas were being intubated either by direct laryngoscopy or by awake fiberoptic access in expected difficult airway scenarios. In the last years, different portable laryngoscopes with integrated fiberoptic systems have been developed. These systems enable an indirect view of the glottis from the tip of the laryngoscope, and transmit that picture via a special monitor. Thus, the view of the glottis is often dramatically improved, enabling successful intubation as compared with conventional direct laryngoscopy.[143,144] It is noteworthy that the view of the glottis via a videolaryngoscope does not automatically signify that intubation will be successful. The human airway is kinked and often it may be necessary to compensate for this through use of a preformed stylet in order to place the tip of the tube into the glottic area during application of videolaryngoscopy.[145] The learning curve for these indirect videolaryngoscopic devices, however, is flat, and rescuers are often able to provide successful intubation after less than a dozen intubation attempts.[143,144,146,147] Thus, employment of videolaryngoscopy may increase in emergency intubation settings within the next years, even in the field, because of high intubation-success rates.

TRACHEOSTOMY AND CRICOTHYROIDOTOMY

When the airway is compromised by trauma, or when massive oropharyngeal or hypopharyngeal pathology is present, emergency access may be possible only through an emergency tracheostomy or cricothyroidotomy. Emergency tracheostomy usually is performed via a vertical incision from the cricoid cartilage down in the direction of the sternal notch. A skilled operator can insert a small, cuffed endotracheal tube rapidly.

Emergency cricothyroidotomy is a valid alternative for a less-skilled operator. The cricothyroid membrane, palpable directly under the skin, is incised in its inferior third to minimize the possibility of bleeding. The cricothyroid membrane is not always easy to appreciate (in obese patients or those with short necks). Cricothyroidotomy is performed infrequently; in inexperienced hands, success is only 60% to 70%.[148] The main advantage of this technique is the blunt dissection of the subcutaneous tissues all the way to the cricoid membrane. An airway catheter is then introduced over a dilator threaded over the guidewire.[149] This technique allows the ultimate insertion of an airway that is considerably larger than the initial needle or catheter. Its internal diameter often is sufficient to allow ventilation with conventional ventilation devices, suctioning, and spontaneous ventilation.

Needle cricothyroidotomy is another alternative, regardless of whether it is surgical or percutaneous. Needle cricothyroidotomy always requires the use of a jet device to provide ventilation. It is associated with a high incidence of complications, such as massive subcutaneous emphysema, barotrauma with pneumothorax or tension pneumothorax, and air trapping with severe hemodynamic instability.

CONCLUSION

The goal of ventilation strategy during resuscitation is to optimize oxygenation and carbon dioxide elimination. This can be achieved in an unprotected airway with techniques

such as mouth-to-mouth ventilation, but preferably with bag-valve-mask ventilation. Because ventilation of an unprotected airway may result in stomach inflation and subsequent severe complications, securing the airway with an endotracheal tube is the "gold standard"; however, poorly performed intubation can result in esophageal intubation and disaster. Thus, and importantly, airway-device complications are more related to training than to the devices themselves. Excellent success in emergency ventilation depends on initial training, retraining, and actual frequency of performing a given procedure on the job. Rescue personnel with less experience in advanced airway management should step back and try to avoid anesthesia induction and intubation when patients can be oxygenated by spontaneous breathing. If artificial ventilation is unavoidable, for example, during CPR, less-experienced rescuers can apply extraglottic airway devices or retreat to bag-valve-mask ventilation with high $F_{I_{O_2}}$. Success in out-of-hospital airway management is often less a question of the "right-tools" than one of the "the right tools in the right hands at the right time."[150]

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27

TRANSPORT OF THE VENTILATOR-SUPPORTED PATIENT

Richard D. Branson
Phillip E. Mason
Jay A. Johannigman

Mechanical ventilation of the critically ill patient is best practiced in the safe confines of the intensive care unit (ICU). Transport of ventilated patients, however, remains a frequent challenge. Successful transport requires effective communication, appropriate planning, key personnel, and compact, rugged equipment. Clinicians should be aware of the physiologic effects of transport, frequency of adverse events, and methods to prevent complications.

INTRAHOSPITAL TRANSPORT

Mechanically ventilated patients are moved frequently within the hospital. The most common destinations for patients transported from the ICU are computed tomography (CT) and the operating room with other radiologic modalities also being common.[1–15] Most transports between the ICU and non–operating room destinations last 40 to

90 minutes.[2,5–7,10,12–14] More recently, portable scanners have been used to perform CT scans in patients with traumatic brain injury to reduce the uncertainties of transport.

Magnetic resonance imaging is an increasingly common destination for the critically ill ventilated patient. Safe transport is more challenging in this setting because of limited patient access and the need for nonferrous equipment.

INTERHOSPITAL TRANSPORT

Interfacility transport has increased in recent years owing to the regionalization of specialty care in neonatology, respiratory failure, trauma, transplantation, stroke, and cardiac disorders. The growth of hospital systems with acute and chronic care facilities represents another reason for interhospital transport as patients travel back and forth based on acuity. The current military operations in Iraq and Afghanistan have generated thousands of long distance interhospital transports requiring mechanical ventilation.

Interhospital transport can be accomplished using ground or air transport. Ground transport is the most readily available and least expensive, while also the least influenced by weather. There are few restrictions on weight and patient access can be quite good. Helicopters offer a significant improvement in speed but are expensive to operate. Patient care is made more difficult by weight limitations and a cramped, noisy cabin. Fixed-wing transport is the only viable option when critical patients must be moved over long distances.

PREPARATION AND PLANNING

The American College of Critical Care Medicine suggests that all hospitals have a formalized plan addressing pretransport coordination and communication, composition of transport team, transport equipment, monitoring during transport, and documentation.[16] Many adverse events associated with transport can be avoided with preparation and communication.[14,15,17–21] Patients having to wait at their destination can be particularly problematic and can be avoided with proper coordination.[8]

An experienced critical care nurse and respiratory therapist should accompany all mechanically ventilated patients during transport.[16,22] The need for physician presence has been evaluated in pediatric transports but has not been clearly elucidated.[23–25] The American College of Critical Care Medicine recommends a physician competent in airway management, advanced cardiac life support, and critical care medicine accompany all unstable patients.[16] The American Association for Respiratory Care does not opine on physician presence, but does suggest that team members be skilled in airway equipment operation and troubleshooting.[22]

RISKS AND BENEFITS OF TRANSPORT

Considerable effort has been expended to catalog the risks of transport.[3–8,10–15,17,18,26,27] The costs associated with transport include transport equipment, personnel, and managing complications of transport. Benefits may include discovering new pathology that changes treatment, intervention to address disease processes, or, in the case of interhospital transport, receiving care not available at the sending facility. Several investigations have noted that in two-thirds of transports to radiology, the patient's treatment course is unaltered.[5,6] Head CT is least likely to result in a change in therapy, whereas abdominal CT is most likely to result in new findings and guide intervention.

PHYSIOLOGIC EFFECTS AND COMPLICATIONS OF TRANSPORT

Transporting ventilated patients requires transitioning to portable equipment, repositioning the patient, and transfer from the ICU bed. Patients are often transported in the supine position, which changes respiratory mechanics and may alter hemodynamics. Many intrahospital destinations are distant from the ICU, located in facilities never designed to house critically ill patients. Both remote locations and poor physical plants may contribute to complications and untoward outcomes. Complications of intrahospital transport are frequently recalled as "the catastrophe in radiology." During interhospital transport, patients must be cared for in the suboptimal confines of a transport vehicle. Transport complications range from minor changes in heart rate to cardiac arrest. Table 27-1 lists common complications. The true complication rate is difficult to ascertain because of inconsistent definitions in existing studies.

Cardiovascular Complications

Cardiovascular events are the most frequent complication during intrahospital and interhospital transport, and are reported in up to 50% of cases.[4–7,11,13,14,17,28–33] An increase in heart rate is seen frequently as a result of anxiety, pain, and activity. Arrhythmias are common during the transport of high-risk cardiac patients, a finding complicated by the fact that routine lead II monitoring may be unable to detect early changes.[34,35] Acute respiratory alkalosis resulting from hyperventilation alters myocardial irritability, leading to dysrhythmias.[4,36–39] This finding commonly is associated with unmonitored manual ventilation but can occur with a ventilator when minute ventilation is unreliable.[39]

Hypotension during transport may result from loss of intravenous access, interruption of vasoactive agents, pneumothorax, or bleeding. Alkalemia associated with

TABLE 27-1: COMMONLY REPORTED COMPLICATIONS DURING TRANSPORT OF THE MECHANICALLY VENTILATED PATIENT

- **Cardiovascular**
  - Arrhythmia
  - Hypotension
  - Hypertension
  - Tachycardia
  - Bradycardia
  - Myocardial ischemia
  - Worsening heart failure
  - Cardiac arrest
- **Respiratory**
  - Hypoventilation
  - Hyperventilation
  - Hypoxemia
  - Barotrauma
- **Neurologic**
  - Elevated intracranial pressure
  - Increased anxiety
- **Other**
  - Increased risk of ventilator-associated pneumonia
  - Bleeding or hemorrhage
  - Hypothermia
  - Effects of altitude on physiology[a]
    - Hypoxic hypoxemia
    - Expansion of trapped gases (endotracheal tube, pneumothorax, ears, gastrointestinal tract)
- **Equipment Failure or Mishaps**
  - Airway obstruction
  - Extubation
  - Intubation of right mainstem bronchus
  - Gastric aspiration around endotracheal tube cuff
  - Loss of battery power to monitoring equipment or ventilator
  - Damage to equipment as a result of mishandling or falls
  - Loss of oxygen supply
  - Failure to reproduce ICU ventilation parameters with a portable ventilator or manual ventilator (loss of positive end-expiratory pressure, failure to trigger, inappropriate tidal volume or frequency)
  - Effects of altitude on equipment performance[a]
  - Loss of venous access/indwelling vascular catheters
  - Interruption of medications—continuous and intermittent
  - Inadequate chest tube drainage

[a]Unique to air transport.

hyperventilation likewise can cause hypotension.[4,39,40] Excessive hyperventilation is associated with increased intrathoracic pressure, reduced venous return, and reduced cardiac output. During cardiopulmonary resuscitation, excessive ventilation reduces the efficiency of cardiopulmonary resuscitation and is referred to as "death by ventilation." Hypertension can result from stress and anxiety, as well as from patient movement that encounters "bumps" in the transport path and jostling of patients that causes pain.[3,5,6,41] Cardiac arrest has been reported during transport, but patient movement per se has not been directly implicated.[17,31,32]

Respiratory Complications

Hypoxemia is a well-documented transport complication.[2,4–6,14,30,32,33,40,42,43] It may result from loss of positive end-expiratory pressure (PEEP), changes in patient position, impaired secretion removal, equipment malfunction, and failure to reproduce ventilator settings adequately. During transport of adult patients, high inspired oxygen concentrations (FI_{O_2}) are used commonly as a matter of convenience.[18,44] Elevated FI_{O_2}, however, may mask deterioration in lung function and contribute to absorption atelectasis. Patients requiring PEEP of more than 10 cm H_2O are vulnerable to deterioration in oxygenation during transport that lasts up to 24 hours.[3]

Hyperventilation is frequent with manual ventilation[4,39,42,45] and with poor control of minute ventilation by portable ventilators.[42] Sudden respiratory alkalosis can result in changes in cardiovascular function. Hyperventilation increases intrathoracic pressure, produces air trapping, reduces cardiac output, shifts the oxyhemoglobin dissociation curve to the left (hindering oxygen unloading), and causes cerebral and myocardial vasoconstriction. These combined effects may adversely affect patient outcome.[46]

Hypoventilation is reported less frequently and generally is better tolerated.[3–6,8,10–13,26,27] Decreased tidal volume contributes to atelectasis and acute respiratory acidosis, which may compromise cardiac function. Sedation and neuromuscular blocking agents may also contribute to hypoventilation.

Unplanned extubation is an infrequent but potentially catastrophic complication.[17,30] Inability to establish an adequate airway is associated with hypoxemia and poor outcome in head-injured patients.[19,47] Unintubated patients with marginal airway control may benefit from intubation before transport. Radiologic procedures requiring the patient to remain supine may compromise the tenuous airway.

Other Complications

Increases in intracranial pressure have been reported during transport and are associated with supine positioning, changes in ventilation, airway compromise, and hypoxemia.[3,19,47]

Hypothermia during transport occurs because hallways, examination areas, and transport vehicles have imprecise environmental controls.[10] Exposure of skin surfaces for adequate radiologic examinations and use of skin preparations for procedures further contribute to temperature loss. Blood loss has been reported during movement of patients with unstable fractures.[10] Transport from the ICU is an independent predictor for the development of pneumonia, although a causative role cannot be definitively established.[9,48] Table 27-2 lists studies evaluating complications of transport.

TABLE 27-2: COMPARISON OF STUDIES EVALUATING COMPLICATIONS AND MISHAPS INTRAHOSPITAL TRANSPORT OF CRITICALLY ILL PATIENTS

Year, Author	Complication Rate	Complications				Type of Ventilation	Attendants
		Cardiovascular	Respiratory	Equipment	Other		
1975, Waddell	7.2%	7.2% Hypotension, hypertension, tachycardia	0%	0%	Bleeding 1.6%	NR	RN, MD
1986, Insel	24%	24% Hypotension, arrhythmia	0%	0%	0%	Manual	RN, MD
1987, Braman	66%	25% Hypotension, arrhythmia	56% Hypocarbia, hypercarbia	5.5% Ventilator battery failure, Disconnected oxygen supply	0%	Manual $n = 20$ Ventilator $n = 16$	RN, MD, RRT
1988, Indeck	68%	61% Tachycardia, hypotension, hypertension	37% Hypoxemia, tachypnea	0%	0%	Ventilator	RN, MD RRT
1989, Weg	15%	0%	10% Hypoxemia, hypocarbia	5% Disconnected oxygen supply	0%	Manual	RN, RRT
1990, Andrews	51%	9% Hypotension 23% Rise in ICP 14% Hypertension	9% Hypoxemia	NR	0%	Ventilator	NR
1990, Smith	34%	NR	NR	34% ECG lead disconnected, monitor battery failure, ventilator disconnection	NR	NR	RN, MD, RRT
1992, Hurst	66%	27% Tachycardia 36% Hypotension, hypertension	20% Tachypnea 2% Hypoxemia	5% Pulse oximeter failure, monitor battery failure	0%	Ventilator	RN, MD, RRT
1995, Szem	5.9%	1% Hypotension 1.5% Cardiac arrest	4% Hypoxemia	NR	NR	Manual or ventilator	MD, RRT
1995, Evans	53%	5.5% Arrhythmia 25% Tachycardia 39% Hypotension	17% Hypoxemia	11%	0%	Ventilator	NR
1995, Wallen	76%	47% Tachycardia 21% Hypotension	29% Tachypnea 6% Hypoxemia	10% Monitoring battery failure, ventilator disconnection	10% Hypothermia	Manual	RN, MD
1998, Stearly	15.5%	NR	NR	NR	NR	NR	RN
2004, Beckman	31%	3% Hypotension 3% Cardiac arrest	11% Hypoxemia or hypoventilation	34% Including unavailable devices, battery exhaustion, ventilator failure, exhaustion of oxygen supply	NR	Ventilator	RN
2006, Maza	46%	17% Hypotension 8% Hypertension	29% Hypercarbia	NR	66% Agitation	Ventilator	MD, RRT, RN
2006, Gilman	23%	1% Hypotension 4% Hypertension 0.3% Bradycardia 2% Tachycardia	0.3% Hypoxemia	9% Equipment "problems"	7% Hypothermia	Ventilator	RN
2009, Zuchelo	100% (112 events in 44 transports)	12% Tachycardia 31% Hypertension	28% Hypoxemia 9% Hypercarbia 17% Acidosis	14% Exhaustion of battery or oxygen supply 3% Oximeter failure	3% Agitation 2% Emesis	Ventilator, manual ventilation	MD, RRT, RN

Abbreviations: ECG, electrocardiograph; *ICP*, intracranial pressure; *MD*, physician; *NR*, not reported; *RN*, registered nurse; *RRT*, registered respiratory therapist.

SPECIAL CONSIDERATIONS FOR AEROMEDICAL TRANSPORT

Air transport subjects patients to altitude-induced physiologic alterations. Fixed-wing aircraft commonly pressurize to a cabin altitude of 8000 feet (barometric pressure of 565 mm Hg). Rotor-wing aircraft do not have pressurized cabins, leaving the patients and crew exposed to ambient barometric pressure. Flight altitudes are typically much lower in fixed-wing flight, but may reach physiologic significance when flying over high terrain.

The most relevant alterations in the hypobaric environment are hypoxemic hypoxia and expansion of gases. A change in altitude from sea level to 8000 feet is associated with hypoxemia in patients with normal and abnormal pulmonary function.[49,50] At similar altitude changes, gases expand in volume by 30%. This may cause injurious pressure increases in endotracheal tube cuffs during ascent.[51–53] Inconsequential volumes of trapped gases at sea level may cause significant physiologic effects at altitude, most dramatically in the setting of untreated pneumothorax. Less severe, but important, effects for patient comfort include ear pain secondary to pressure changes and expansion of gas in the gastrointestinal tract.

Ventilator performance can be adversely affected by changes in barometric pressure. Pneumatically operated devices will have alterations in tidal volume, frequency, and inspiratory time as altitude increases. Even sophisticated transport ventilators may deliver excessive tidal volumes in hypobaric environments.[54] Some newer ventilators automatically compensate for hypobaric effects on gas density.

CONTRAINDICATIONS TO TRANSPORT

There are few absolute contraindications to transport. Transport of the ventilated patient is best considered as transferring the ICU with the patient, not transferring the patient from the ICU. Patients occasionally are deemed too sick to transport. The specific contraindications to transport are (a) inability to maintain acceptable hemodynamic status, (b) inability to establish an adequate airway, (c) inadequate personnel, (d) inability to maintain adequate gas exchange, and (e) inability to monitor patient status effectively. Rescue therapies for acute respiratory distress syndrome are a relative contraindication to transport. If transport is required for potentially lifesaving therapy, then it should be considered. Safe transport with aggressive rescue therapies, including inhaled nitric oxide, prone ventilation, inhaled prostacyclin, and high-frequency percussive ventilation, has been described.[55–59]

EQUIPMENT AND MONITORING DURING TRANSPORT

Appropriate equipment and monitoring are important to maintaining homeostasis and ensuring safety (Table 27-3). Monitoring during transport should emulate the ICU. Minimum requirements include electrocardiographic monitoring of heart rhythm and rate, invasive or noninvasive blood pressure monitoring, and pulse oximetry. Continuous capnography greatly enhances safety by immediately detecting inadvertent extubation, circuit disconnection, or ventilator failure. Its importance cannot be overstated. Monitoring should adapt to the needs of the patient and include additional pressure monitoring if intracranial pressure or central venous pressure catheters are present. Battery-powered intravenous pumps for medication delivery also are required.

Equipment for transport should be rugged, lightweight, reliable, and operate from battery power for at least 1 hour. Required equipment for all transports includes a physiologic monitor; pulse oximeter; ventilator; manual resuscitator with a PEEP valve and mask; oxygen supply with sufficient reserve; stethoscope; and emergency airway-management equipment. Sedative, analgesic, and neuromuscular blocking agents, as well as resuscitation drugs and fluids should be readily available during transport. Some means to humidify inspired gases and suction the airway should be available for interhospital and long intrahospital transports. A spirometer to monitor tidal volume is useful with ventilators that fail to provide a reliable tidal

TABLE 27-3: MONITORING AND LIFE-SUPPORT EQUIPMENT FOR TRANSPORT OF THE VENTILATOR-DEPENDENT PATIENT

Monitoring
- ECG monitoring (rate and rhythm)
- Arterial blood pressure monitoring (invasive or noninvasive)
- Pulse oximetry
- Additional pressure monitoring (e.g., pulmonary artery, intracranial)
- Stethoscope
- End-tidal CO_2 monitor
- Portable spirometer (if not integral to ventilator)

Support equipment
- Portable ventilator capable of providing required mode, tidal volume, and PEEP
- Airway maintenance (should include a difficult airway kit)
- Manual resuscitator and mask
- Oxygen supplies (one or two cylinders)
- Drug box (emergency drugs, patient-specific drugs, sedatives, IV fluids)
- Infusion pumps (battery-operated)
- Defibrillator (optional)
- Portable suction (optional)

volume and during the use of pressure ventilation. Airway carbon dioxide monitoring can be helpful when sedation reduces minute ventilation.

A dedicated transport cart or trolley may simplify transport but is an inefficient use of resources.[6,34,45,60,61] The advantage of the cart is immediate availability of required devices. The disadvantages are cumbersome size and cost. A dedicated trolley for transport perhaps is best suited for interhospital transport.[59]

EQUIPMENT MALFUNCTION AND/OR MISHAPS

Mishaps range from benign to catastrophic. The frequency of mishaps varies widely with the definition. Using a broad definition of mishap, up to one-half of patients suffer a mishap during transport, most of which are minor and do not cause adverse effects.[8,14,15,17] Common mishaps include loss of vascular access or intravascular monitoring devices, disconnection from oxygen supply, disconnection from the ventilator, and improper care of chest tubes.[4,6,8,13–15,17,30,31,41]

Equipment failure remains a common mishap during transport, frequently attributed to poor planning and carelessness.[13,41] Reported failures include depletion of battery power of ventilator or monitoring equipment, exhaustion of portable oxygen supplies, ventilator failure, and damage to devices resulting from falls to the floor.[4–6,8,13–15,17,26,30,31] Exhaustion of a compressed oxygen supply during use of a pneumatically powered ventilator terminates ventilation and can be a life-threatening mishap. Table 27-2 provides a comparison of studies evaluating complications and mishaps in intrahospital transport of critically ill patients.

Rationale for Use of a Portable Ventilator

Manual ventilation is commonly used during transport. It is inexpensive, simple, and requires only human power. During manual ventilation, however, the volume, frequency, and pressure applied are unknown. Several investigators have noted hyperventilation and acute respiratory alkalosis during manual ventilation resulting in cardiovascular complications.[34,39,40,42,43,45–47] Aggressive manual ventilation can result in excessive airway pressures, causing barotrauma or volutrauma and worsening air trapping.[62]

Manual ventilation can be successful in the hands of a skilled clinician with additional volume-monitoring and pressure-monitoring capabilities.[10,13] Monitoring end-tidal CO_2 also may prove helpful in preventing hyperventilation.[40] Simple reasoning, however, dictates that manual ventilation cannot replicate the tidal volume, frequency, FI_{O_2}, PEEP, and mode of ventilation with the consistency and precision of a ventilator. Maintaining constant PEEP with a manual resuscitator is difficult and failure to do so can lead to hypoxemia.[2,18,43] Finally, manual resuscitators cause excessive work of breathing when spontaneous ventilations are present.[63,64]

Comparisons of manual ventilation with a transport ventilator uniformly support the use of a ventilator to preserve normal gas exchange.[4,39,42] A mechanical ventilator also allows monitoring and alarms. Modern transport ventilators provide the most commonly used ventilator modes, flow triggering, and constant FI_{O_2} and PEEP.

Portable ventilators are more expensive than manual resuscitators, and many require a high-pressure (50 pounds per square inch gauge [psig]) gas supply. Although manual ventilation of the postoperative patient with normal lungs during transport to the recovery room is safe, ventilation of the patient requiring PEEP, elevated FI_{O_2}, and constant volume is best accomplished by a ventilator.

TRANSPORT VENTILATORS

Technically, any ventilator that operates from a battery and either an internal gas source or a compressed gas cylinder could be considered a transport ventilator. Because of the demands of patient transport, however, these simple criteria are inadequate. Using performance to discriminate transport ventilators yields three categories: automatic resuscitators, pneumatically powered transport ventilators, and sophisticated transport ventilators.

Automatic Resuscitator

Automatic resuscitators provide ventilation at a set pressure. The user has limited control over respiratory parameters, and some do not allow any control of respiratory rate or tidal volume. The ability to apply PEEP is limited or nonexistent. As a function of pressure cycling, the respiratory rate and tidal volume vary with lung compliance. When compliance is low, tidal volume is small and frequency rapid; when compliance is high, tidal volume is high and frequency slow. These devices are powered pneumatically (requiring no electricity), and have only a mechanical, audible high-pressure alarm, and disposable pressure manometers. Spontaneous ventilation requires entrainment of ambient air, which reduces FI_{O_2}. Spontaneous respirations will cause dyssynchrony and increased work of breathing because of limited inspiratory flow rate and difficulty triggering. Automatic resuscitators are designed for use in the prehospital setting by personnel with limited expertise in mechanical ventilation.

The Vortran and Oxylator EM-100 are inexpensive examples of automatic resuscitators (Fig. 27-1). The Vortran has proven unreliable when the orientation is changed, failing to cycle.[65,66] In the presence of a leak, if the set peak pressure cannot be reached, both devices will remain stuck in inspiration. Despite these limitations, successful use of the Vortran in intubated, closely monitored subjects has been reported.[67]

FIGURE 27-1 Examples of automatic resuscitators, the Vortran (left) and Oxylator (right).

Our experience with the Vortran, however, suggests it is unsuitable for transport of patients with even minor lung disease.

Simple Transport Ventilator

The simplest transport ventilators provide mechanical ventilation at a specified rate and volume and include a pressure-relief valve with an audible mechanical alarm. Most are powered and controlled pneumatically. In some instances, a battery allows for simple low-presure and high-pressure alarms, as well as monitoring and display of airway pressure. Simple transport ventilators also are used primarily in prehospital settings by personnel with some training in mechanical ventilation. More complex than automatic resuscitators, they offer respiratory rate and tidal volume adjustment and can be used with spontaneously breathing patients.

EXAMPLES OF SIMPLE TRANSPORT VENTILATORS

The AutoVent 2000 (Fig. 27-2) and 3000 are pneumatically powered transport ventilators operating in the intermittent mandatory ventilation mode. FI_{O_2} is 100% and cannot be adjusted, and PEEP is not available. Mandatory breaths are time-triggered, flow-limited or pressure-limited, and time-cycled, while spontaneous breaths are pressure-triggered, pressure-limited, and pressure-cycled. During spontaneous breaths, the patient breathes from the demand valve at

FIGURE 27-2 The AutoVent 2000 simple transport ventilator.

48 L/min. If patient demand exceeds 48 L/min, ambient air is drawn into the valve, diluting the FI_{O_2}. There is no monitoring. An audible alarm sounds if airway pressure exceeds 50 cm H_2O.

The AutoVent 2000 is designed for adults and allows control of breath rate and tidal volume. The AutoVent 3000 is designed for adults and children and allows the user to control inspiratory time. The AutoVent 4000 offers additional alarms, manometer, adjustable airway pressure relief valve, and continuous positive airway pressure (CPAP) mode; it allows selection of FI_{O_2} 0.65 or 1. The ability of the AutoVent 4000 to provide a consistent FI_{O_2} is altered by reduced compliance. As the lung becomes stiffer, the venture mechanism reduces air entrainment and FI_{O_2} increases while tidal volume falls.

The AutoVent ventilators consume approximately 0.5 L/min of gas to operate the logic. The higher the frequency setting, the higher is the gas consumption. The inspiratory flow is fixed at 48 L/min. In patients with an active respiratory drive, the flow capabilities of the AutoVent devices may result in flow starvation, increased work of breathing, and asynchrony.

The Uni-Vent 706 (Fig. 27-3) is a pneumatically powered, electronically controlled ventilator delivering an FI_{O_2} of 1. Controls set inspiratory flow and a series of rate, inspiratory time, and inspiratory-to-expiratory timing (I:E) ratio combinations appropriate for adult and pediatric ventilation. Inspiratory flow is limited from 0 to 90 L/min, and a high-pressure limit can be set (60 or 80 cm H_2O) at the patient valve, which activates an audible alarm when exceeded. Prehospital use of the Uni-Vent 706 by paramedics during cardiopulmonary resuscitation of intubated victims has proven successful.[68]

Sophisticated Transport Ventilator

A sophisticated transport ventilator is capable of performance comparable to an ICU ventilator. These devices may have built-in compressors or turbines to generate positive

FIGURE 27-3 The Uni-Vent 706 simple transport ventilator.

pressure without compressed gas and contain an air–oxygen blender. Most offer extensive control of ventilator parameters and comprehensive alarms. Sophisticated transport ventilators are intended for interhospital or intrahospital transport of critically ill patients. These devices should be capable of ventilating the sickest patients.

EXAMPLES OF SOPHISTICATED TRANSPORT VENTILATORS

The IC-2A is a flow controller that can be triggered by pressure or time or manually; it is also pressure- or flow-limited and time-cycled (Fig. 27-4). It requires a compressed-gas source for delivery to the patient, as well as for the fluidic logic circuit. The IC-2A delivers an FI_{O_2} of 1. Controls include the mode of ventilation, inspiratory and expiratory time, inspiratory flow, sensitivity, and PEEP/CPAP level. Airway pressure is displayed on an aneroid pressure gauge. The IC-2A is often used for ventilation in the magnetic resonance imaging scanner because it has no ferrous components. The excessive gas consumption should be considered when gas supplies are limited. The IC-2A operation during synchronized intermittent mandatory ventilation limits the flow delivered to the set flow on the ventilator, potentially increasing the work of breathing. Our experience with this ventilator suggests most patients have to be sedated to tolerate the operational limitations.

The LTV 1200 offers the performance of a critical care ventilator at a size and weight appropriate for a transport ventilator (Fig. 27-5). It provides synchronized intermittent mandatory ventilation, controlled mechanical ventilation, pressure support, and CPAP modes. Pressure-controlled and volume-controlled breaths are possible. The integral turbine

FIGURE 27-4 The MRI compatible IC-2A.

FIGURE 27-5 The LTV 1200 sophisticated transport ventilator.

permits mechanical ventilation without a compressed gas source. Oxygen can be supplied from a low-flow or compressed-gas source. The user has extensive control of ventilator parameters. Airway pressure, total breath rate, exhaled tidal volume, total minute volume, I:E ratio, calculated peak flow, and patient effort are monitored and displayed. The bias flow during exhalation (10 L/min) increases gas consumption and should be considered when planning transports. The LTV 1200 offers additional features, including ventilator presets, and an oxygen conservation feature to decrease gas consumption during transport. The LTV 1200 also utilizes an electronic control of PEEP, compared to the a spring-loaded valve used with the LTV 1000. This allows the LTV 1200 to apply pressure breaths relative to baseline pressure.

The Uni-Vent 754 is an electrically powered flow or pressure controller offering controlled mechanical ventilation, synchronized intermittent mandatory ventilation, and CPAP modes of ventilation. The internal compressor allows use without a compressed gas source. The operator can set mode of ventilation, breath rate, inspiratory time, tidal volume, sensitivity, PEEP, FI_{O_2}, and peak inspiratory pressure limit. Airway pressure is displayed, as well as the airway pressure waveform, ventilator breath rate, inspiratory time, I:E ratio, tidal volume, FI_{O_2}, mean airway pressure, and baseline airway pressure. A full set of alarms is present. Inspiratory flow is limited to 60 L/min, which can cause dyssynchrony in spontaneously breathing patients. The inability to provide pressure-limited breaths is a minor limitation. The Uni-Vent 754 has a proven track record in transporting ventilated military casualties by U.S. Air Force critical care, air transport teams.

The Uni-Vent 731 transport ventilator (Fig. 27-6) is the next generation of Impact ventilators and is an electrically powered device that offers multiple improvements over the Uni-Vent 754. Most notable is the ability to provide pressure-limited breaths, integral pulse oximeter, and a 10-hour battery life. The peak flow in volume ventilation has also been increased to 100 L/min. The 731 has the capability to provide closed-loop control of inspired oxygen concentration using the pulse oximeter input. The target arterial oxyhemoglobin saturation (SpO_2) can be set between 92% and 99%. If SpO_2 falls below 88%, the FI_{O_2} is increased rapidly to alleviate hypoxemia. This system has potential important advantages during transport when physiologic changes occur quickly and access to the patient may be limited. At the time of writing, this system is not available in the United States.

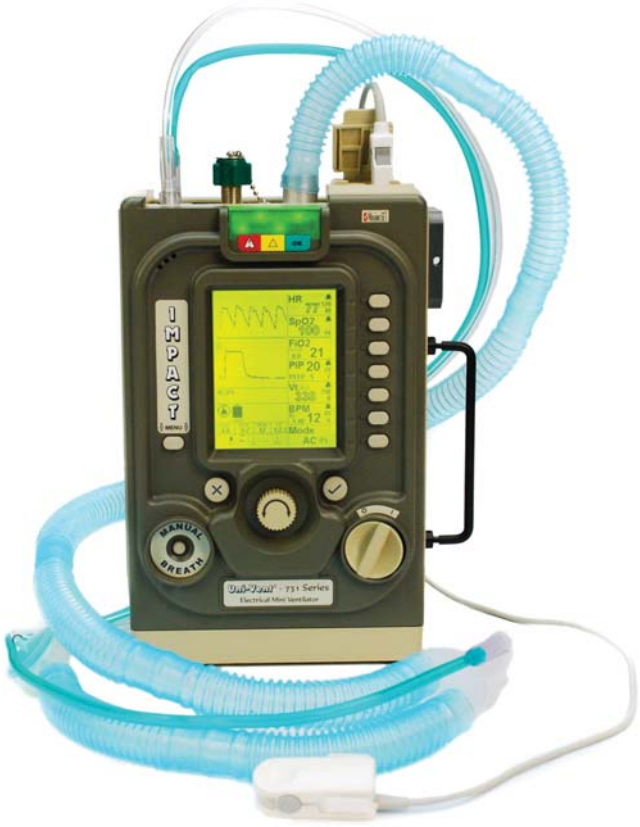

FIGURE 27-6 The Impact 731 sophisticated transport ventilator.

ATTRIBUTES COMMON TO ALL TRANSPORT VENTILATORS

Weight

These devices must be person-portable and able to be mounted on a variety of platforms. In our mind, portable means that a respiratory therapist can carry the device to and from destinations. In our opinion, ICU ventilators that can be mounted on the ICU bed are in reality not portable. A maximum weight of 8 kg facilitates these requirements.

Durability

These devices should be compact, simple to operate, durable, and unaffected by extremes of heat, cold, or vibration. Proper shielding is required to limit emission of unacceptable levels of electromagnetic energy. Automatic resuscitators in particular should function properly after prolonged storage with minimal maintenance.

Power Requirements

Automatic resuscitators are pneumatically powered, negating the need for batteries. Simple and sophisticated transport ventilators often are powered electrically and pneumatically.

Transport ventilators use a variety of battery supplies. Sealed lead-acid batteries have a low energy density but are durable and inexpensive. Sealed lead-acid batteries hold a charge even when stored for long periods of time. Nickel-cadmium (NiCad) batteries have a higher energy density but are more expensive. Nickel-metal hydride batteries have even a higher energy density than NiCad batteries and are more expensive. Lithium-ion batteries have the

highest energy density and are the most expensive. NiCad, and to a lesser extent nickel-metal hydride, batteries (but not sealed lead-acid or lithium-ion batteries) can suffer from voltage memory and should be stored in the discharged state. Both lithium-ion and NiCad batteries will self-discharge during storage. Duration of ventilator operation on battery is significantly impacted by ventilator settings in all devices.

Oxygen consumption should be less than 5 L/min, keeping in mind that oxygen consumption varies with ventilation mode and the use of PEEP. The device should have the capability of generating flow without a compressed-gas source and offer a means of enriching the inspired-gas mixture with oxygen from a low-pressure source such as a concentrator.

Controls

Controls should be large and not easily adjusted accidentally. Any display should be viewable from an angle and in variable ambient light.

Safety

Automatic resuscitators and simple transport ventilators have basic safety features, whereas sophisticated transport ventilators possess safety features comparable with those of critical care ventilators. A pressure-relief valve that vents gas to the atmosphere at a preselected peak inspiratory pressure is essential. Violation of the high-pressure limit should be signaled by a visual or audible alarm. An antiasphyxia valve that allows the patient to breathe from ambient air in the event of power source failure is desirable.[69] Battery-powered ventilators should be equipped with a "low battery" alarm as the battery nears depletion. If the compressed-gas source falls below operating pressure of the ventilator or is empty or disconnected, an audible or visual alarm should sound. Visual alarms are critical when ventilators are used in environments with high levels of ambient noise such as aircraft.

Assembly and Disassembly

These devices should be designed so that incorrect circuit installation is impossible. Typically, there is a single-limb circuit with an external expiratory valve. Patient valves located at the endotracheal tube should be cleared of secretions easily.

PERFORMANCE ISSUES RELEVANT TO ALL TYPES OF TRANSPORT VENTILATORS

Delivered Tidal Volume

Several investigators have demonstrated unreliable tidal volume delivery with transport ventilators, encouraging monitoring with a portable spirometer.[54,70–76] This includes low tidal volumes in the face of low lung compliance and excessive tidal volume under normal loads and at altitude.

Imposed Work of Breathing

Transport and home-care ventilators often used for transport have been shown to have an unacceptable imposed work of breathing.[74–76] Recent studies of new devices show a wide range of capabilities among transport ventilators.[70,76,77] Transport ventilators with flow triggering and PEEP compensation consistently offer the least imposed work of breathing.

Battery Life

Exhaustion of equipment batteries, including transport ventilators, has been reported in multiple studies of critical care transport.[8,14,15,17,30] The consequences of ventilator battery exhaustion can be catastrophic during long transport of patients requiring advanced mechanical ventilation. The battery life among common transport ventilators varies greatly and may differ from values in the user's manual.[78–80] Use of PEEP, pressure-control ventilation, and increasing FI_{O_2} will shorten battery life in electrically powered ventilators while having little effect on pneumatically driven models.[79,80] Battery life should be considered when planning transport. Provisions should be made for extra batteries or use of AC power if the transport duration exceeds battery life.

Oxygen Consumption

It is critical to estimate expected oxygen consumption to plan for a safe transport. It is intuitive that high FI_{O_2} will increase oxygen consumption, but accounting for bias flow, leaks, changes in patient condition, and variability between ventilators is more difficult. A study of military patients found oxygen consumption was 1.6 to 10.2 L/min using the Uni-Vent 754, with a broad range of mechanical ventilation parameters.[80] The LTV 1000 and LTV 1200 offer a cylinder-duration calculator that slightly underestimates cylinder duration.[81] The Dräger portable ventilators and Impact 731 have a continuous display of oxygen consumption on the front panel display. Continuous assessment of oxygen consumption will allow early identification of consumption exceeding estimates, which should prompt a search for leaks, increase efforts to conserve oxygen, and take steps to terminate or divert the transport as needed.

Operation in a Hazardous Environment

Worldwide concern over terrorist events and natural disasters has led manufacturers and investigators to consider use of portable ventilators in hazardous environments. This includes following radiation exposure and airborne biologic

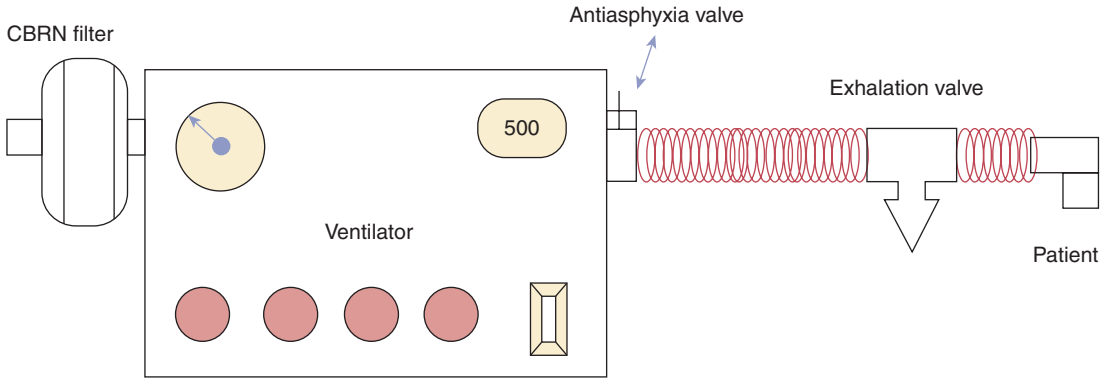

FIGURE 27-7 Placement of the chemical-biologic-radiologic-nuclear (*CBRN*) filter on the ventilator and position of the antiasphyxia valve. Under normal conditions, if patient demand exceeds ventilator output (flow), room air is entrained, which allows contamination of the patient gas and reduces FI_{O_2}.

hazards (anthrax, botulism, nerve agents). A chemical-biologic-radiologic-nuclear filter can be placed on the inlet of the compressor of the ventilator to protect the gas delivered to the patient. A recent study demonstrates that most portable ventilators fail to isolate the patient from ambient air during normal operation.[77] In ICU ventilators, the antiasphyxia valve is kept closed by an electric circuit. The antiasphyxia valve is only opened in the instance of ventilator failure. Portable ventilators typically use a one-way leaf valve in the inspiratory limb between the ventilator outlet and the patient (Fig. 27-7). If patient demand exceeds ventilator output under normal conditions, gas can enter the circuit. This not only exposes the patient to any ambient agents, but reduces FI_{O_2}. Only the Impact 731 routes all gas, including gas via the antiasphyxia valve, through the chemical-biologic-radiologic-nuclear filter. Breathing through the antiasphyxia valve prevents contamination of inspired gas, but does so at the cost of increased work of breathing for the patient secondary to increased resistance.

ANCILLARY EQUIPMENT FOR TRANSPORT

Oxygen Supply

All ventilators require an oxygen supply source. Both compressed-gas cylinders and liquid systems can fulfill this need. Intrahospital transport usually is accomplished with an E cylinder or two E cylinders yoked together. These provide 630 and 1260 liters of gas, respectively. An H cylinder contains 6900 liters and may be required for longer transports. The H cylinder is 152 cm in height, weighs 68 kg, and requires its own attendant.

Liquid-oxygen systems can provide 860 cubic feet of gaseous oxygen for every liquid cubic foot. Most liquid systems, however, cannot operate at 50 psig.

Oxygen concentrators designed for home and ambulatory use have recently been investigated for use during mechanical ventilation.[82] Their utility has not been fully defined, but the concept is theoretically very promising.

Humidification

A passive humidification device, or "artificial nose," is ideal for transport. Use of an artificial nose may result in a progressive increase in breathing circuit resistance, and the patient should be monitored for signs of expiratory–flow restriction. Dead space should be accounted for during low-volume ventilation. Premoistening an artificial nose is inadvisable, does not improve efficiency, and only serves to further increase flow resistance.

SUMMARY

Safe transport of the mechanically ventilated patient requires effective communication, appropriate planning, the presence of key personnel, and compact, rugged equipment. Equipment should meet the demands of patient acuity, and personnel should have the requisite skills and training for the task at hand. Clinicians should be aware of the most frequent complications of transport along with methods of prevention and treatment. The nuances of individual ventilators from battery life and oxygen consumption to imposed work of breathing must be appreciated.

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HOME MECHANICAL VENTILATION

Wolfram Windisch

Over the last three decades, home mechanical ventilation (HMV) has become a widely accepted treatment option for patients with chronic hypercapnic respiratory failure that arises from different etiologies such as chronic obstructive pulmonary disease (COPD), restrictive thoracic disorders, neuromuscular disorders, and obesity hypoventilation syndrome.[1,2] There is increasing evidence that HMV is capable of improving symptoms, health-related quality of life (HRQL), and long-term survival in most of these patients,[1–3] although the impact of HMV on survival in patients with COPD is still a matter of debate.[4,5] Thus, HMV should be considered in every patient presenting with symptomatic chronic hypercapnic respiratory failure.

In principle, HMV can be delivered by the application of long-term invasive mechanical ventilation, which requires the insertion of a tracheal tube following tracheostomy. Alternatively, noninvasive ventilation can be used to implement HMV via two possible routes. First, by application of negative pressure ventilation, which achieved international renown in the days when iron-lung ventilation was the preferred method for treating poliomyelitis; nowadays, this technique is seldom used.[2] Second, noninvasive positive-pressure ventilation (NPPV) can be delivered by connecting the natural airways of a patient and the artificial airways of the ventilator system by the use of face masks, which cover either the nose alone (nasal masks) or both the mouth and nose (oronasal masks).[6] Mouthpiece ventilation is an additional option, particularly for neuromuscular patients.[7]

According to a large European epidemiologic study covering more than 21,000 HMV patients from sixteen different countries (Eurovent survey), the overall prevalence of HMV reportedly was 6.6 per 100,000 inhabitants.[8] Substantial variation, however, has been identified among countries in terms of (a) prevalence, (b) the relative proportions of specific patient groups receiving HMV, and (c) HMV techniques. Nevertheless, the number of HMV patients is steadily increasing,[9] and the Eurovent survey only refers to the time span of 2001 to 2002.[8] Moreover, the survey was confined to selected HMV centers that were invited to participate, whereas HMV is increasingly being implemented by many hospitals that are not officially known as HMV centers. Thus, the prevalence of HMV varies substantially between different countries and is at present much higher, at least in some Western countries, than what was estimated by the Eurovent study. Of similar importance is the fact that the pattern of

different conditions underlying chronic respiratory failure is changing over time, with patients suffering from COPD and obesity hypoventilation syndrome experiencing the largest increase in prevalence.[9]

The Eurovent study also identified 13% of the survey population as recipients of invasive ventilation, with the highest percentage comprising patients with neuromuscular disorders (24%). Most patients received NPPV and only 0.005% received other forms unlike positive-pressure ventilation. Thus, NPPV has become the predominant means of delivering HMV.

RATIONALE

The Respiratory System

The respiratory system consists of two independent parts, each of which can be selectively impaired by different pathologies (Fig. 28-1):[10] (a) the lungs, which are responsible for gas exchange, and (b) the respiratory pump, which regulates mechanical movements to ventilate the lungs.

Basically, pulmonary insufficiency leads to hypoxemic respiratory failure, indicating impaired gas exchange; here, oxygen is primarily affected because of its poorer diffusion capacities compared to carbon dioxide. In contrast, ventilatory insufficiency primarily leads to hypercapnia, indicating reduced alveolar ventilation, although hypoxemia also occurs as a result of hypoventilation. This is most often the result of increased load on the respiratory muscles, decreased respiratory muscle capacity, or both, although it can also result from decreased respiratory drive.[10,11]

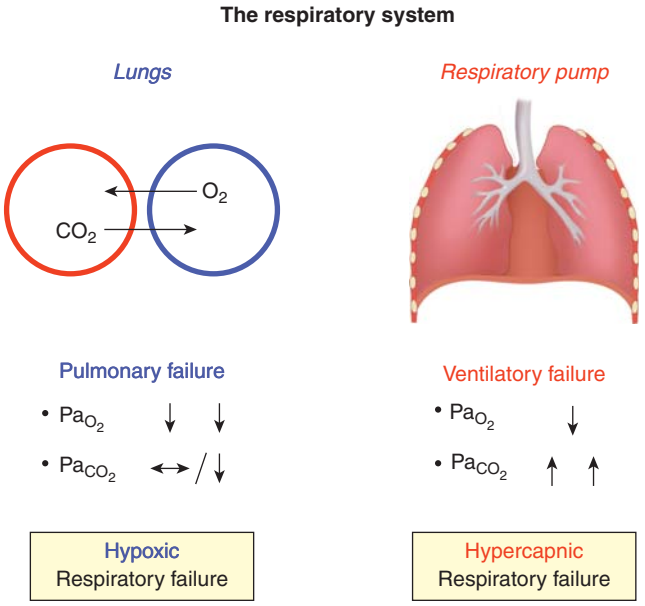

FIGURE 28-1 The two components of the respiratory system. In the lungs, oxygen (O_2) diffuses from the alveolus (*blue*) into the capillary (*red*), while carbon dioxide (CO_2) diffuses from the capillary into the alveolus. The respiratory muscles (*right panel:* diaphragm, intercostal muscles and accessory muscles) are essential for sufficient respiratory pump function. Pa_{O_2}, partial pressure of oxygen; Pa_{CO_2}, partial pressure of carbon dioxide.

The Respiratory Pump

Treatment of chronic respiratory failure primarily depends on which part of the respiratory system is impaired. Chronic pulmonary failure is a well-justified basis for long-term oxygen treatment, with documented improvements in long-term survival in patients with COPD.[12,13] In contrast, chronic failure of the respiratory pump coupled with reduced alveolar ventilation requires artificial augmentation of alveolar ventilation, which can only be achieved by long-term mechanical ventilation, that is, HMV. The indications for HMV are heterogeneous, in accordance with the complexity of the respiratory pump (Fig. 28-2).

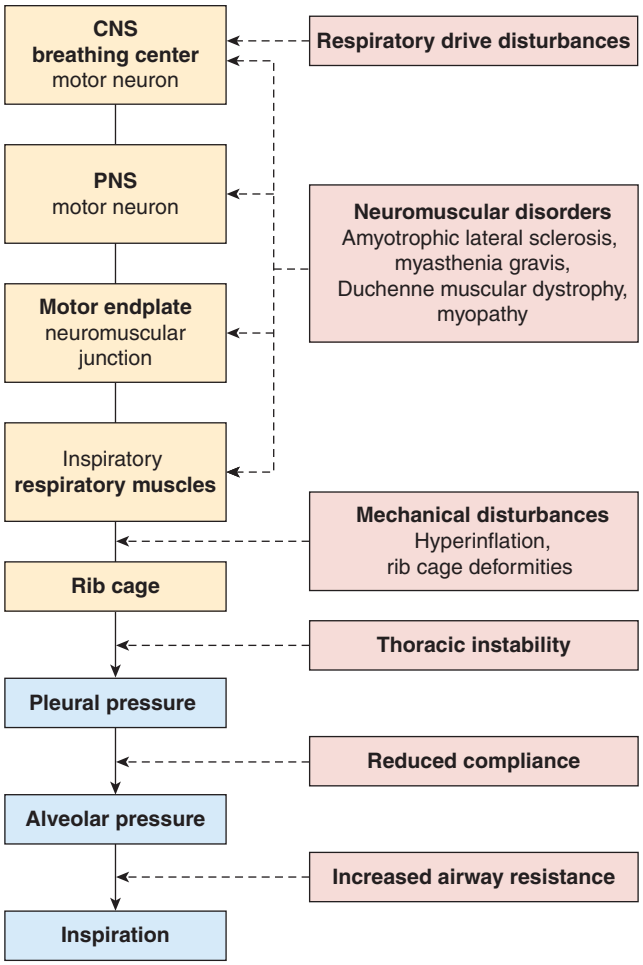

FIGURE 28-2 Primary components of the respiratory pump and the main conditions responsible for impairment, according to anatomical location. *CNS,* central nervous system; *PNS,* peripheral nervous system.

Mechanisms of Home Mechanical Ventilation

Several trials have established that in most patient groups, NPPV used for HMV is capable of improving physiologic variables, the most important of these being blood gases.[1–4,9,14–20] Conflicting results in patients with COPD have been published; the effect of NPPV on blood gases was negligible in some trials,[5,21–23] but a positive effect was clearly documented in other trials.[3,4,24–27] NPPV improves blood gases not only during the time of application, but also during subsequent spontaneous breathing. This benefit has been attributed to an improved breathing pattern with increased tidal volume at an unchanged respiratory rate.[18]

Although the mechanisms by which intermittent NPPV improves subsequent spontaneous breathing remain unclear, three theories have been advanced: (a) respiratory muscle resting; (b) resetting of CO_2 sensitivity in the central breathing center; and (c) changes in pulmonary mechanics.[1,2,20,28,29] The mechanisms are considered complementary rather than contradictory.[1,2] It is, however, still unclear if these mechanisms are unique to all conditions leading to chronic ventilatory failure or are disease related. More recent research suggests that the principal mechanism in patients with restrictive thoracic disorders is an increased ventilatory response to CO_2.[20]

Regarding the assessment of respiratory muscle strength, there is a lack of reliable methodology available. Volitional tests such as the widely used maximal inspiratory pressure method are highly dependent on the patient making a truly maximal effort.[30] In addition, normal values rely greatly on the study cohort and on several methodological aspects; this has resulted in contradictory regression equations for calculating normal values for maximal inspiratory pressure.[31] Thus, this technique is not suitable for physiologic studies. In studies using nonvolitional gold-standard techniques, however, no changes in diaphragmatic muscle strength—as assessed by transdiaphragmatic twitch pressures following magnetic phrenic nerve stimulation—could be observed following initiation of HMV in restrictive thoracic disorders[20] and in COPD.[32]

Another theory for improved spontaneous breathing stems from reports of improved lung function in patients with COPD in whom a substantial reduction in partial pressure of arterial carbon dioxide (Pa_{CO_2}) could be achieved.[3,4,25,26] It has been speculated that the improvement results from a reduction in airway edema.[25,33] Edema is a common finding in patients with COPD and might be related to *cor pulmonale* or possibly volume overload secondary to activation of sodium-retaining mechanisms. This, in turn, is thought to result from a reduction in effective circulating volume, secondary to a fall in total peripheral vascular resistance caused by hypercapnia-induced dilation of the precapillary sphincters.[34] A decrease in hypercapnia by means of HMV would then reverse dilation of the precapillary sphincters and thereby impact positively on the edema, which could improve respiratory mechanics in patients with airway edema.

SELECTION OF PATIENTS

Prerequisites for Home Mechanical Ventilation

There are three mandatory conditions for commencing HMV:[1,2,35] (a) presence of an underlying condition or disease that potentially causes impairment of the respiratory pump and ultimately chronic ventilatory failure; (b) typical symptoms accompanying chronic ventilatory failure, despite optimal treatment; and (c) evidence of a chronically decompensated respiratory pump with reduced alveolar ventilation.

UNDERLYING CONDITION AND/OR DISEASE

Before the commencement of HMV, the cause of the chronic respiratory pump failure needs to be identified and all appropriate treatment strategies instituted. It is necessary to bear in mind that more than one condition can be responsible for the development of chronic ventilatory failure in some patients. Chronic ventilatory failure from the combination of COPD and obesity is especially common. All diseases affecting the respiratory pump may warrant HMV treatment, and the most frequently reported conditions are listed in Table 28-1.

SYMPTOMS AND CLINICAL SIGNS OF CHRONIC VENTILATORY FAILURE

No specific set of symptoms is reliably associated with chronic ventilatory failure because many occur in other conditions. In addition, symptoms (Table 28-2) depend on the underlying disease, its time course, comorbidities, and several other factors, such as medication and symptom perception. Some symptoms, however, are often falsely attributed to other conditions, leaving chronic ventilatory failure undiagnosed. Because one major goal of HMV is to alleviate symptoms, patients should be carefully screened for these symptoms both before and after the commencement of HMV (Table 28-2).

EVIDENCE OF CHRONICALLY REDUCED ALVEOLAR VENTILATION

The most important indicator of reduced alveolar ventilation is an elevated level of partial pressure of carbon dioxide (P_{CO_2}), which can be detected by arterial or capillary blood gas analysis, end-tidal recording, or transcutaneous measurement (Table 28-3).

Although arterial measurement is regarded as the reference standard, transcutaneous measurements are increasingly recognized as being reliable. This has been attributed to technical refinements, which include the prevention and correction of measurement drifts.[36,37] The advantage of transcutaneous measurements is that they enable noninvasive and continuous assessment. The technique is especially attractive

TABLE 28-1: CONDITIONS MOST COMMONLY MANAGED BY HOME MECHANICAL VENTILATION

Obstructive disorders

- Chronic obstructive pulmonary disease
- Cystic fibrosis
- Bronchiectasis
- Bronchiolitis obliterans

Restrictive thoracic disorders

- Kyphoscoliosis
- Posttuberculosis sequelae
- Thoracoplasty
- Restrictive pleural disease
- Bechterew disease
- Severe kyphosis

Neuromuscular disorders

- Amyotrophic lateral sclerosis
- Muscular dystrophy (Duchenne and others)
- Critical illness polyneuropathy and myopathy
- Paraplegia
- Phrenic nerve paralysis
- Postpoliomyelitis
- Myopathy (congenital, metabolic)
- Spinal muscular atrophy
- Myasthenia gravis
- Curschmann-Steinert disease

Obesity-hypoventilation syndrome

Central respiratory drive disturbances

- Primary: Ondine's Curse
- Secondary: brainstem alterations

TABLE 28-2: KEY SYMPTOMS AND CLINICAL SIGNS RELATED TO CHRONIC RESPIRATORY FAILURE

Symptoms and signs of the underlying disease

Symptoms and signs of the mechanical imbalance

Dyspnea
Tachypnea
Pathologic breathing pattern (depending on the underlying disease)

Symptoms and signs related to sleep disordered breathing

Tiredness
Daytime sleepiness
Nonrestful sleep
Poor concentration
Mental alterations

Symptoms and signs related to hypercapnia-induced vasodilation

Vasodilation in the eyes
Headache (particularly in morning)
Peripheral (airway) edema

TABLE 28-3: P_{CO_2} MONITORING

Method	Advantages	Disadvantages
Arterial (Pa_{CO_2})	• Reference standard • Other parameters coeval	• Invasive and painful • Selective
End-tidal ($P_{ET}CO_2$)	• Continuous • Noninvasive	• Unreliable in case of leakage • Unreliable in $\dot{V}/\dot{Q}$ mismatch
Transcutaneous ($PtcCO_2$)	• Continuous • Noninvasive	• Drift of values over time • Problematic in skin abnormalities

Abbreviations: Pa_{CO_2}, arterial partial pressure of carbon dioxide; $P_{ET}CO_2$, end-tidal partial pressure of carbon dioxide; $PtcCO_2$, transcutaneous partial pressure of carbon dioxide; $\dot{V}/\dot{Q}$, ratio of ventilation and perfusion.

during sleep, because sleep is not disturbed by an invasive procedure and it also captures any variations in alveolar ventilation (Fig. 28-3.)

Indications for Home Mechanical Ventilation

HYPERCAPNIA

Initially, hypercapnia typically occurs during the night, and the patient may still be normocapnic during the day. Therefore, nocturnal measurements of P_{CO_2} are required to avoid overlooking the onset of chronic ventilatory failure. There are, however, no established cutoff values for nocturnal or daytime P_{CO_2} that would reliably indicate the need for HMV. Previous international recommendations have provided P_{CO_2} cutoff values for specific disease groups, but these recommendations are based on expert consensus rather than reliable research[1]; moreover, this report only refers to NPPV, thus excluding invasive mechanical ventilation. The report[1] recommends long-term NPPV for restrictive patients when Pa_{CO_2} is equal to or higher than 45 mm Hg, while a Pa_{CO_2} equal to or higher than 55 mm Hg is recommended in patients with COPD. In cases where nocturnal desaturations occur, despite oxygen treatment, or in cases with recurrent hospitalizations in order to manage acute hypercapnic respiratory failure, a Pa_{CO_2} reading of 50 to 54 mm Hg warrants long-term NPPV.[1] Although detailed criteria are provided in the recently published German guidelines for HMV,[35] and a Canadian guideline is in preparation (personal communication), an international consensus on when to start HMV has not been reached. However, HMV needs to be carefully considered, not just in terms of Pa_{CO_2} levels. Patients should be severely symptomatic with reduced quality of life, and should also be very likely to benefit from the therapy. This is particularly important for patients with COPD in whom clear improvements in long-term survival have yet not been scientifically

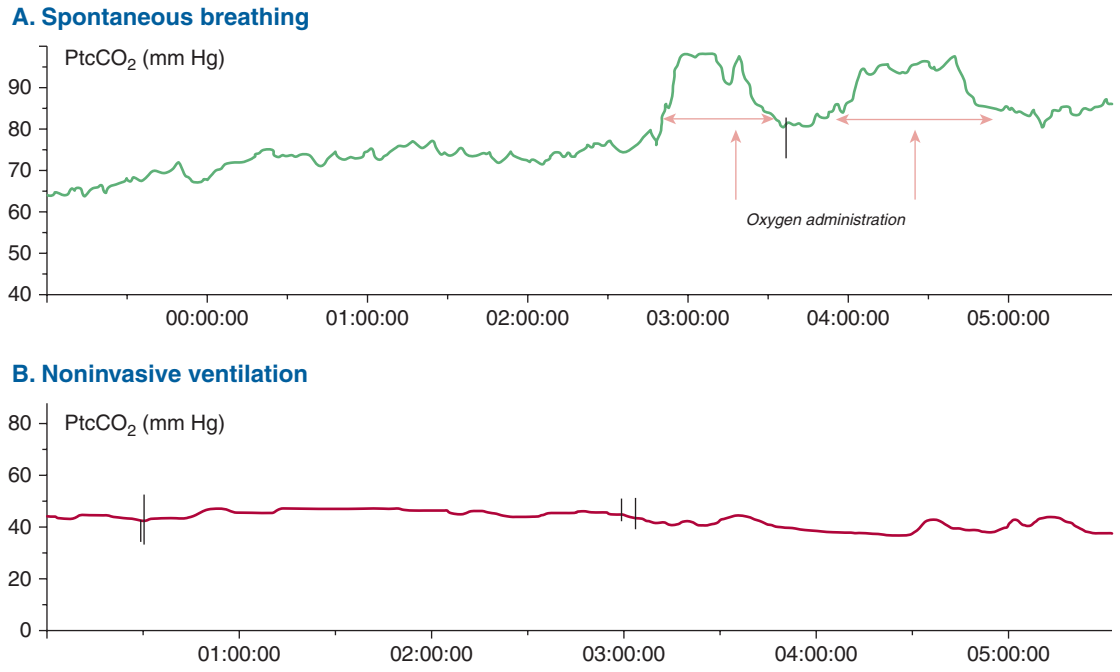

FIGURE 28-3 Transcutaneous carbon dioxide tension ($PtcCO_2$) monitoring in a 49-year-old patient with chronic ventilatory failure secondary to amyotrophic lateral sclerosis. **A.** $PtcCO_2$ starts with values of 65 mm Hg during spontaneous breathing and progressively increases during sleep. Administration of oxygen produces an increase in $PtcCO_2$, likely caused by reduced alveolar ventilation. **B.** Home mechanical ventilation by means of noninvasive ventilation produces normalization of $PtcCO_2$.

established.[5,22,23] Nevertheless, the use of HMV for preventive purposes in nonhypercapnic patients should be avoided.[38]

For the commencement of HMV, chronic hypercapnic failure with normal pH (resulting from bicarbonate retention) should be established and distinguished from acute hypercapnic respiratory acidosis (Table 28-4).

NONINVASIVE VERSUS INVASIVE LONG-TERM MECHANICAL VENTILATION

In general, NPPV should be used in preference to invasive mechanical ventilation, which is used more often in neuromuscular patients following tracheostomy than in other disease groups.[8] In particular, tracheostomy is indicated for the following conditions[39–43]: lack of mask fitting; intolerance of, or claustrophobia with, mask ventilation; ineffective ventilation; impaired bulbar function with recurrent episodes of aspiration; insufficient noninvasive management of secretions requiring suction via a tracheal cannula; and failure to wean off invasive mechanical ventilation following intubation.

It is extremely important to comprehensively inform the patient and the family members about tracheostomy and its consequences. Patients' self-determination is a top priority, and decision making should be based not only on objective circumstances but also on the subjective perspective of the patient.

TABLE 28-4: BLOOD-GAS DIFFERENCES DEPENDING ON THE TIME COURSE OF VENTILATORY FAILURE

	Acute	Acute on Chronic	Chronic
pH	Lowered	Lowered	Normal
Pa_{CO_2}	Increased	(Greatly) increased	Increased
HCO_3	Normal	Increased	Increased

Abbreviations: HCO_3, bicarbonate; Pa_{CO_2}, arterial partial pressure of carbon dioxide.

ORGANIZATION

Specialized Center for Home Mechanical Ventilation

Patients receiving HMV should be managed in a specialized center that is familiar with the specific circumstances and problems occurring in such patients.[35] Here, high-quality, individually customized care is paramount, and it is essential that the treatment plan can be readily adapted to any necessary changes in the ventilator mode, settings, and interface, as well as in the duration, of mechanical ventilation. In all cases where the proposed treatment is

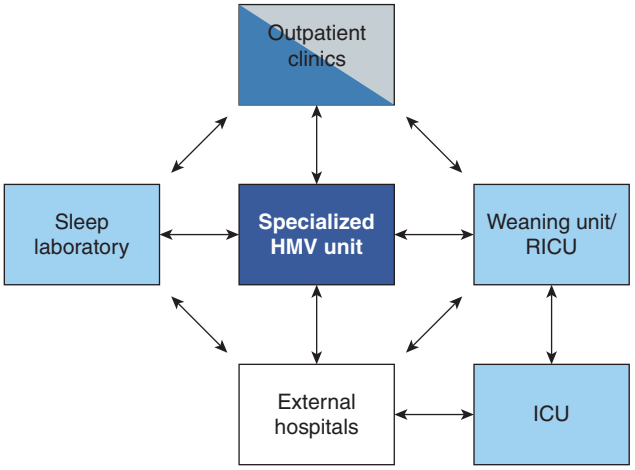

FIGURE 28-4 Specialized center for home mechanical ventilation. Patients are usually transferred to the HMV unit from other units within the specialized center, such as the sleep laboratory and weaning unit (*light blue*), or from external facilities (*white*) including outpatient clinics and external, nonspecialized hospitals. Return transfer should be facilitated at all times, according to patient's needs. *ICU,* intensive care unit; *RICU,* respiratory intensive care unit.

subject to alteration, the patient, together with relatives and all associated therapists, must be included in the decision-making process, which must include close consultation and good organization between all participating individuals.

It is well recognized that the organizational structures vary considerably among countries and regions.[8] Preferably, a specialized unit is set up exclusively for HMV and integrated into a network of specific units qualified for treating patients with mechanical ventilation (Fig. 28-4). Patients are usually admitted to the HMV unit from different sites within the same center, or from external sites (Fig. 28-4). Because many patients have sleep-disordered breathing, the center should provide easy access to full polysomnography, preferably within an in-house sleep laboratory. Many patients, particularly those with obesity hypoventilation syndrome, are primarily admitted to a sleep laboratory for diagnosis of sleep disturbances. In this case, sleep-related hypoventilation with deteriorating hypercapnia must not be overlooked, thus requiring close monitoring of nocturnal P_{CO_2} and the transfer to the HMV unit where appropriate.

Especially confounding is the fact that HMV candidates are not always patients electively admitted to hospital: Some patients may also present with weaning failure consequent to ventilator management for acute respiratory failure (see Fig. 28-4). These patients are usually transferred from the intensive care unit to the HMV unit via a weaning unit ("step-down").[43] With the marked increase in the number of severely ill weaning-failure patients being admitted to a weaning unit,[44] close cooperation between the weaning and the HMV units is mandatory, because many weaning-failure patients are ultimately established on HMV.[43,44]

Staffing and Training

Hospital staffing requirements depend on the type and severity of a patient's underlying disorder. Staffing also relies on the local conditions of the center, such as experience, size, and country-specific organization of health care.[8] Accordingly, great variation in staffing demands exists amongst different centers. Nevertheless, the global standards for staff include satisfactory training in mechanical ventilation techniques that covers both invasive and noninvasive ventilation. The team must be familiar with specific treatment modalities, such as airway clearance techniques, management of acute respiratory failure, and disease-specific issues.[45,46] It is the responsibility of the center to provide sufficient staff training for all professionals involved, which may include: nurse, physician, physiotherapist, equipment provider, psychotherapist, respiratory therapist, and social worker.

In addition, a speech therapist, a nutritionist, or other therapist may be necessary at some point during the treatment of patients with HMV.

Transferring patients from hospital-based to home-based treatment is always a challenge.[35,45–48] The challenge results from the necessity of replacing the in-hospital care team with an out-of-hospital care team, which may also include lay helpers, most importantly relatives. Training of all people caring for HMV patients in the home environment is essential.[35,45,46] In addition, the specialized center and the provider should always be contactable for solving medical and technical problems, respectively.[35,45,49]

Discharge from the Center and Transfer to Home Mechanical Ventilation

Both the underlying and secondary illnesses need to be in a stable condition before discharge.[50] If an optimal level of function and performance is not yet reached, (early) rehabilitative measures should be considered.[35,45] In addition, the fulfilment of costs and provision of the necessary equipment, resources, and materials need to be ascertained in advance.[35] Individual requirements for patient discharge and subsequent setup of the home-ventilation station vary significantly from patient to patient. Table 28-5 is a checklist of the minimal requirements.[35]

Control Visits

Control visits include the collection of data on compliance, side effects, ventilation techniques, and daytime respiratory function, and also on nocturnal diagnostics, particularly nocturnal assessment of alveolar ventilation. Preferably, this should be performed in the specialized center where the patient has been initially treated. The first control examination after commencement of HMV should take place 4 to 8 weeks after discharge.[35,47,51] Subsequent

TABLE 28-5: CHECKLIST OF MINIMAL REQUIREMENTS FOR PATIENT DISCHARGE AND SUBSEQUENT SETUP OF A HOME VENTILATION STATION

Full technical installation of the ventilator machinery and surveillance systems
Surveillance standards in terms of personnel (nurse attendance time)
Time schedule and content of nursing procedures
Type of ventilation interface and the corresponding cleaning and exchange intervals
Detailed description of ventilator mode and associated parameters
Duration of assisted ventilation and, if applicable, phases of spontaneous ventilation
Oxygen flow rates during assisted and spontaneous ventilation
Procedures for managing secretions
Application of inhaled medication
Planning for nutritional needs
Psychosocial care of the patient and, if applicable, the relatives
Additional therapeutic and educative measures
Additional resources (e.g., rollator, therapeutic bed, communication aids)

Based on Windisch et al.[35]

control visits typically occur once or twice a year and are carried out on an individual basis, depending on the type and progression of the underlying disease.

SPECIFIC ASPECTS OF NONINVASIVE VENTILATION UNIQUE TO HOME MECHANICAL VENTILATION

Impact of Ventilator Modes and Settings

VOLUME-LIMITED VERSUS PRESSURE-LIMITED NONINVASIVE POSITIVE-PRESSURE VENTILATION

Volume-limited NPPV initially served as the primary mode for HMV, but pressure-limited NPPV has become the dominant mode,[8,9] probably because constant peak inspiratory pressures (provided by pressure preset) are better tolerated than varying peak inspiratory pressures (provided by volume preset). In addition, ventilators providing pressure-limited ventilation are cheaper. According to the Eurovent study, volume-limited forms of mechanical ventilation were used in only 15% of patients with chronic lung diseases and in 28% of patients with restrictive thoracic disorders, although in a relatively higher number (42%) of patients with neuromuscular disorders.[8]

Physiologic studies show that leak-compensation capabilities, that is, increases in inspiratory flow in the event of air leakage, are only available for pressure-limited ventilator modes, and this holds true for both in vitro[52] and in vivo[53] conditions. Early comparative trials revealed conflicting results, but interpretation of the findings is hindered by short observational periods, uncontrolled study design, and the lack of concomitant sleep studies.[54–57] Two randomized, controlled, crossover trials, however, confirmed that the two modes were, on average, equally effective in improving alveolar ventilation during sleep, both in a mixed cohort that included patients with COPD[17] and in a group of patients with restrictive thoracic disorders.[58] The first trial also indicated that pressure preset is better tolerated secondary to less gastrointestinal side effects,[17] while the second trial suggested that switching from one mode to the other mode can provide individual benefits in terms of gas exchange.[58] Thus, there is no clear global advantage for one or the other mode, although changing the mode might be worthwhile for individual patients.

TARGET VOLUME

Most of the new-generation HMV ventilators provide the opportunity to set a so-called target volume. This expression describes a feature, in which the advantages of pressure preset (better tolerance because of less variation in peak inspiratory pressures) and volume preset (volume stability) are combined. Primarily, a pressure-limited mode is used, but instead of a fixed peak inspiratory pressure, a pressure range with minimal and maximal pressure is set at the ventilator. In accordance with the automatic calculations and adjustments of the ventilator, the pressure is thereby changed within a range so as to reach the preset target volume. Nomenclature and algorithms used for pressure adaption vary considerably among different types of ventilators.

Despite target volume being increasingly implemented in HMV ventilators, evidence supporting this new feature is sparse and long-term trials are nonexistent. The first randomized, controlled, crossover trial demonstrated that after 6 weeks of HMV using target volume settings, bi-level positive airway pressure ventilation was more effective, in comparison to settings without target volume, in improving gas exchange in patients with obesity hypoventilation syndrome; moreover, quality of life and polysomnographic sleep quality showed a comparable improvement following HMV.[59] Two further studies predominantly in patients with obesity-related chronic ventilatory failure revealed improvements in respiratory function through use of target volume settings[60,61]; in one study, however, this occurred at the expense of objective and subjective sleep quality and comfort during ventilation.[61] Finally, a randomized, controlled, crossover study on patients with COPD showed comparable results after 8 weeks of HMV.[62]

HIGH-INTENSITY NONINVASIVE POSITIVE-PRESSURE VENTILATION

High-intensity NPPV has been described as a new approach in patients with COPD (Table 28-6).[4,18,25–27,36,53,63,64] In an attempt to decrease elevated Pa_{CO_2} values, controlled ventilation with high inspiratory pressures (range: 20 to 40 cm H_2O) is implemented in the hospital setting and subsequently

TABLE 28-6: HIGH-INTENSITY NONINVASIVE POSITIVE-PRESSURE VENTILATION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Definition	• NPPV aimed at maximally reducing elevated Pa_{CO_2} values with the major goal of achieving normocapnia or minimal Pa_{CO_2} values using high ventilator settings, as maximally tolerated or necessary.
Procedure	• Mode: assisted or controlled, preferably pressure-limited, NPPV. • Use daytime NPPV first, with the primary aim of establishing tolerance, but also with control of blood gases and vital parameters. • Start with lowest backup respiratory rate and most sensitive trigger threshold (assisted NPPV); use low IPAP levels, typically ranging from 12 to 16 cm H_2O, and the lowest EPAP levels. • Then, carefully increase IPAP in a stepwise approach until maximal tolerance is reached, usually up to 30 (range: 20 to 40) cm H_2O. • Then, increase the respiratory rate just beyond the spontaneous rate to establish controlled ventilation. • Then, set EPAP so as to avoid dynamic hyperinflation according to subjective comfort (usually 3 and 6 cm H_2O), and similarly, set the I:E ratio to 1:2 or lower. • Once daytime tolerance is acceptable, apply nocturnal NPPV. • Adjustments to ventilator settings are made according to subjective tolerance and nocturnal monitoring of blood gases.
Pitfalls and practical advice	• Tolerance of higher IPAP levels can last from minutes to several days; individual adjustment is inevitable. • In cases of coexisting upper airway obstruction, higher EPAP levels are required. On the other hand, higher EPAP reduces the effective IPAP (which is IPAP minus EPAP); thus, avoid high EPAP levels if not required. • For controlled NPPV (final aim), respiratory rates are typically set to 1 breath/min higher than during spontaneous breathing; thus, avoid excessively high respiratory rates, although try to establish controlled ventilation. • Try out several masks: for nocturnal NPPV, use oronasal masks because of potentially substantial leakage; for daytime NPPV, a nasal mask is often better tolerated. Again, individual adjustment is mandatory. • Several days in hospital are usually necessary to establish high-intensity NPPV. • Use humidification in cases of dry mucous membrane. • Leakage is unavoidable, but should be kept as low as possible. • Gastrointestinal side effects can be managed by medication, positioning, and adjustment (reduction) of ventilator settings.
Physiologic effects	• Improvement in blood gases during NPPV.[4,18,26,27] • Improvement in blood gases during subsequent spontaneous breathing.[3,4,18,25–27] • Improvement in breathing pattern during spontaneous breathing.[18] • Improvement in lung function.[3,4,25,26] • Improvement in global inspiratory muscle strength.[18] • Increases in hematocrit in anaemic patients.[25] • Reduces hematocrit in patients with polyglobulia.[25] • Superior to low-intensity NPPV using assisted ventilation with low IPAP regarding the improvement of blood gases.[4,63]
Clinical effects	• Improvement in health-related quality of life.[3,4,18] • Improvement in dyspnea while spontaneous breathing during walking.[4] • Improvement in dyspnea and walking distance during NPPV-aided walking compared to unaided walking.[64] • Acceptable sleep quality.[17,63] • Superior to low-intensity NPPV using assisted ventilation with low IPAP regarding adherence to therapy.[4]
Important unknowns	• Improvement of long-term survival?

Abbreviations: EPAP, expiratory positive airway pressure; *I:E*, inspiratory-to-expiratory timing; *IPAP*, inspiratory positive airway pressure; *NPPV*, noninvasive positive–pressure ventilation; Pa_{CO_2}, arterial partial pressure of carbon dioxide.

used for HMV. Several physiological and clinical variables are reportedly improved by this approach (Table 28-6). This technique contrasts with the conventional approach of using assisted ventilation with low inspiratory positive pressures (typically 10 to 16 cm H_2O), defined as low-intensity NPPV,[5,21–23,65–68] which fails to effectively improve respiratory function. Direct comparisons following two randomized crossover trials clearly show the superiority of high- over low-intensity NPPV (Table 28-6).[4,63] Consequently, high-intensity NPPV is the first choice for HMV in patients with COPD.

QUALITY CONTROL OF VENTILATOR SETTINGS AT HOME

For HMV to be successful, it is essential that patients use the prescribed equipment as well as the ventilator modes and settings that were established in the hospital. Changing the system or the settings can reduce the quality of ventilation and result in either hypoventilation or hyperventilation. For this reason, a quality assessment of ventilator performance at home has been proposed.[51] A recent survey including 326 centers visited by more than 20,000 patients in sixteen European countries revealed significant deficits

in quality control; only 56% of centers assessed whether the patients and/or caregivers correctly cleaned or maintained the ventilator.[51] Considerable intercountry and intracountry differences were observed, and the size of the center was a major determinant of several quality-control aspects.[51] Considerable differences were found between several prescribed versus actually implemented ventilator variables, and important alarm functions, such as power off, disconnection, and obstruction, were sometimes defective.[48]

Different interfaces used for HMV have varying physical characteristics. This is particularly true for the resistance component, which is known to be flow-dependent, and applies to interfaces used for both noninvasive[69] and invasive mechanical ventilation.[70] Therefore, changing the interface in the home environment without control measures can produce alterations in the quality of HMV. Indeed, the type of interface has been shown to affect NPPV outcome even more than the ventilator mode.[71] Thus, changes to the ventilator system, the settings or interface should be done with adequate control in cooperation with the HMV-prescribing center.

Side Effects

Most side effects of HMV arise from the mismatch between the artificial airway and the natural human airway, although complications may also be caused by the ventilator itself. Side effects are highly dependent on whether invasive or noninvasive HMV is used (Table 28-7). Although side effects are common,[2,3,17] NPPV is safe. Nevertheless, side effects can impair HRQL and necessitate the discontinuation of ventilator treatment. Every effort should be made to minimize side effects. For example, humidification should be provided in cases of dry mouth or throat, and facial soreness or erythema or ulceration, resulting from mask pressure, can be ameliorated by minimizing strap tension or switching to an alternative interface. Despite frequently reported side effects, NPPV can improve symptoms and HRQL in many patients.[3]

The frequency and dimension of side effects depends on several factors including the ventilator modes, settings and interfaces. For example, volume-limited NPPV produces more gastrointestinal side effects because of higher and more variable peak inspiratory pressures as compared with pressure-limited NPPV.[17] Side effects of NPPV tend to diminish once patients become more familiar with HMV.[3]

TABLE 28-7: THE MOST RELEVANT SIDE EFFECTS OF HOME MECHANICAL VENTILATION

Noninvasive Home Mechanical Ventilation	Invasive Home Mechanical Ventilation
Mask-related:	*Canula-related:*
• Facial and/or nasal soreness • Facial and/or nasal erythema or rash • Facial and/or nasal ulceration • Gum pain	• Tracheal injury and/or bleeding/pain • Tracheal stenosis and/or tracheomalacia • Tracheal granulation tissue • Tracheal stenosis and/or fistula • Dislocation and/or obstruction • Difficulties in speaking and/or coughing • Infections
Airflow and air pressure or leakage related:	*Airflow and air pressure related:*
• Dry nose and/or throat and/or bronchial tree • Nasal congestion • Eye irritation • Ear and/or sinus pain • Epistaxis • Gastric insufflation and/or distension • Belching and/or flatulence • Abdominal pain • Nausea/vomiting	• Barotrauma • Volutrauma
Sleep problems:	*Sleep problems:*
• Not falling asleep • Sleep disruption	• Not falling asleep • Sleep disruption

OUTCOME

Long-Term Survival

There is overwhelming evidence that following the commencement of HMV, long-term survival is markedly improved in patients with restrictive thoracic diseases and neuromuscular disorders, particularly those that are slow-progressing,[19,72] although the effect of HMV on outcome in patients with COPD is still a matter of debate.[4,5,21–23] Evidence for improved survival in restrictive and neuromuscular patients is derived mostly from uncontrolled trials, but the data are sufficiently robust enough to support the conclusion that survival is increased in these patients. Randomized controlled trials in these patient groups presumably will never be conducted because of ethical concerns.[72]

Detailed information for six diseases typically treated by HMV follows.

EARLY KYPHOSCOLIOSIS

In landmark observational trials of the 1990s, 1-year survival rates reached 90% in patients with kyphoscoliosis following the commencement of NPPV treatment.[14,15] The 5-year survival rate was almost 80%,[9,15] and the 9-year survival rate reported by the Swedish registry reached 55%.[73] Survival was better in kyphoscoliosis patients receiving HMV compared to patients receiving long-term oxygen treatment, even though the HMV patients were deemed to be more ill.

POSTTUBERCULOSIS SEQUELAE

Five-year survival rates in patients with posttuberculosis sequelae were higher than 90% in one study,[15] although survival was considerably lower (50%) in two other trials.[9,74] This discrepancy is likely related to differences in baseline ages of patients: mean age was 61 years in the first trial, but 72 years[74] and 75 years[9] in the other two trials. The Swedish registry revealed that approximately 21% of patients had a 9-year survival rate when HMV was started at a baseline age of 72 years.[74] Uncontrolled data of the Swedish registry reveals that survival in posttuberculosis sequelae patients who received HMV was higher than in those who received oxygen treatment.[74]

DUCHENNE MUSCULAR DYSTROPHY

The mean age at death in patients with Duchenne muscular dystrophy is approximately 19 years if long-term mechanical ventilation is not instituted, and most die from ventilatory failure.[75] Although invasive mechanical ventilation,[75] mouthpiece ventilation,[76] and negative pressure ventilation[77] have shown beneficial effects on long-term outcome, NPPV is considered to be the treatment of choice.[78] Given that mean survival without HMV is less than 10 months once chronic hypercapnic respiratory failure has occurred,[79] the reported 5-year survival rate of 73% in patients with Duchenne muscular dystrophy who received long-term NPPV is phenomenal.[80] Thus, HMV must not be withheld in these patients. These positive results encouraged researchers to apply prophylactic long-term NPPV in nonhypercapnic patients. Unfortunately, NPPV did not ameliorate the respiratory handicap and even reduced survival.[38] Consequently, prophylactic HMV must be avoided. If NPPV is used, additional techniques for clearance of secretions are often required; if invasive ventilation is used, tracheal suction can easily be performed via a canula. The use of NPPV in addition to technically assisted coughing prolongs survival while significantly decreasing the pulmonary morbidity and hospitalization associated with conventional invasive technical ventilation.[81]

AMYOTROPHIC LATERAL SCLEROSIS

In contrast to Duchenne muscular dystrophy, amyotrophic lateral sclerosis tends to progress more rapidly. In addition, bulbar involvement may prevent the patient from receiving NPPV, although tolerance may be feasible in patients with mild-to-moderate bulbar involvement.[78,82] In severe and rapidly progressive neuromuscular disorders, as with amyotrophic lateral sclerosis, fears exist that use of HMV in advanced disease might simply protract death rather than prolong good quality of life.[19] Nevertheless, early, uncontrolled studies suggest that survival can be improved by the addition of NPPV,[82–85] and one randomized controlled trial demonstrated that NPPV improves survival and HRQL in patients with amyotrophic lateral sclerosis, although the survival benefit was restricted to patients without severe bulbar dysfunction.[86]

OBESITY-HYPOVENTILATION SYNDROME

Uncontrolled data suggest that prognosis of untreated obesity-hypoventilation syndrome is poor,[87–90] with a mortality rate of 23% after 18 months in one trial.[90] This contrasts with more recent long-term data on 126 patients showing 1-, 2-, and 5-year survival rates of 97%, 92%, and 70%, respectively, in patients treated with NPPV. A reduction in nocturnal Pa_{CO_2} by 23% or more was associated with improved survival rates in this trial.[91] Large randomized controlled, long-term trials do not exist, and several issues still need to be addressed, including the need to define clear treatment goals.[87] It is also unclear which type of ventilator support should be used in which patient. Recent data has convincingly shown that continuous positive airway pressure and bi-level ventilator support were equally effective in improving daytime hypercapnia in patients without severe nocturnal hypoxemia,[92] although differences in the effects on long-term survival still need to be established.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

In contrast to restrictive and neuromuscular patients, HMV has not been convincingly shown to improve survival in COPD. The approximate 5-year survival rate is 43%, which is much lower than in restrictive patients (excluding those with rapidly progressive diseases).[14] Two randomized controlled trials showed no survival benefit.[22,23] An Australian randomized controlled trial observed an improvement in survival, but this applied to the adjusted, but not to the unadjusted model; this minor effect occurred at the cost of worsening HRQL.[5] Low-intensity NPPV was used in most randomized controlled trials, and also failed to effectively improve respiratory function.[5,21–23] One could argue that improved survival cannot really be expected if the specific modality fails to improve physiology, that is, if NPPV is relatively ineffective. In contrast, high-intensity NPPV has indeed been shown to improve several physiological and clinical variables[3,4,18,25–27,63,64] and 5-year survival (58%) was higher than that previously reported.[18] This promising approach needs to be tested for survival benefits in randomized controlled trials.

Health-Related Quality of Life

HOW CAN HEALTH-RELATED QUALITY OF LIFE BE MEASURED IN PATIENTS WITH HOME MECHANICAL VENTILATION?

Evaluation of HRQL provides an important means of evaluating the human and financial costs and benefits of modern medical treatment modalities.[93–95] HRQL evaluation is particularly important for patients with chronic and noncurable disorders, and from a patient's point of view,

TABLE 28-8: THE MOST FREQUENTLY USED INSTRUMENTS FOR ASSESSMENT OF HEALTH-RELATED QUALITY OF LIFE IN PATIENTS RECEIVING HOME MECHANICAL VENTILATION

Instrument	First Author	Subscales (n)	Items (n)
Generic instruments			
Sickness Impact Profile (**SIP**)[96,97]	Bergner M	12	136
Nottingham Health Profile (**NHP**)[98]	Hunt SM	6	38
Hospital Anxiety and Depression Scale (**HAD**)[99]	Zigmond AS	2	14
MOS 36-Item Short-Form Health Survey (**SF-36**)[100–102]	Ware JE	8	36
COPD-specific instruments			
Chronic Respiratory Disease Questionnaire (**CRQ**)[103]	Gyatt GH	4	20
St. George's Respiratory Questionnaire (**SGRQ**)[104]	Jones PW	3	76
Instruments specific for chronic respiratory failure			
Maugeri Foundation Respiratory Failure item set (**MRF-28**)[105]	Carone M	3	28
Severe Respiratory Insufficiency questionnaire (**SRI**)[106,107]	Windisch W	7	49

the effect of HMV on HRQL may be more important than its effect on long-term survival.

Questionnaires are the most frequently used tool for HRQL assessment, and it is crucial that essential psychometric properties—the most important being objectivity, reliability, validity, sensitivity, and responsiveness—are established before they are used as an HRQL assessment tool in clinical trials.[93] Although generic questionnaires are not tailored to a particular disease and can thus be applied comparably in different diseases, they lack sufficient responsiveness and sensitivity to specific treatment interventions; thus these instruments only qualify for comparative, cross-sectional HRQL assessments. The opposite is true for disease- or condition-specific instruments, which are primarily designed to longitudinally assess changes in HRQL, but restricted to the particular condition for which they are developed.[93] Table 28-8 lists the instruments most frequently used in HMV cohorts.

The Severe Respiratory Insufficiency Questionnaire is a multidimensional health measure (Fig. 28-5), developed exclusively for patients receiving HMV.[106,107] It is valid for a broad variety of diseases, including restrictive thoracic and neuromuscular disorders, and obesity hypoventilation syndrome,[106] and additional research supports the questionnaire's validity for patients with COPD.[107] Intercultural

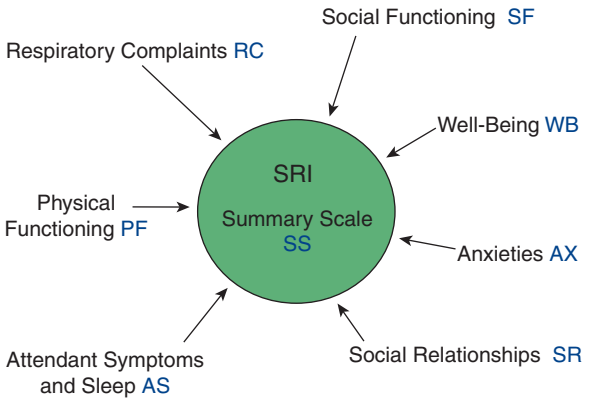

FIGURE 28-5 The multidimensional Severe Respiratory Insufficiency (SRI) Questionnaire with seven subscales.

adaption is currently in progress, with ten professional translations in the process of validation or consideration (Table 28-9.)

IMPACT OF THE UNDERLYING DISEASE ON HEALTH-RELATED QUALITY OF LIFE

The first study to systematically analyze HRQL in HMV patients readily established that the underlying disease is a main determinant of HRQL, with patients suffering from posttuberculosis sequelae experiencing worse HRQL than other restrictive patients, particularly those with kyphoscoliosis.[114] This study indicated that patients who are stable while receiving HMV have only minor impairments in psychosocial components of HRQL, similar to that of patients with other chronic diseases. The underlying disease has also been shown to be a determinant of HRQL in patients with chronic ventilatory failure who are not receiving HMV.[115] More recent research demonstrated that patients with COPD and posttuberculosis sequelae have more HRQL impairments than patients with other restrictive thoracic or neuromuscular disorders,[106,116,117] and that

TABLE 28-9: INTERCULTURAL ADAPTION OF THE SEVERE RESPIRATORY INSUFFICIENCY QUESTIONNAIRE

Language	Status	Literature (Refs.)
German	Original version validated	106, 107
Spanish	Translated version validated	108, 109
English	Translated version validated	110
Norwegian	Translated version validated	111
Dutch	Translation finished	112
French	Translation finished	113
Swedish	Translation finished	
Greek	Translation finished	
Japanese	Translation finished	
Hebrew	Translation in progress	

mental health can be well preserved, despite severe physical handicaps, particularly in patients with Duchenne muscular dystrophy.[116] HRQL as assessed by the Severe Respiratory Insufficiency Questionnaire was an overall predictor of long-term survival in patients without COPD receiving HMV.[117]

IMPACT OF HOME MECHANICAL VENTILATION ON HEALTH-RELATED QUALITY OF LIFE

Numerous studies have investigated the influence of HMV on HRQL. Many of these trials used generic HRQL measures because specific instruments were not widely available at the time. Interpretation of these trials is limited because generic instruments do not cover the specific issues relevant to patients with chronic respiratory failure and are postulated to be less sensitive to any changes occurring.[93]

Compared to the effect on survival, there is little doubt that HMV substantially improves both HRQL (as assessed by the Severe Respiratory Insufficiency Questionnaire)[3,59] and sleep quality[16,17,59] in patients with restrictive diseases. In contrast, longitudinal studies, mostly using COPD-specific HRQL measures, have only recorded minor and inconsistent improvements in HRQL following HMV in patients with COPD.[118–120] One randomized controlled trial reported that application of the COPD-specific St. George's Respiratory Questionnaire revealed no differences in HRQL when HMV plus long-term oxygen therapy was compared to long-term oxygen therapy alone; in contrast, application of the more condition-specific Maugeri Foundation Respiratory Failure item set showed that HMV improved HRQL.[23] Thus, even COPD-specific instruments may fail to reliably show HRQL changes in patients with severe COPD. This observation is probably attributable to the fact that these instruments were developed for patients with milder COPD.[105] Nevertheless, the Severe Respiratory Insufficiency Questionnaire revealed substantially improvements in HRQL in patients with COPD following commencement of HMV.[3,4,18] These improvements were similar to those seen in restrictive patients. Therefore, robust data support the conclusion that HMV can improve HRQL in several different disease groups including patients with COPD.

IMPORTANT UNKNOWNS AND FUTURE CONSIDERATIONS

Despite HMV being fully accepted as a treatment option for patients with chronic respiratory failure, some important questions remain open.

First, new features and modes are being developed by the manufacturers of home ventilators. These are aimed at not only improving the tolerance and quality of ventilation, but also at facilitating the application of home ventilators. Scientific evidence, however, for these developments is lacking. A good example is target volume. Its rationale is clear and target volume has been implemented in various ventilators, although robust evidence to support its use is not available. New features with new names and abbreviations inevitably overwhelm the user. From a technical point of view, HMV has been extremely successful for decades and although technical refinements are warranted, the challenge for future research is to differentiate between the innovations that help patients and those that cause confusion without any benefit.

Second, a pressing issue to determine circumstances in which HMV can prolong life in patients with COPD. Here, the new approach of high-intensity NPPV is promising and needs testing with regards to its potential for improving survival. It is not just different ventilator strategies that need to be investigated; clearly specified criteria for starting HMV also need to be established. Recent research has demonstrated that institution of HMV following an acute exacerbation complicated by respiratory acidosis and the need for acute mechanical ventilation was capable of preventing recurrent clinical deterioration.[121,122] Whether further acute readmissions to hospital can be prevented by HMV application and whether this impacts survival is a question that needs to be elucidated in the future.

Third, HMV undoubtedly improves HRQL. Nevertheless, the clinical status of patients eventually deteriorates, ultimately leading to death, and there is no conclusive information about end-of-life issues and decision making in the terminal phase of seriously ill HMV patients. There is only one study, which indicates that many HMV patients during their last 3 months of life frequently had respiratory symptoms and received inadequate medication.[123] The family burden was high and more than 50% of patients were eventually hospitalized and many died in the hospital or even in the intensive care unit. Research should not only focus on physiologic, epidemiologic, technical, structural, financial, and outcome aspects, but also study how patients with HMV eventually die and how HRQL in the terminal phase can be improved so as to enhance the quality of dying.[124]

SUMMARY AND CONCLUSION

HMV has become a standard treatment for patients suffering from chronic ventilatory failure, with the most frequently treated diseases being COPD, restrictive thoracic disorders, neuromuscular disorders, and obesity-hypoventilation syndrome. NPPV using face masks has become the modality of choice, although some patients, particularly those with neuromuscular disorders and difficulties in clearing their secretions, still use invasive mechanical ventilation via tracheostoma, which enables tracheal suctioning.

HMV should be started when a disease or a particular circumstance is causing impairment of the respiratory pump, and there is evidence of chronic ventilatory failure together with symptoms related to chronic hypoventilation, especially dyspnea and sleep-disordered breathing,

headache, or edema. Ventilation should be commenced in specialized centers with suitable experience. Staff training and close collaboration between the ventilation center and the people caring for the patient in the home environment are essential for successful treatment. HMV has been shown to improve symptoms, quality of life, and long-term survival in most of these patients, but its full impact on long-term survival in patients with COPD still needs to be established. Finally, understanding how patients receiving HMV die and how the quality of dying can be improved needs to be elucidated in the future.

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MECHANICAL VENTILATION IN THE ACUTE RESPIRATORY DISTRESS SYNDROME

John J. Marini

Few areas of critical care medicine have been the subject of as much investigative attention or clinical concern as the set of problems grouped under the label *acute respiratory distress syndrome* (ARDS). This syndrome, first formally described in 1967,[1] continues to be recognized clinically as a rapidly developing impairment of pulmonary oxygen exchange accompanied by diffuse infiltrates and altered respiratory system mechanics that cannot be attributed solely to hydrostatic forces. Fueled by better characterization of innate pathophysiology and of iatrogenic factors, considerable progress has been made in recent years toward reducing the adverse consequences of this condition. Yet, after more than four decades, active debate continues regarding key elements of the ventilatory prescription and appropriate therapeutic targets.

From the outset, mechanical ventilation with positive pressure has been essential in addressing the life-threatening gas exchange abnormalities and otherwise unsustainable workloads associated with ALI. Only in the relatively recent past, however, has there been clear documentation that the tidal pressures of mechanical ventilation can impact morbidity and survival.[2,3] This awareness has caused a conceptual shift away from attempting to restore normal blood gases at the costs of high pressure and toward adopting the avoidance of preventable iatrogenicity ("lung protection") as the first priority.

Many aspects of the debate concerning appropriate ventilator management of this group of conditions can be traced to the heterogeneity of the patient population, to our still imperfect comprehension of the mechanisms of

TABLE 29-1: CONCEPTUAL PRINCIPLES IN ACUTE RESPIRATORY DISTRESS SYNDROME VENTILATION

ARDS is a heterogeneous problem
Between patients
Over time
Between lung regions
Risk for ventilator-induced lung injury is proportional to *transalveolar* pressure
Lung recruitment is essential to avoid ventilator-induced lung injury
The chest wall influences regional lung volumes, tolerated pressures, and recruitability

ventilator-associated lung injury (VILI) and to the relative imprecision of the criteria upon which the label *ARDS and/or acute lung injury* (*ALI*) is assigned.[4] Despite an incomplete and still evolving understanding, a rich experimental and clinical database—much of it collected over the past two decades—allows for the development of a rational set of principles upon which to formulate an effective ventilation strategy.[5–7] Definitive answers for many important clinical questions related to this topic are not available; what is presented here reflects a pathophysiology-guided approach to accomplish essential clinical objectives while avoiding VILI (Table 29-1).

GENERAL OBJECTIVES FOR VENTILATOR SUPPORT

In the clinical setting, mechanical ventilation ensures adequate oxygenation of arterial blood, provides sufficient oxygen transport to vital organs and tissues, assists in eliminating carbon dioxide, relieves excessive burdens placed upon the respiratory muscles, helps maintain alveolar stability, and allows therapeutic measures that require controlled ventilation. Despite its undeniable value, however, mechanical ventilation also has the potential to inflict adverse clinical outcomes. The task of accomplishing ventilation safely in patients with injured lungs is made far more difficult by the mechanical heterogeneity of the respiratory system and the diversity of pathophysiology encountered among different patients who satisfy extant operational criteria for this condition.

DEFINING THE PROBLEM

The terms *ALI* and *ARDS* comprise a category of patients with varied pathoanatomy and mechanical characteristics. According to the widely used American-European consensus guideline,[4] the primary criteria relate to pulmonary oxygen exchange, the appearance of the plain chest radiograph, and to a clinical assessment of left ventricular function. Although such broadly inclusive criteria may be useful for some purposes, they prove problematic for others. In formal definitions, for example, no provision is made for the level of positive end-expiratory pressure (PEEP) at which the arterial sample is obtained or the chest radiograph is exposed. No stipulation requires that the defining criteria be met under standardized conditions and remain reproducible over time. Chest wall properties and body weight are left unaccounted for. Yet, pulmonary oxygen exchange is influenced not only by the properties of the lung, but also by end-expiratory lung volume, body position, mixed venous oxygen content, pulmonary blood flow, and the integrity and intensity of hypoxic pulmonary constriction. The chest radiograph is interpreted subjectively, and expert assessments often differ.[8] Moreover, it is clear that the lungs of different patients with ARDS vary with regard to radiographic appearance, inherent recruitability, and histopathology. Even within the same individual, assessed at the same moment, the pathoanatomy and mechanical environment varies from site to site within the injured lung. Such regional differences are partially explained by the properties of the surrounding chest wall, which profoundly influence the inflation characteristics of the integrated respiratory system as well as their regional distribution.[9,10]

Similar clinical presentations can mask radical differences in lung pathology, mechanical properties, and response to ventilator settings and maneuvers. Lungs of patients with ARDS resulting from pneumonic consolidation, for example, are less likely to inflate easily than are lungs made edematous by the circulating mediators of extrapulmonary sepsis.[11] Computed tomographic (CT) patterns may reflect these differences.[12] Moreover, inflexibility of the chest wall may substantially increase the pressures required to inflate the respiratory system (Fig. 29-1).[13] From these considerations, it is clear that inflexible guidelines for selecting PEEP and tidal volume that advise specific numerical values of these settings will be variably effective in accomplishing the goal of minimizing tissue stresses, depending on the type and severity of lung injury, the compliance of the chest wall, and the ranges for opening pressures and closing tendencies among the multiplicity of the lung units that comprise the injured lung.

PATHOPHYSIOLOGIC FEATURES RELEVANT TO VENTILATORY SUPPORT

A major conceptual advance of the past 25 years is the recognition that the lungs of patients with ARDS are mechanically heterogeneous and vary enormously in their patterns of infiltration, their inflation and collapse properties, and their regional expressions of pathology. CT scanning has revealed densities that may be localized or diffuse—with implications for response to ventilator interventions such as PEEP.[12] Variation in the underlying conditions that give rise to the clinical problem described as ARDS precludes categorical histologic descriptions that apply across the full range of

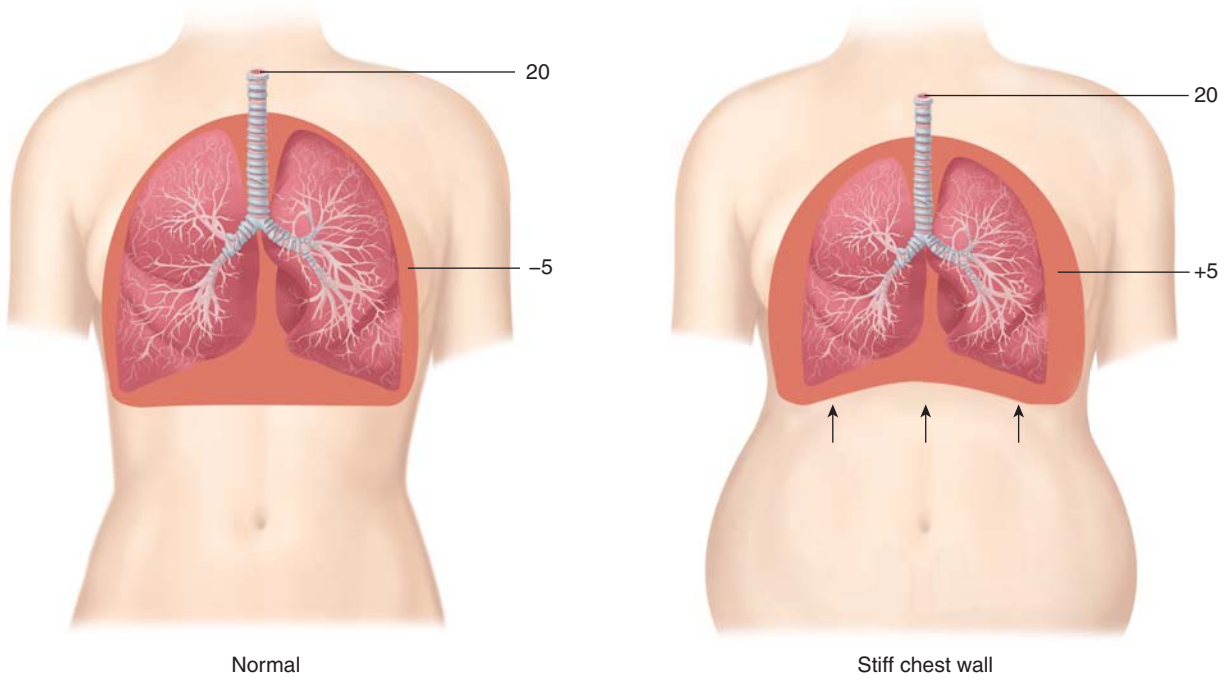

FIGURE 29-1 Influence of chest wall compliance on transpulmonary pressure and lung volume. Any specified airway pressure is associated with less transpulmonary pressure in the presence of chest wall stiffness or expiratory effort.

clinical experience. A few salient characteristics, however, are shared by most. In its earliest phase, noncardiogenic (high permeability) edema gives rise to a lung whose parenchymal airspace is partially occupied by proteinaceous edema and cellular infiltrate. A relatively large proportion of the lung—often exceeding 50%—is airless at end expiration, with the exact percentage depending jointly on severity, disease stage, etiology, and PEEP. Destruction of surfactant-producing type 2 alveolar cells leads to its diminished production, while exuded proteins and inflammatory products compromise the viability of the surfactant that remains.[14] Surfactant plays several important biologic and physiologic roles. From a purely mechanical standpoint, the loss of functional surfactant increases surface tension, thereby contributing to alveolar flooding, increased tissue elastance, small airway closure and atelectasis—particularly at low lung volumes.

The relative proportions of airless and aerated tissue also vary with disease type and stage. Although some controversy persists, CT scan estimates of gas and tissue volumes suggest that potentially "recruitable" tissue comprises only a minority of radiographic density at functional residual capacity in most cases.[15] Flooded and consolidated lung units comprise the remainder. Although clearly a minority viewpoint, a plausible argument has been advanced that "reopening" of lung units by alveolar pressure may occur primarily by redistributing alveolar liquid and shifting fluid volume from the alveolar to the interstitial compartments of the lung—not by atelectasis reversal ("recruitment").[16] The rapidity with which CT tissue density develops and resolves, however, as changes of alveolar pressure are imposed, as well as direct observations by intravital microscopy of alveoli at the lung's surface,[17] cast doubt on the primacy of the "fluid-shift hypothesis."

Mechanical Properties of the Injured Lung

Replacement of airspaces by inflammatory debris, cells, and fluid results in a lung whose aeratable capacity and compliance (measured in terms of volume accepted per unit of pressure) is severely reduced. The compliance of the respiratory system (lungs and chest wall) falls during ARDS for two reasons. First, airspace is lost to fluid and cellular infiltrates. Second, many functional lung units operate near their elastic limit because many fewer are available to accept the tidal volume. Under normal conditions, surfactant-modified surface forces allow the lung to inflate and deflate at similar pressures. In contrast, the injured lung is characterized by a right-shifted pressure volume loop, made so by its reduced aeratable capacity and by surfactant depletion.[13,18,19] For the same tidal volume, therefore, the mechanical work of breathing is dramatically increased.

Although clinicians characterize the mechanics of the injured lung by airway pressure and flow measurements made at the airway opening—the common entry and exit point for gas exchange with the environment—the mechanical properties of the lung's individual subunits are hardly uniform, even in health. In part, this heterogeneity relates to regional variations of pleural (and therefore transpulmonary) pressure that arise from interactions of the chest wall

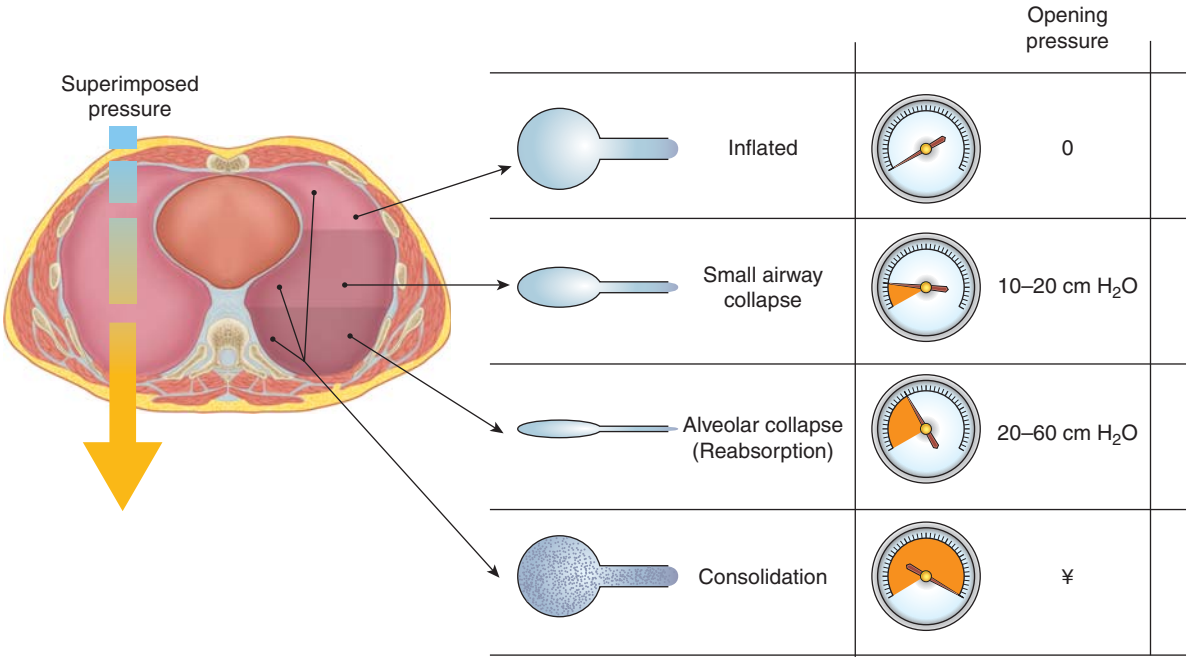

FIGURE 29-2 Spectrum of opening pressures associated with lung units within the injured lung. Lung units located in dependent areas are compressed by the weight of the overlying lung and mediastinum. Local transpulmonary pressures vary considerably, so that some lung units remain fully inflated throughout the tidal cycle, whereas others cannot be aerated. Less pressure is required to open small airways when the alveoli remain aerated than when all alveolar gas has been absorbed. (Image provided by Luciano Gattinoni and used with permission.)

with the injured lung and from the need for dependent tissues to support the weight of the mediastinal contents and the edematous lung (Fig. 29-2). This underlying mechanical heterogeneity is implied by quantitative CT imaging techniques that characterize the topographical anatomy in response to changing patterns of airway pressure, or more directly in real time by imaging of ventilation with radiotracer gases or electrical impedance tomography.[20,21]

For any specified airway pressure, some lung units are closed and others are open. Among the population of open units, there exists a range of states of lung unit expansion, depending on the local transpulmonary pressures that distend them. Even at airway pressures that are generally considered modest, some of the open lung units verge on overdistension, while others are on the compliant portion of their pressure volume relationship (Fig. 29-3). Alveolar distension that approaches the elastic limit stimulates surfactant production, but the repetitive application of nonphysiologic stretching forces, as during high tidal volume or high-pressure tidal ventilation, initiates molecular signaling of a local inflammatory response.[22,23]

Mechanical interdependence among the lung units of a heterogeneously affected lung amplifies the stresses of high pressure at the junctions of closed and open lung units in a nonlinear fashion (Fig. 29-4).[23,24] Such recurring forces at the points of stress focusing not only strain the lung's structural meshwork to initiate inflammation, but also assist in reopening potentially recruitable (atelectatic) lung units.[25] When atelectatic tissues are subjected to high pressures, amplified shearing forces within these zones at high risk for damage may be of sufficient magnitude to tear the delicate terminal airways or alveoli themselves, creating micro wounds that produce tissue hemorrhage and incite inflammation as a secondary phenomenon. Stress amplification at the margins of dissimilar tissues is at least partially a function of their relative volumes. (A flooded, gasless alveolus of volume similar to its air-filled neighbors may experience forces that are no

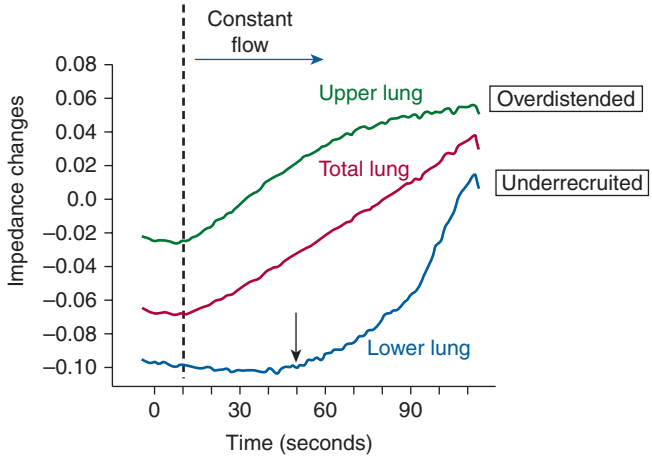

FIGURE 29-3 Mechanical characteristics of lung units in dependent (*lower*) and nondependent (*upper*) lung regions. As the lung is inflated by constant flow of gas, electrical impedance increases in proportion to aerated volume. Although the relationship of volume to impedance for the total lung appears roughly linear, upper lung regions are relatively overdistended whereas lower lung regions are relatively underrecruited until total lung capacity is achieved. (Image provided by Marcelo Amato and used with permission.)

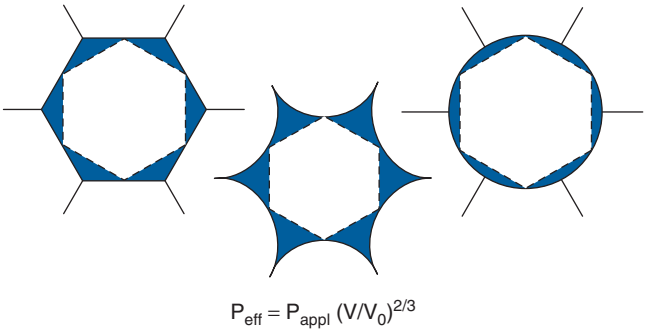

FIGURE 29-4 Amplification of tension at the boundaries of open end collapsing lung tissue. Normally distended (*left*), collapsing (*center*), and overdistended (*right*) states of inflation. Because of interdependence, the tensions applied to a collapsing alveolus are amplified. A simple mathematical model predicts that the tensions resulting from an alveolar pressure (P_{appl}) produce a tension comparable to an effective pressure (P_{eff}) described by the equation. At 30 cm H_2O applied pressure, the volume of an aerated alveolus (V) is approximately ten times that of a collapsed alveolus (V_0). Thus, the estimated pressure necessary to mimic the tensions at the interface is approximately 4.5 times as great as that applied, or 140 cm H_2O. (Used, with permission, from Mead et al.[23])

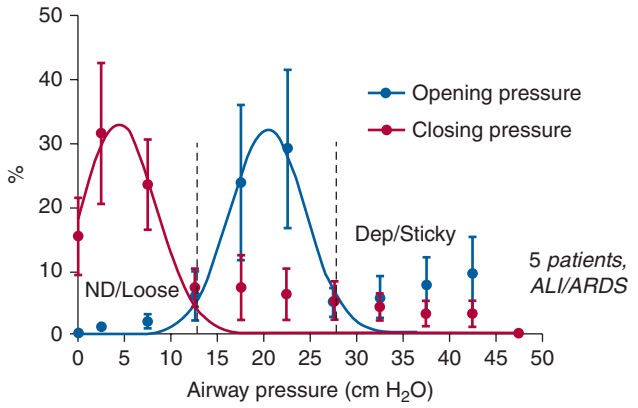

FIGURE 29-5 Histograms relating percentage of potentially recruitable lung units that are open to inflation and deflation airway pressures. Unstable airways open at relatively modest pressures, whereas alveoli that have undergone absorption collapse require much higher pressures to open. The spectrum of closing pressures is left shifted. Note that some lung units begin to collapse at relatively high airway pressures. (Reprinted with permission of the American Thoracic Society. Copyright © 2012 American Thoracic Society. Crotti S, Mascheroni D, Caironi P, Pelosi P, Ronzoni G, Mondino M, Marini JJ, Gattinoni L. Recruitment and derecruitment during acute respiratory failure. A clinical study. *Am J Resp Crit Care Med*. 2001;164(1):131–140. Official Journal of the American Thoracic Society. Adapted from original article.)

more intense.) Because mechanical forces are amplified at the junctions of dissimilar tissues, it seems likely that injury abets the process of ventilator associated injury, so that damage propagates outward from injured into previously healthy zones. Whether injury results from the process of repetitive popping open of lung units under high pressure or simply is the cumulative result of high tension stretching at the interface remains to be resolved. It appears, therefore, that there are at least two critical elements that place the injured lung at risk for ventilation associated lung damage: high inflating pressures and the prevalence of collapsed lung units that interface with open ones.

Atelectasis

At the microscopic level, lung unit collapse may be thought of in two broad categories: "loose" atelectasis that arises primarily from compressive forces of the heavy lung acting to close small airways and responds to relatively low levels of transpulmonary pressure, and adhesive or "sticky" atelectasis that results from gas absorption and requires very elevated pressures to reverse.[26] High concentrations of inspired oxygen encourage the latter in poorly ventilated regions, as well as interfere with surfactant kinetics. These hard to recruit units may be among the first to close as high airway pressure is withdrawn. Loose and sticky types of atelectasis often coexist, perhaps accounting for the fact that lung units open throughout the entire range of total lung capacity (Fig. 29-5).[25–27] In the setting of severe ARDS, pressures that exceed 60 cm H_2O may be needed to complete the recruiting process. Although opening of lung units is primarily a function of transalveolar pressure, the duration with which pressure is applied also contributes; that is, a lower pressure may be sufficient if applied for an adequate period. Moreover, atelectatic lung units tend to "yield" (open) in a stuttering, discontinuous fashion, with high sustained pressure causing a serial snapping open of small blocks of units.[28] Discontinuous lung opening during the tidal cycle may give rise to audible crackles, usually best heard in dependent regions.

Pulmonary Edema

The increased microvascular permeability of ALI and/or ARDS renders it vulnerable to edema formation and impedes its relative rate of edema clearance. The weight of the normal lung does not begin to rise significantly until pulmonary venous pressure exceeds 20 mm Hg. Unlike the healthy lung, however, extravascular water in the injured lung bears a strong quasilinear dependence on hydrostatic microvascular pressure, a relationship that begins from capillary pressures that are considered low by most clinical standards.[29] The term *noncardiogenic pulmonary edema*, therefore, does not imply that gas exchange cannot improve by lowering the hydrostatic pressure gradient across the injured lung. Because extraalveolar microvessels as well as capillaries can leak,[30,31] numerous factors influence the vascular pressures relevant to edema formation. These include left ventricular filling pressure, cardiac output (which increases the pressure needed to drive blood flow through the lung with limited capillary recruiting reserve), the plasma oncotic pressure, the interstitial fluid pressure, and the integrity of the alveolar and lymphatic lung water clearance mechanisms. Clearance mechanisms are influenced by the degree of lung stretch. Translocation of blood from infradiaphragmatic vascular capacitance beds to the central vessels of the thorax can occur as intraabdominal pressure rises.[32]

MECHANISMS AND CONSEQUENCES OF VENTILATOR-INDUCED LUNG INJURY

For more than three decades, experimental studies have shown that *excessive mechanical stresses* developed during mechanical ventilation can inflict injury upon both normal and acutely injured lungs, and once injured, retard their healing.[33,34] Injury may result from overstretching of tissues that are already open, from shearing forces at the junctions of expandable and unyielding tissue, or from repeated percussion of closed terminal airways (Fig. 29-6). Repeated application of transalveolar pressures exceeding those corresponding to the inflation capacity of a healthy lung may disrupt the alveolar epithelial barrier, especially in the absence of sufficient end-expiratory pressure to reduce stress focusing by holding open mechanically unstable lung units.[33,35] From a theoretical standpoint, sustained recruitment reduces the potential for damaging forces to concentrate at the boundaries of inflating lung and unyielding or collapsed structures. Indeed, an overwhelming body of experimental work indicates the lung protective effect of sustained "recruitment" when high tidal inflation pressures are used.[36,37] Mechanosignaling at moderately high airway pressures may induce the formation and release of inflammatory mediators,[22,37–42] initiate programmed cell death (apoptosis), or produce necrosis.[38,41] Excessive strain may exceed cytoskeletal tolerances, causing physical tears and stress fractures of endothelium, epithelium, and intercellular matrix (Fig. 29-7).[38,39] Scientific data suggest that when the ratio between tidal volume and aerated functional residual capacity exceeds 2, the resulting transalveolar forces are sufficient to cause tissue damage.[40] Furthermore, the tendency for translocation of inflammatory mediators and bacteria into the bloodstream is influenced by the ventilator pattern.[42–44] Such observations suggest possible links between adverse patterns of ventilation and dysfunction in remote vital organs.

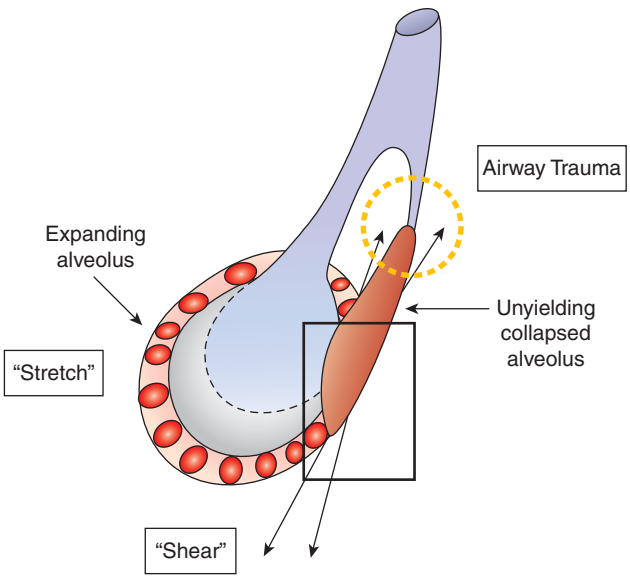

FIGURE 29-6 Forms of tissue stress that occur near the junctions of open and closed lung units.

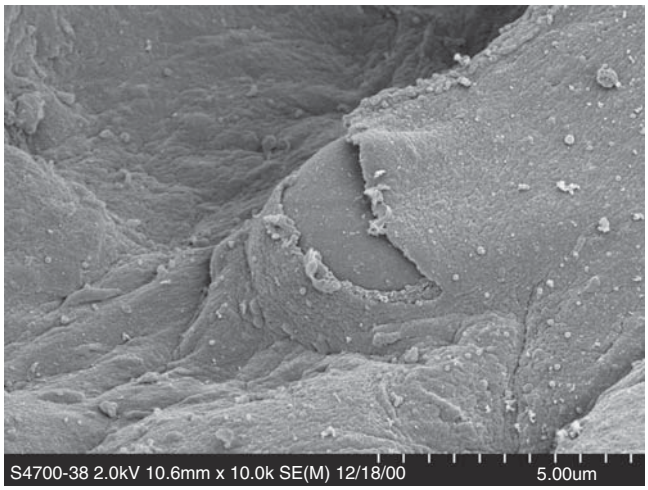

FIGURE 29-7 Stress fracture of the alveolar capillary membrane resulting from ventilator-induced lung injury in a previously normal rat lung. Similar tears have also been demonstrated to occur in human patients with ARDS.

Pathophysiology and Prevention of Ventilator-Induced Lung Injury

From available data, VILI appears to be a complex process initiated by the repetitive application of excessive, stress/strain to the lung's fibroskeleton, microvasculature, terminal airways, and delicate juxtaalveolar tissues. Defining the linkage between stress, strain, and diffuse alveolar damage is currently a subject of intense investigation.[22,37,38,42,43,45] It seems undeniable, however, that high levels of mechanical stress disrupt the normal functioning of cells that populate the pulmonary microenvironment and that sufficient dimensional strain triggers the release of inflammatory mediators and destructive enzymes (Fig. 29-8).[43,46,47] Under moderate degrees of strain, such mechanosignaling may be the primary pathway to injury. When the applied mechanical stress is very high, fibroelastic structural integrity may be directly breached, with the inflammatory process a consequence rather than initiator of the observed histopathology. These high tissue-rupturing forces are especially likely to be generated in dependent lung regions, where unstable alveoli are most prevalent (Fig. 29-9). Another important mechanism in the causation of lung tissue damage may occur at the level of the terminal airways as they remain closed as airway pressures build or open and reclose with each tidal cycle.[36] Damaging shear forces (those that run tangential to the structure) appear to rip the epithelium from its attachments. The rate at which these tissues expand, conditioned by the inspiratory flow profile, may also play an important role.[48] Although relatively few studies have focused on this aspect,

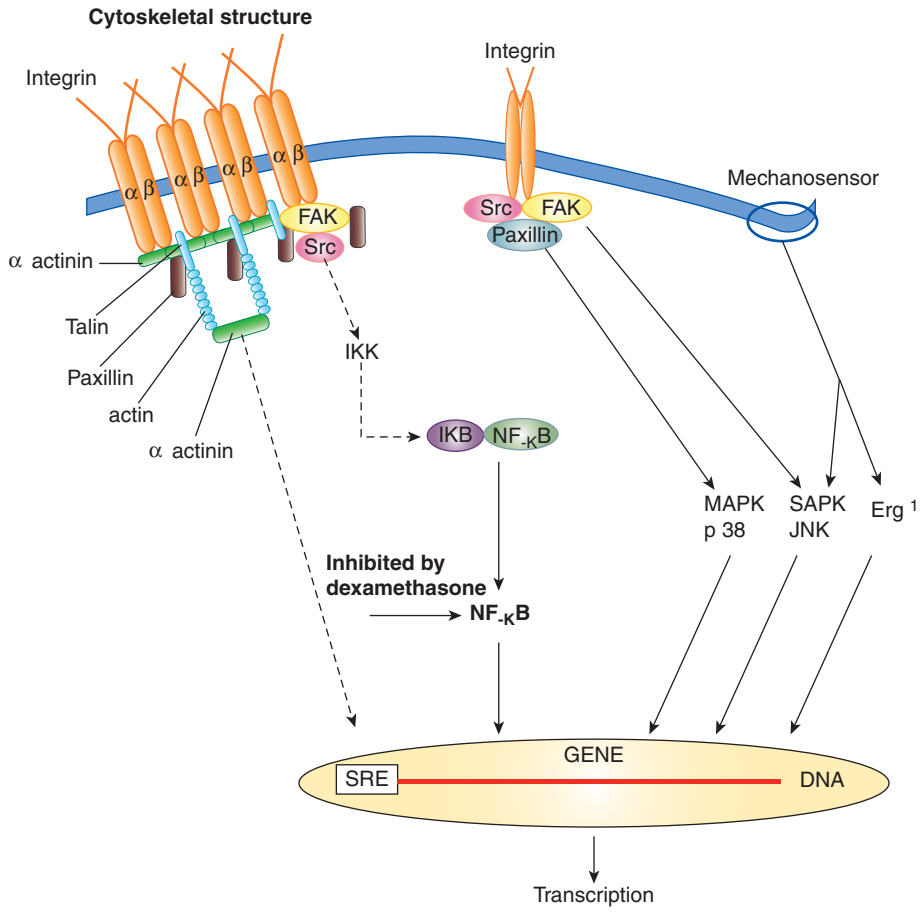

FIGURE 29-8 Mechanosignaling pathways of inflammation under conditions of excessive tissue strain. (Used, with permission, from Dos Santos and Slutsky.[37])

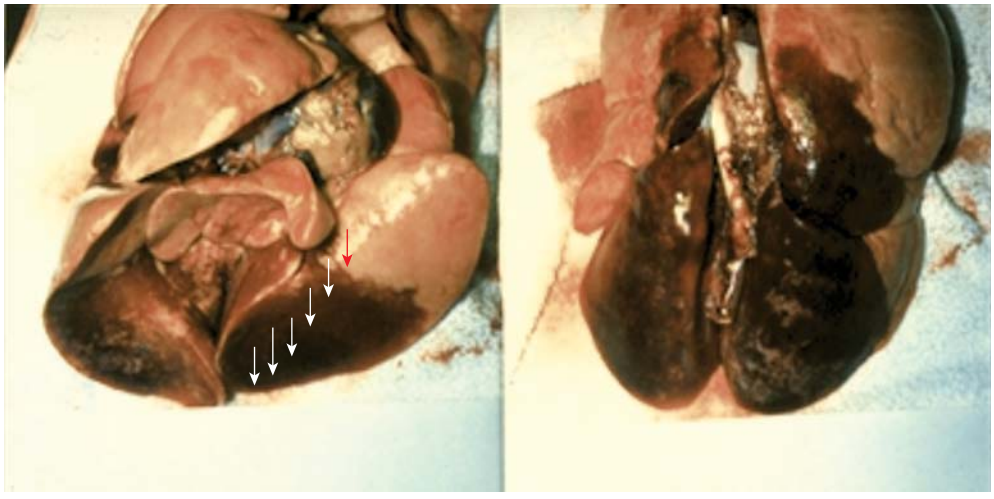

FIGURE 29-9 Excised heart–lung block from a previously normal animal subjected to high inflation pressure and low levels of positive end-expiratory pressure (PEEP). Specimen is shown inflated at 20 cm H_2O airway pressure in the supine (*left panel*) and prone (*right panel*) conditions. Note the sharp demarcation of hemorrhagic edema from relatively normal appearing lung. Damage may progress sequentially from dependent to nondependent regions, as indicated by the sequence of *arrows*.

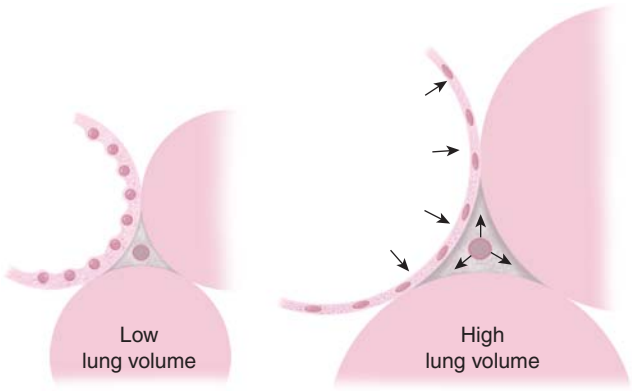

FIGURE 29-10 Mechanical behavior of capillaries embedded in the wall of inflatable alveoli and those microvessels within the interstitial spaces. Wall-embedded capillaries are compressed, whereas extraalveolar microvessels (and perhaps corner vessels) are dilated by lung expansion.

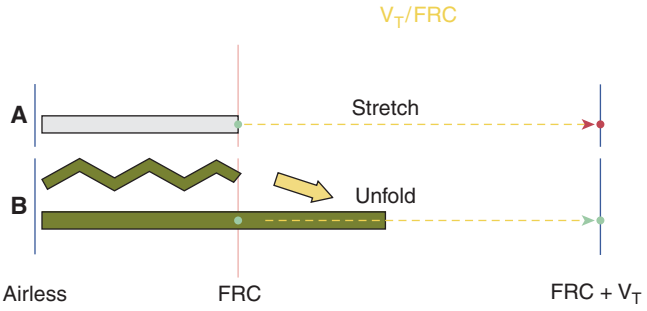

FIGURE 29-11 Concept of strain as relates to tidal volume (V_T) and functional residual capacity (*FRC*). Assuming that the lung has few recruitable units at rest (*A*), doubling of FRC by the applied V_T will result in excessive tissue strain (V_T/FRC ≥2). Peak transalveolar pressure would reflect that damaging stress. If tidal recruitment occurs during delivery of the V_T (*B*), the recruited tissue will relieve the stress even though the calculated ratio of V_T to FRC initially is the same. Peak transalveolar pressure would not rise as high as in situation *A*, but depending on driving pressure amplitude, tidal recruitment might have potential to injure secondary to stress amplification.

such a contribution seems likely, as the expansion velocity of the parenchyma is amplified by the reduced number of functioning airways that must accept what is typically an elevated total minute ventilation.

From an engineering perspective, mechanical *stress* is a function of transstructural tension; *strain* is the dimension-altering consequence of high transstructural pressure, conditioned by the elastance of the element in question. Although by no means the only determinant of tissue forces, the measurable analog of the stress across the entire lung is transpulmonary pressure—crudely estimated as the difference between static airway pressure (the "plateau" pressure) and average pleural pressure (often estimated by use of an esophageal balloon).[49] Regional transpulmonary pressures vary considerably, because of the influence of gravity, chest wall irregularities, intraabdominal pressure, mediastinal weight, and vascular-filling pressure (see Fig. 29-2).[50,51] Available laboratory data illustrate that pleural pressure, however measured, does not accurately reflect interstitial pressure when the lung is edematous and inflamed.[51,52] Even directional changes of pleural and interstitial pressures may not track together in a nonuniform environment (Fig. 29-10). Although not directly measurable, strain correlates with aerated volume as a fraction of aeratable capacity. As already noted, excessive strain may be experienced when VT exceeds the aerated functional residual capacity of a well-recruited lung by a factor of 2.0[40] (Fig. 29-11).

HOW DOES TIDAL VOLUME RELATE TO TISSUE STRESS?

Once this latter concept is understood, it becomes clear that tissue stress is not a predictable function of tidal volume but rather is strongly influenced by tidal volume in relation to the size (and compliance) of the compartment forced to accept it. Logically, the developed transpulmonary pressure would seem a variable that integrates these relationships. Even this, however, is not the full story—stress amplification and flow-influenced shearing forces at the boundaries of tissues with differing capacities to expand must be considered. Peak tidal transalveolar pressure interacts with end-expiratory transalveolar pressure to determine measurable stress, which varies markedly from site to site across the damaged lung. The alveolar pressures resulting from tidal volume and PEEP are both interactive elements in the injury process, but even when considered together cannot precisely estimate tissue stresses, as interstitial pressure is an unmeasured variable that differs throughout.

Moreover, the damaging *strain* that results from a given stress depends on tissue fragility. In the setting of ARDS, tissue integrity is likely to be at least normally delicate or even compromised, especially in its earliest phase. The low compliance typically associated with ALI results primarily from the reduced number of aeratable lung units—not from increased stiffness of the individual lung units themselves.[26,52] The tidal volumes pulled during exercise by a healthy athlete may exceed 25 to 30 mL/kg of lean body weight, whereas much smaller breaths eventually cause damage or lung rupture in the setting of ALI. Although increasing the tidal volume delivered to the same individual will invariably cause tissue stresses to rise in some lung units, a raised tidal volume may actually cause the stresses in other units to *fall*. This apparent paradox owes to the recruiting effect of the higher pressures and perhaps improved ventilation of marginally ventilated units predisposed to absorption collapse.[53] At any clinically selected tidal volume, tissue stresses may be reduced or accentuated by the application of PEEP, depending on whether PEEP effectively recruits vulnerable tissue or simply raises plateau pressure. Quests for a universally applicable predetermined tidal volume or PEEP value applicable to all patients would seem destined to be a fruitless exercise.

Modifying the characteristics of the chest wall (e.g., by prone positioning[54,55]) is an effective mechanism for altering the regional distribution and amplitude of transpulmonary

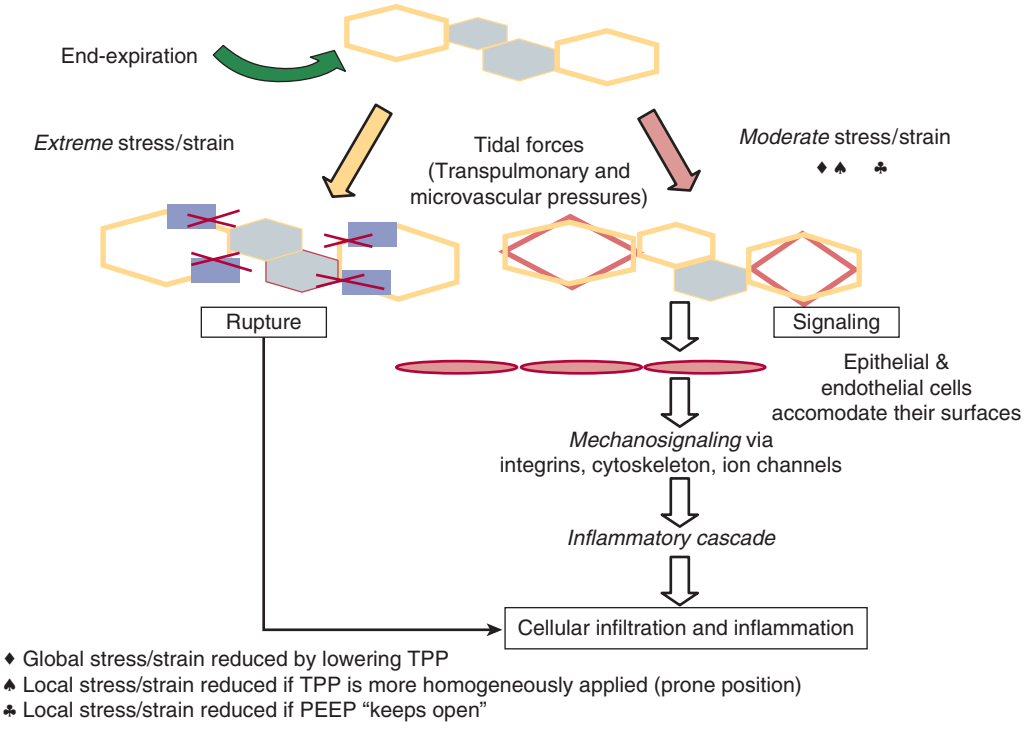

FIGURE 29-12 Hypothetical relationship between tissue damage and the severity of mechanical stress or strain during the tidal cycle. Moderate forces applied repeatedly to junctional tissues may result in mechanosignaling of inflammation. Extreme stress or strain causes micro wounds to develop, with inflammation occurring as an epiphenomenon. *PEEP*, positive end-expiratory pressure; *TPP*, trans-pulmonary pressure. (Used, with permission, from Marini JJ, Gattinoni L. Ventilatory management of ARDS: a consensus of two. *Crit Care Med.* 2004;32(1):250–255.)

pressure. Even within the same small region, inflationary stresses can vary markedly in magnitude and even in direction between structures situated within microns of one another. Shearing forces, one of the varied forms of mechanical stress resulting from lung inflation, intensify at the junctions of tissues with different compliance values and anchoring attachments.[23] Minimizing or eliminating these irregularities reduces the potential for adverse "stress focusing" and tissue strain. In such a microenvironment, limiting end-tidal alveolar pressure assumes major importance for two primary reasons: (a) A high plateau pressure may overstretch open alveoli, and (b) perhaps more importantly, because junctional tension rises in nonlinear proportion to airway pressure,[23] the plateau pressure acts as a potent lever arm at stress focus points.

By reducing the number of junctional interfaces and by preventing the repetitive opening of terminal lung units at high pressure, recruitment of lung tissue—defined as the sustained reversal of atelectasis on whatever scale it occurs—may be lung protective. When nearly all potentially recruitable tissue is aerated, the lung is said to be "open."[56] A given transpulmonary pressure applied to a fully open lung should be associated with less stress than the same pressure applied to a lung with closed units juxtaposed to open ones (Fig. 29-12). Some authors argue that the injured lung should be fully "opened" so as to reduce the potential for repetitive opening and reclosure.[56] Presently, however, it is not clear that this should always be given highest priority; to what extent repetitive opening and closure of small airways produces injury and whether the prevention of such behavior is the key to lung protection remain debatable, especially when peak tidal pressures are restrained; modest airway pressures may not inflict shearing injury when opening occurs at low pressure. In addition, because the difference between opening and closing pressures is often quite narrow in units that do open at higher pressure, some degree of tidal recruitment may be unavoidable. Therefore, how much of the lung should be "opened" and what pressure cost is acceptable remain key unresolved questions.

PATHOGENETIC COFACTORS OF VENTILATOR-INDUCED LUNG INJURY

Experimentally, a variety of cofactors apart from end-inspiratory, end-expiratory, and driving tidal transpulmonary pressures are important in the generation or prevention of VILI (Table 29-2). Prone positioning confers a protective advantage in both normal and preinjured animals.[57,58] A potential role for high inspired oxygen fraction as a contributor to iatrogenic injury has been intimated for many years but never convincingly documented in the clinical setting.[1,37] As other examples, higher precapillary[59] and lower postcapillary[60] vascular pressures intensify the injury caused by a fixed ventilatory pattern. As the lung expands, alveolar and extra-alveolar microvessels are compressed and dilated,

TABLE 29-2: CLINICALLY MODIFIABLE COFACTORS INFLUENCE THE EXPRESSION OF VENTILATOR-INDUCED LUNG INJURY

Vascular pressure
High inflow or low outflow pressures
Ventilation frequency and/or minute ventilation
Hypercapnia may be protective
Position
Body temperature
Inspired oxygen percentage
Pharmacologic interventions

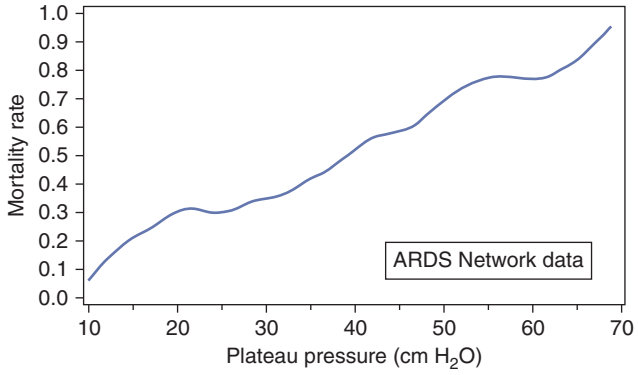

FIGURE 29-13 Relationship of mortality rate to plateau pressure generated during the National Institutes of Health-sponsored ARDS Network multicenter trial of high versus low tidal volumes. Note the quasilinear relationship of mortality rate to plateau pressure. (Used, with permission, from Brower et al.[70])

respectively (see Fig. 29-10). At some intermediate point on the luminal pathway that links them, the pushes and pulls are oppositely directed, giving rise to forces that stress the microvascular endothelium. Energy dissipation across the waterfall created by intermittent zone 2 conditions, vascular interdependence, and opening and closure of the microvascular endothelium could potentially explain the damaging influence of reduced postalveolar vascular pressure.

For identical tidal inflation and end-expiratory pressures, reducing respiratory frequency and minute ventilation attenuates or delays damage, provided that the tidal ventilatory stresses are sufficiently high.[61] Large tidal breaths and sighs occur infrequently as part of an inherent pattern of normal breathing. Sighs, for example, are inherent to the natural breathing pattern and are not injurious.[62] Multiple high-tension tidal cycles are required to signal inflammation. Experimental evidence also demonstrates that effective repair of minor defects within the cell membrane may occur within seconds of reducing stress,[63,64] and reducing respiratory frequency may allow these repair processes sufficient time to run to completion. Alternatively, less cumulative damage to the lung may occur per unit time as injurious forces unzip structural elements of the lung's fibroskeleton.

What level of transpulmonary pressure is likely to be damaging, therefore, depends on variables other than the tidal "plateau" pressure. Moreover, when the lung is comprised of large numbers of recruitable units, PEEP attenuates the tendency for high plateau pressures or tidal volumes to cause injury.[65–67] Consequently, it is difficult to specify an exact level of transpulmonary pressure that serves as an appropriate threshold criterion for safety. From a theoretical standpoint, repeated tidal application of a transpulmonary pressure of 15 to 20 cm H_2O (corresponding in a patient with a normal chest wall to a plateau pressure that may be in the range of 25 to 35 cm H_2O) gives cause for concern, as some higher compliance regions of the injured lung may approach their elastic limits at this pressure. It is worth noting that a transpulmonary pressure of only 15 cm H_2O subjects the normal lung to about two-thirds of its total capacity and is associated with a tidal volume exceeding 2500 mL.[13]

Experimental data suggest that lung tissues can be injured by mechanical stretching forces more easily in the setting of other noxious influences. In other words, it takes a higher stretching force to cause injury in a previously healthy lung than in one that has been exposed previously or concurrently to another inflammatory stimulus, such as endotoxin, hyperoxia, or cytotoxic drugs.[68,69] Such observations have given rise to the "two-hit hypothesis" for VILI, and underscore the potential vulnerability of the preinjured lung to imprudent ventilatory prescriptions. At the same time, such vulnerability can be viewed as an opportunity to modulate the severity of VILI by altering both nonventilatory and ventilatory factors.

A post hoc analysis of the ARDS Network tidal volume trial (ARMA) indicates that observed mortality paralleled plateau pressure to very low values—considerably lower than 20 cm H_2O (Fig. 29-13).[70] This correlation, which is difficult to explain entirely by indices of disease severity, suggests the possibility that for the injured lung there is no obvious safety threshold below which ventilator-associated lung damage does not occur. Other data suggest danger at relatively low plateau pressures,[71] but detailed analysis of human clinical trials argue that plateau pressures less than 30 cm H_2O have little impact on mortality once PEEP and disease severity are accounted for.[72] (Tidal volume must correlate with plateau pressure in any given individual; prestudy tidal volume and plateau pressure data from the ARMA trial, however, showed remarkably poor correlation because compliance [the inverse of elastance] is the missing parameter [Fig. 29-14].)

ACTIONS OF POSITIVE END-EXPIRATORY PRESSURE

Elevating the pressure baseline from which breaths are taken or delivered raises mean and end-expiratory lung volumes. Doing so nearly always improves oxygenation to some extent—primarily a function of keeping the lung open. When the breaths are drawn spontaneously or with pressure support, it is customary to call the end-expiratory pressure *continuous positive airway pressure* (*CPAP*); during breaths of predetermined length, the term is *PEEP*. Both are instrumental in the supportive care of patients with ARDS.

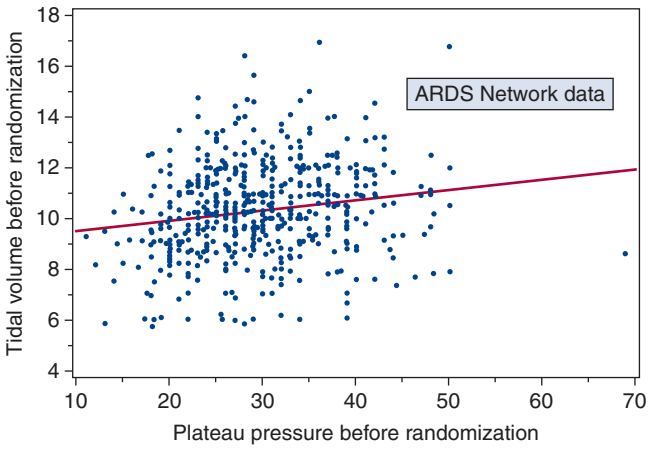

FIGURE 29-14 Scatterplot of tidal volume versus plateau pressure before randomization to the limbs of the National Institutes of Health-ARDS Network ARMA trial. (Used, with permission, from Brower et al.[70])

Gas Exchange. The potential clinical utility of PEEP in improving oxygenation was mentioned in the paper that first brought ARDS to widespread clinical attention.[1] Subsequent work demonstrated its potential to increase ventilation dead space and impair cardiac output by impeded venous return and increased right ventricular afterload.[73] In patients in whom PEEP stabilizes lung units that are susceptible to collapse, the response to increasing PEEP is generally to improve pulmonary oxygen exchange efficiency. Many patients show limited or negligible response, however, presumably because the recruitable population of lung units under baseline conditions is small. Infrequently, increasing PEEP can actually cause the partial pressure of arterial oxygen (Pa_{O_2}) to fall, presumably by redirecting pulmonary blood flow, by causing pulmonary arterial pressure to rise high enough to shunt venous blood through a patent foramen ovale, or by causing sufficient reduction in oxygen delivery to force an increase in systemic O_2 extraction and desaturate venous blood (see Chapter 37).

The benefit of PEEP on oxygenation depends on improving functional residual capacity. When patients labor to breathe, as during hyperpnea, expiratory efforts made against PEEP may force the lung's volume to fall below its equilibrium value, effectively storing elastic energy to aid inspiration but interfering with improvement in O_2 exchange. Under these circumstances, eliminating forceful expiratory muscle action (as by sedation) tends to improve O_2 exchange efficiency.[74]

Alteration of Tissue Stress. Because PEEP has the potential to maintain recruitment of unstable lung units (thereby reducing "stress amplification"), there has been intense interest in its role as a core element of a lung protective ventilating strategy. When plateau pressure is held constant, raising PEEP not only reduces the number of closed lung units, but also shortens the lever arm ("driving pressure") applied to the unstable lung units at risk to open forcefully (Fig. 29-15). Yet, when tidal

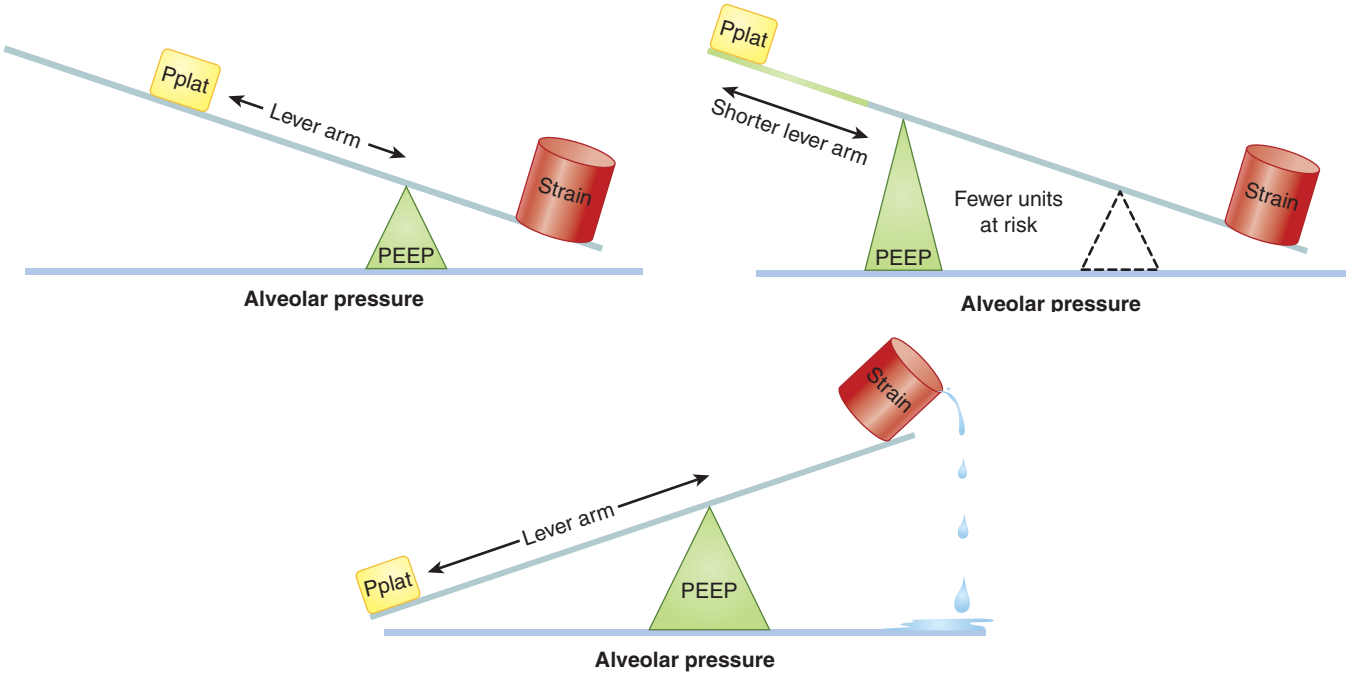

FIGURE 29-15 Hypothetical relationship among plateau pressure PEEP and tissue strain. In the generation tissue strain, the driving pressure for tidal volume (the difference between plateau pressure and PEEP) acts as a force lever arm, whereas PEEP is the fulcrum. *Upper Left.* Levels of plateau pressure (*Pplat*) and PEEP produce strain within acceptable limits. *Bottom Center.* Increasing Pplat while keeping PEEP at a level insufficient to hold open unstable units lengthens the lever arm and produces excessive tissue strain. *Upper Right.* When PEEP is increased, the same high Pplat that caused damage previously is better tolerated in that fewer lung units are placed at risk after recruitment and the lever arm of driving pressure is shortened.

driving pressure is preserved, PEEP raises both mean and peak tidal pressures, distends lung units that are already open, redirects blood flow, and alters cardiac loading conditions. Moreover, those lung units at the interface of closed and open units that remain unopened or continue to undergo repeated cycles of tidal recruitment despite an increase of PEEP are subjected to any PEEP-related elevation of end-inspiratory pressure, increasing the tendency for damage to those specific units. Thus, PEEP has the clear potential for benefit or harm depending on the balance among its multiple effects. Prone positioning tends to even the distribution of ventilation and reduce the gradient of transpulmonary pressure across the lung that exists in the supine position.[55,75] Airway and lymphatic drainage also tend to improve. This improved uniformity facilitates the selection of a single combination of PEEP and tidal volume that achieves a protective strategy for the entire organ.

RECRUITING MANEUVERS

A major clinical challenge is to apply sufficient pressure to keep the lung fully recruited without either increasing the stress applied to tissue that remains closed or overdistending alveoli that remain patent. Certain steps can be taken to minimize the number of unstable units by reversing those conditions that predispose to compressive and absorptive atelectasis (Table 29-3). PEEP cannot keep open lung units that were never open, and the recruiting process is not completed until pressures are reached that considerably exceed the total capacity of the healthy lung (Fig. 29-16). Although most lung units open at pressures less than 25 cm H_2O, some refractory units of the acutely injured lung may require much higher pressures to establish patency. To reach the "yield" (opening) pressures of refractory lung units requires the initial application of pressures that would be hazardous during tidal ventilation.[15,27,76] Newly opened lung units tend to close at lower pressures, allowing ventilation with the same tidal volume and PEEP to occur in the context of a more open lung with fewer lung units at risk for opening and closure (Fig. 29-17).

Because of viscoelastance and other time-dependent force-distributing phenomena, the tendency of a previously collapsed airway to open (or "yield") is a jointly hyperbolic function of both transmural pressure and time.[76] Of these, pressure is the most important variable. A variety of techniques, known as recruiting maneuvers, are designed to "open" the lung so that safe and effective combinations of PEEP and tidal volume can be utilized. Each recognizes that recruitment depends not only on the magnitude of transpulmonary pressure, but also on the duration of its

TABLE 29-3: HOW IS THE INJURED LUNG BEST RECRUITED?

Prone position
Adequate positive end-expiratory pressure
Adequate tidal volume (and/or sighs?)
Recruiting maneuvers
Minimize edema (?)
Lowest acceptable FI_{O_2} (?)
Spontaneous efforts (?)

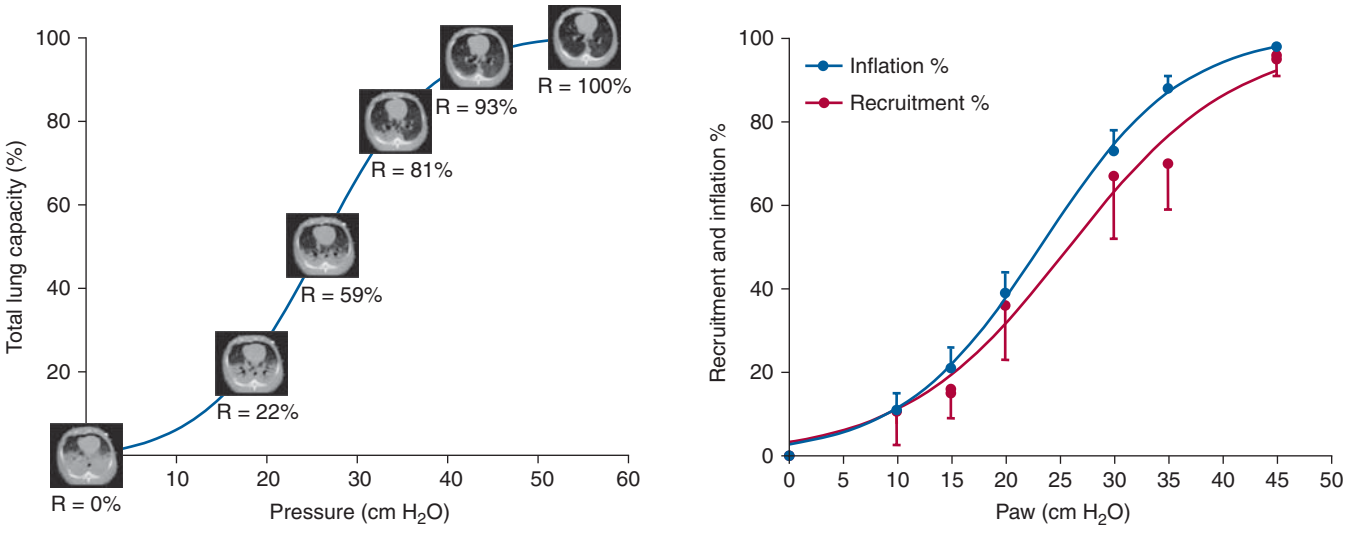

FIGURE 29-16 *Left.* CT scan slices obtained after oleic acid injury of the lung superimposed on the pressure-volume relationship of the respiratory system. Consolidation and radiographic density are greatest in the dependent lung regions and high pressures must be applied, even in this "highly recruitable" lung model, to fully reverse the radiographic evidence for collapse. Percentages denote aerated recruitable tissue. *Right.* Recruitment and inflation percentages as functions of static airway pressure. In these five patients with ARDS, the pressure–recruitment curve parallels the pressure–inflation curve when both are expressed as percentages of their maximum ranges. (Used, with permission, from Pelosi et al[27] and Crotti et al.[15])

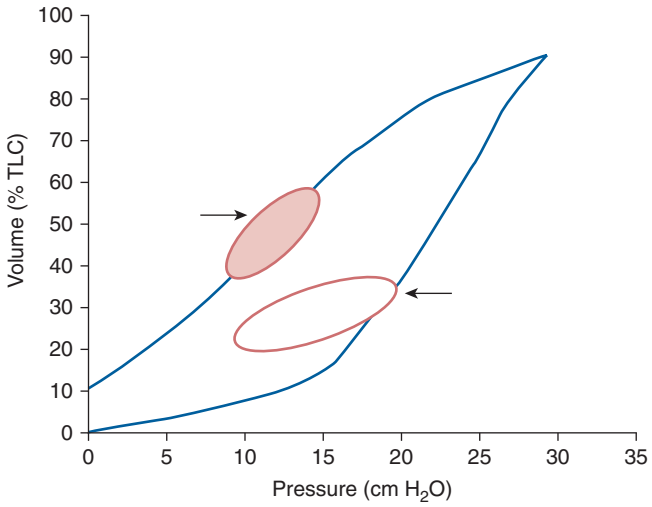

FIGURE 29-17 Effect on the tidal pressure volume relationship (*small loops*) before and after a sustained inflation recruiting maneuver. Hypothetically, first opening the lung by increasing pressure to high values allows tidal ventilation to occur at similar or lower pressures with more lung units open at end-expiration. Note that any volume gained is quickly lost after recruitment if original PEEP and position remain the same.

application (Fig. 29-18). To consolidate benefit after a successful "recruiting maneuver," end-expiratory pressure must remain high enough to hold open these newly recruited units once safe tidal plateau pressures are resumed. With few exceptions, this "stabilizing" value of PEEP is higher than

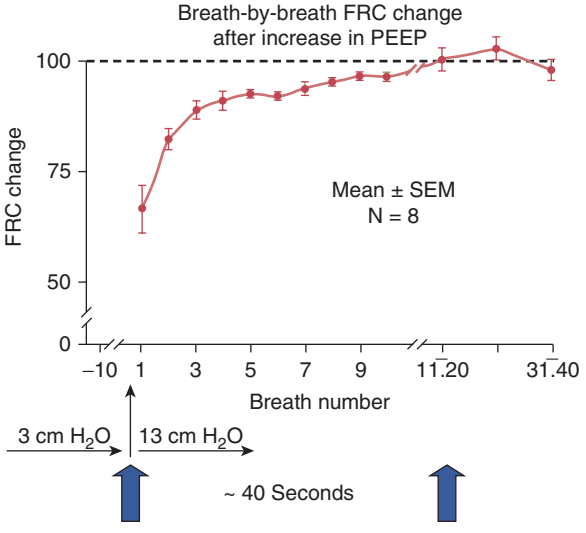

FIGURE 29-18 Time course of functional residual capacity (*FRC*) changes in respiratory failure following a step increase of PEEP from 3 to 13 cm H_2O. Multiple tidal cycles are required to fully achieve the ultimate increase in an expiratory lung volume. Although tidal volume would affect the time needed to equilibrate, in this instance, approximately 40 seconds were required. (Used, with permission, from Katz JA, Ozanne GM, Zinn SE, Fairley HB. Time course and mechanisms of lung-volume increase with PEEP in acute pulmonary failure. *Anesthesiology*. 1981;54(1):9–16.)

TABLE 29-4: DETERMINANTS OF RECRUITMENT MANEUVER EFFECTIVENESS

ARDS category
Inherent *potential* for response
ARDS stage
Responsiveness diminishes over time
Starting PEEP and tidal volume
Was the lung well recruited to start with?
How much higher than the tidal plateau is the recruiting pressure?
How many more units can be opened?
Postrecruitment PEEP
Duration of response
Aggressiveness and type of recruiting method
Often limited by tolerance

the initial one before recruitment.[77–80] Any benefit from a recruiting maneuver is extremely short lived if PEEP returns to its original value.[80]

Although most unstable lung units can be kept open with end-expiratory alveolar pressures (total PEEP) of approximately 10 cm H_2O (assuming a normally compliant chest wall), some units close at pressures considerably higher than those that are safe to apply with each tidal breath (see Fig. 29-5).[15,27] It is a fallacy to consider all injured tissue as potentially recruitable. Unlike most experimental models of ALI,[27,80] only a small fraction of the lungs of pneumonia-caused ("primary") ARDS, for example, can be "opened."[80–82]

Although a variety of recruiting maneuvers have been described, their efficacy depends on numerous factors (Table 29-4). Moreover, even when indicated, the best technique with which to perform a recruitment maneuver is currently unknown and may well vary with specific circumstances and repeated recruiting maneuvers may be required for maximum benefit. The two most commonly used are the sustained-inflation and the incremental-PEEP and/or fixed driving-pressure methods (Fig. 29-19).[81] The latter is often applied by PCV. When sustained pressure is applied without relief, mean and peak airway pressures are equivalent. This imposes extraordinary backpressure to venous return and poses a high afterload to the right ventricle for the period of its application. Both in experimental models and the clinical setting, ARDS caused by pneumonia (a "primary" form of alveolar damage) appears to be the condition with greatest risk for hypotension and least responsiveness to the sustained-inflation recruiting maneuver.[83]

Sustaining high pressure is believed to be an important component of the recruiting process, whereas the length of time required for its effect remains unsettled. Moreover, it is possible that for the same maximum pressure, briefer applications more frequently may be as effective as fewer cycles applied for a longer time. Recruitment tends to maximize early, while hemodynamic compromise continues to

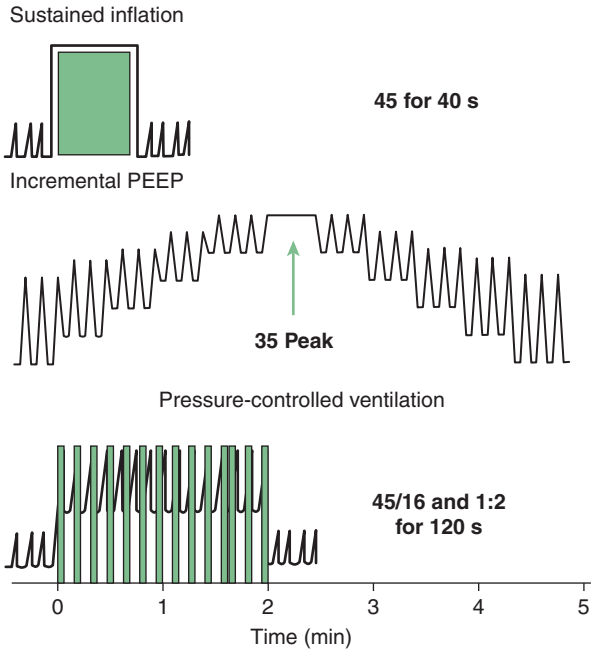

FIGURE 29-19 Three types of recruiting maneuver that combine high pressures with extended application time. Recruitment that employs tidal ventilation with pressure control (pressure-controlled ventilation [PCV]) achieves the same peak pressure for the same cumulative time as sustained inflation but at considerably lower mean airway pressure. PCV also provides multiple recruiting cycles and ventilates during the maneuver. (Used, with permission, from Lim S-C et al.[81])

worsen as the high airway pressure is sustained. Mean airway pressure can be considerably reduced while maintaining the same peak airway pressure value—the actual recruiting pressure—using a limited period of tidal ventilation with a constant driving pressure (e.g., <1 minute of pressure control with driving pressure 30 cm H_2O and high PEEP [e.g., 25 cm H_2O]). Thus, the pressure control recruiting maneuver may hold an advantage if pressures beyond those tolerated during the sustained high-pressure method are needed to complete lung opening.[81,83]

SPONTANEOUS VENTILATORY EFFORTS

Preservation of spontaneous breathing efforts during assisted ventilation may help to improve ventilation–perfusion matching by preferentially ventilating the peridiaphragmatic regions that receive disproportionate blood flow.[84–86] For the same minute ventilation, varying the amplitude of tidal breaths may also be helpful, either because of better recruitment or improved distribution of blood flow during biologically variable ventilation or "noisy" pressure support.[86] Whether this redistribution of ventilation and/or perfusion aids *sustained* recruitment, and thus whether it reduces or augments the tendency for VILI, currently remains unknown. The answer may well vary with the intensity of the breathing efforts and the vigor of expiratory muscle activity. It is seldom prudent to preserve spontaneous breathing at the expense of high exertion.

VENTILATING OBJECTIVES AND DECISIONS IN ACUTE RESPIRATORY DISTRESS SYNDROME

The foregoing discussion suggests that a rational lung-protective ventilator strategy should include the following elements: (a) avoidance of high tidal end-inspiratory alveolar pressures; (b) provision of adequate end expiratory pressure to avoid extensive end-expiratory tidal collapse and damaging driving pressures; (c) reduction of regional nonuniformity of mechanical properties; and (d) to the extent possible, avoidance of cofactors that abet the development of VILI, such as high inspired concentrations of oxygen and increased metabolic demands for ventilation and cardiac output. Choice of the appropriate therapeutic targets is fundamentally linked to lowering the risk for iatrogenic lung injury.

Therapeutic Targets

There is little evolutionary precedent for surviving ARDS that requires advanced levels of life support. Yet, the limits of tolerance to abnormalities of gas exchange in this setting and the capacity for the patient to adapt to abnormal blood gases have not been extensively explored and remain largely unknown. Trade-offs must be made when intervening to sustain life, as the supports applied to maintain oxygenation and ventilation—inspired oxygen and positive pressure—are both potentially injurious to the lung.[68,69,87] The discipline of intensive care evolved as an extension of postoperative care. Therefore, it was natural to employ ventilatory parameters that serve well in that setting, where the general aim is to hold arterial blood gases reasonably close to their preoperative values and large tidal volumes are needed to forestall atelectasis and to avert dyspnea. Three decades ago, awareness of oxygen toxicity was well entrenched, and the acutely injured lung was viewed on the basis of the plain frontal chest radiographs as mechanically uniform—diffusely stiff and therefore tolerant of the high ventilating pressures needed to maintain normal blood gases.

These assumptions were eventually challenged. Premature infants ventilated for infantile respiratory distress syndrome were clearly vulnerable to the application of high ventilating pressure. In adults, the high mortality rate of survivable diseases, such as asthma,[88] the high incidence of radiographically evident barotrauma,[89] and newfound awareness of dynamic hyperinflation[90,91] brought the wisdom of traditional practices and therapeutic targets into question. Reducing ventilatory requirements by allowing partial pressure of arterial carbon dioxide (Pa_{CO_2}) to rise was first successfully implemented in the care of patients with

status asthmaticus.[92] Five years later, the same strategy was reported to have been successfully implemented in patients with ARDS.[93] Subsequent research has emphasized that acute hypercapnic acidosis occurring in this setting is a complex phenomenon with diverse physiologic effects that include those with potential benefit (e.g., inhibiting inflammation) as well as those with potentially undesirable consequences (e.g., stimulation of ventilatory drive and cerebral vasodilation) (see Chapter 14).[94] Although guidelines for selecting the most appropriate values for pH and Pa_{CO_2} are elusive and should undoubtedly vary with the individual in question, it is clear from accumulated experience that mild to moderate deviations from the normal ranges of both parameters are generally well tolerated. At present, the dangers of VILI are perceived to outweigh those attributable to either inspired oxygen or hypercapnia.

Implementing Ventilator Support

Important principles gathered from laboratory experiments, shared clinical experience, observational studies, and randomized clinical trials have emerged regarding the application of ventilatory support to lung-injured patients (see Table 29-1). Noninvasive ventilation has been reported to be successful in patients with mild to moderate severity of injury,[95–97] and when feasible to employ, benefit is likely to accrue from the need for less sedation and the lower incidence of infection associated with this approach.[96,97] Although the interface between ventilator and patient continues to improve, only limited pressure can be tolerated, many patients cannot protect the upper airway, and the lung must be kept well recruited to avoid hypoxemia, precluding intermittent removal. For these reasons, airway intubation is virtually always required in cases of severe lung injury. That said, efficient and less-invasive extrapulmonary gas exchangers may complement noninvasive ventilation to make avoidance of invasive ventilation a genuine possibility for the alert and cooperative patient.[98,99]

Patterns of lung expansion differ for passive and actively assisted breathing. Preservation of muscular effort conceptually holds an advantage regarding the matching of ventilation to perfusion—at least in the healthy lung. The same advantage may hold for the acutely injured lung as well, provided that breathing remains comfortable and unlabored. Vigorous efforts, however, are undesirable for several reasons: increased ventilatory workload, oxygen consumption and CO_2 production, increased cardiac output and pulmonary blood flow (which may accelerate edema formation and possibly VILI), and expiratory muscle contraction that counters the effects of PEEP.[100] Whether gentle or vigorous, it has yet to be convincingly shown that patients who expend effort in breathing experience a lower risk of mortality. In fact, a recently published study demonstrated a potential survival advantage for patients receiving paralytic agents in the early phase of ARDS.[101]

Modes of Ventilation for Acute Respiratory Distress Syndrome

An extensive array of ventilatory options is available to the clinician for treating patients with ARDS. Each of these methods is described in detail elsewhere in this volume. As a general statement, it is accurate to state that the choice of ventilating mode is of much less importance than how the selected mode is implemented. When guided by the principles of attaining efficient gas exchange, targeting appropriate therapeutic objectives, and protecting the lung against iatrogenic damage, many different selections can be justified. What is presented here is a brief outline of some of the more important characteristics applicable to ALI.

For the past two decades, four modes have served to ventilate patients with ARDS at conventional frequencies: (a) flow-controlled, time-cycled, or volume-cycled ventilation (*volume control*); (b) pressure-targeted, time-cycled ventilation (*pressure control*); (c) pressure-targeted, flow-cycled ventilation (*pressure support*); and (d) combination modes in which a specified number of stereotyped time-limited machine cycles (pressure or volume controlled), which are specified by the clinician and synchronized to be triggered by patient effort, are delivered intermittently at evenly spaced intervals among additional breaths of variable size and depth taken by the patient (synchronized intermittent mandatory ventilation). As described in detail elsewhere in this book, flow and pressure cannot be controlled simultaneously, as the energetics of ventilation require one or the other to become a dependent variable in order to satisfy the equation of motion for ventilating the respiratory system.[102]

Flow control ensures that the desired tidal volume will be delivered reliably but obligates the patient to a specified inspiratory flow contour, independent of flow demand. Therefore, alveolar pressure, a function of delivered volume and compliance during passive ventilation, has the potential to ascend to dangerous levels. The flow profile delivered may be unchanging ("square") or decelerating. Pressure control offers the flexibility to satisfy flow demand and under passive conditions ensures that alveolar pressure rises no higher than a known peak airway pressure. (During active breathing [assisted cycles], the maximum transpulmonary pressure is not regulated by pressure control.) Flow is inherently decelerating, which may moderately improve distribution of ventilation among heterogeneous lung units, as compared with constant flow. The potentially adverse trade-off with using pressure control is that the delivered volume is a function of the impedance to breathing and any backpressure opposing inspiratory flow, so that tidal volume may change abruptly with muscular activity, airway resistance, lung and chest wall compliance, or auto-PEEP. It is worth noting that with airway pressure capped and the patient passive, the "strain ratio" of tidal volume to functional residual capacity tends to decline as disease worsens, conferring a lung-protective effect not seen with volume-controlled ventilation[103]

In recent years, the imperative to maintain consistent ventilation and nearly normal levels of Pa_{CO_2} has declined in its relative importance. Awareness of the potential for high ventilating pressures to inflict iatrogenic lung injury, coupled with a growing clinical experience that suggests the safety of higher than normal Pa_{CO_2} values (permissive hypercapnia) have caused many clinicians to adopt pressure control as the default mode. In the absence of effort and provided that both tidal volume and end-inspiratory pause pressure are closely monitored, the choice of pressure or volume control makes little practical difference to physiology or outcome.

Inverse-ratio ventilation, a mode that extends inspiratory time with the intent of raising mean airway pressure and capping applied airway pressure while maintaining adequate ventilation, is typically applied with pressure control.[104,105] Preventing airway closure at end expiration, however, may require generation of auto-PEEP that narrows the inspiratory pressure difference and limits tidal volume (Fig. 29-20). Although there may be rare exceptions, inverse-ratio ventilation appears not to offer any notable advantage over conventional-ratio ventilation that is applied with adequate PEEP.

During vigorous breathing, as during the first days of severe ARDS, it may be difficult to avoid patient–ventilator dyssynchrony with either assist-control or pressure-control ventilation because both require preset inspiratory times. Pressure limitation and failure to deliver full tidal volumes may then occur. In these instances, high-level pressure support, a flow-cycled mode, offers response flexibility. When the chest is very stiff, however, pressure rise time should be slowed and flow offswitch trigger minimized so as to avoid overly abrupt and ineffective tidal cycling. When used alone or in combination with intermittent time-limited mandatory machine cycles (synchronized intermittent mandatory ventilation), pressure-support ventilation may minimize the timing collisions that otherwise occur between the cycling phases of patient and machine. In any form of pressure-targeted or flow-regulated breathing, the ventilator's alarms should be carefully set so as to avoid over application of pressure or underventilation.

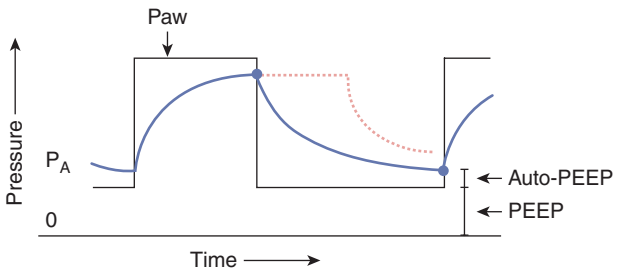

FIGURE 29-20 Concept of inverse-ratio ventilation using pressure control. As airway pressure is applied and released, alveolar pressure rises and falls exponentially (*heavy line*). Extending the inspiratory time fraction increases mean airway pressure and levels of auto-PEEP, without changing peak alveolar pressure. PA, alveolar pressure; Paw, airway pressure.

NEWER MODES OF VENTILATION

For patients capable of sustaining ventilatory effort, it is an option to elevate the airway pressure baseline, allowing the patient to draw breaths from that higher volume level. When airway pressure is maintained relatively constant throughout both phases of the breathing cycle, the condition is termed CPAP.[106] If the baseline shifts periodically with the patient able to draw breaths unimpeded through a valveless system at each level, ventilator assistance is given to an extent governed by the difference between pressure baselines and the frequency with which these baseline shifts occur. This mode is known as *biphasic airway pressure* (BIPAP).[107] When a high CPAP baseline is released only for a very brief period and then quickly restored to its original level, BIPAP contracts into *airway pressure release ventilation* (APRV).[108,109] The putative advantage of each of these modes for the care of patients with ARDS is that they encourage maintenance of an open lung with their high pressure baselines and ensure that the spontaneous breathing pattern is preserved. Neurally adjusted ventilator assist and proportional-assist ventilation regulate airway pressures in direct accordance with spontaneous respiratory motor output and have been used effectively in some patients with ALI, but their safety and effectiveness for this condition remain to be shown (see Chapters 12 and 13).[110,111] As with so many mode options, however, no definitive evidence exists to confirm their relative advantage over a well-adjusted traditional approach with similar mean airway pressure.

High-Frequency Ventilation. Awareness of the tissue-damaging potential of applying high end-inspiratory plateau pressures with insufficient end-expiratory pressure to keep unstable alveoli open ignited interest in using methods that apply very small tidal volumes so rapidly that alveolar collapse has no time to occur. Over the past three decades, various techniques for providing high-frequency ventilation have been explored with enthusiasm, tried tentatively in the clinical setting, and then reluctantly set aside.[112,113] These have included positive-pressure ventilation with valved-circuit closure to separate the phases of the ventilatory cycle (as traditionally done) but applied at nonconventional frequencies and tidal volumes. The technical demands of such high-frequency valving have limited its operating frequency range, efficiency, and safety. Another form of high-frequency ventilation, jet ventilation, uses a lung-directed injector pulsating at rapid frequencies into an open circuit. Problems with gas trapping, drying of airway secretions, and limited efficacy have dampened enthusiasm for its use in critically ill patients. At present, a third form, high-frequency oscillation, is in most widespread clinical use for patients with ARDS.[114–116] This "open circuit" technique uses a rapidly reciprocating piston-like action to rapidly vibrate the air column, building and releasing small alveolar pressure excursions in the process. A fresh-gas source allows effective gas exchange via mechanisms that complement the bulk flow

responsible at lower frequencies (see Chapter 19). Deep sedation is usually required, and mean alveolar pressure is maintained at a high level. Although experimental and clinical data amply document the feasibility of high-frequency oscillation for the setting of ALI in adults, the prevailing opinion is that this unfamiliar and seemingly exotic technique seems to offer little advantage over ventilation performed conventionally with equivalent attention to the principles of lung protection.[117]

The combination of conventional ventilation with superimposed oscillation of the airway-pressure baseline (vibropercussive ventilation) has been used with the objective of improving secretion elimination and reopening plugged or collapsed airways.[118] Here again, the mode has its advocates and adherents, but convincing evidence to substantiate its advantage has not yet appeared.

Adjuncts to Mechanical Ventilation

Attention to limiting tissue strain mandates that the pressure driving each tidal cycle (the difference between end-inspiratory and end-expiratory pressures), as well as the number of high-pressure cycles applied per unit time be kept within acceptable bounds. These requirements limit tidal volume and minute ventilation and stimulate interest in methods that reduce the demands for ventilation and oxygenation, reduce local tissue stresses, and improve the efficiency of pulmonary gas exchange, all without the need for additional ventilating pressures or higher ventilating frequency (Table 29-5). The majority of these "adjunctive" techniques are discussed in detail elsewhere in this book. Here it should be emphasized that perhaps the most effective and universally applicable means for avoiding the need for high ventilator pressures is to reduce the demand for them by the patient or to readjust the clinician's therapeutic targets for ventilator support. Thus, avoidance of high fever, pain, agitation, and metabolic acidosis reduces oxygen and ventilation demands, as well as the need for cardiac output—an important potential cofactor for VILI in the experimental setting. Optimizing oxygen delivery by improving cardiac performance and providing adequate hemoglobin concentration also minimizes the ventilatory requirements. At present, improved and simplified technology has spurred enthusiasm for using extracorporeal CO_2 removal to reduce ventilator demand and for extracorporeal membrane oxygenation when oxygenation cannot be assured by conventional means. Both were used extensively and effectively during recent epidemics of H1N1 influenza-induced ARDS.[119]

Using the prone position evens the distribution of transpulmonary pressure, reducing local tissue strains and effectively recruiting well-perfused dorsal parenchyma, thereby improving oxygenation in most patients.[55] Methods for improving gas-exchange efficiency include those directed at oxygenation (inhaled nitric oxide[120–122] or inhaled prostacyclin[123]), and those that lessen wasted ventilation (tracheal gas insufflation[124–126] or reduction of apparatus dead space[126]). Although often considered to be a ventilatory adjunct of limited value, recruiting maneuvers are incorporated by many practitioners, including this author, as an entrenched part of clinical practice.[127] In difficult cases, the recruiting maneuver affords a logical means of reopening the atelectatic lung so that the appropriate values of PEEP and tidal volume may be selected (see the section General Guidelines for Ventilatory Management).

TABLE 29-5: THERAPEUTIC ADJUNCTS TO MECHANICAL VENTILATION OF ACUTE RESPIRATORY DISTRESS SYNDROME

Minimize O_2 demands
Optimize O_2 delivery
Recruiting maneuvers
Prone positioning
Inhaled nitric oxide/inhaled prostacyclin
Tracheal gas insufflation
Corticosteroids and (?) other drugs

SETTING THE VENTILATOR: RECOMMENDATIONS FOR PRACTICE

Given the joint potential for the ventilator to offer life support or to extend the severity and duration of the illness, the prescribed settings for the ventilatory cycle are of unquestioned importance. How best to achieve the appropriate trade-off, however, remains a topic of active debate. The available clinical database, albeit difficult to reconcile, appears broadly consistent with the highly consistent scientific body of information that addresses ventilator usage in the setting of ALI.

Insights from Clinical Trials of Lung Protection

With the rise of "evidence-based practice," physicians have sought guidance from clinical trials that have addressed the relative merits of different ventilation strategies.[2,3,128–130] Generally speaking, these well-intentioned efforts have been compromised by overly broad disease definitions and loose co-intervention controls. Yet some valuable insights have been generated. Studies in which the highest tidal volumes and pressures were applied in the "control arm" have shown benefit from low-tidal-volume ventilation.[2,3] Results were particularly impressive when higher PEEP was used in conjunction with small tidal volumes in a setting where emphasis was placed on establishing stable recruitment, avoidance of high ventilating pressures, and managing clinical cointerventions consistently.[2,131]

Only one of the several studies that randomized selectively on tidal volume—by far the largest yet published—successfully demonstrated mortality benefit for a smaller-tidal-volume approach.[3] The physiologic impact of tidal volume—mediated through transalveolar pressure—depends on compliance. The ratio of tidal volume to functional residual capacity may crudely approximate tissue strain,[40] as do the magnitudes of transalveolar pressure and its tidal excursion. In the clinical setting, the former can be readily measured by some ventilators, while the latter is computed by the difference between static airway and esophageal pressures.[49] Provocative examinations of the data collected in the ARDS Network ARMA study and a meta-analysis of all published trials addressing the selection of tidal volume have suggested that "lower is not necessarily better," especially when compliance is less severely impaired and periodic sighs or recruiting maneuvers are not employed.[132,133] Knowing that tidal volume is only indirectly linked to tissue strain, inflammation, and rupture (consider the noninjurious effects of high tidal volumes during exercise), it is interesting to speculate that the recruiting effects of higher tidal volumes might actually have a salutary effect on inflammatory signaling if peak transpulmonary pressure were kept below the "overstretch" signaling threshold and an appropriate level of PEEP were used. Whatever the validity of that controversial argument, the collective results of these clinical studies have focused attention on transalveolar stresses rather than on tidal volume per se. They have also demonstrated that the levels and effects of hypercapnia experienced during low-tidal-volume ventilation, although complex,[94,134–136] generally are modest and well tolerated.

The National Institutes of Health-sponsored trial of high versus moderate PEEP failed to demonstrate a significant survival advantage for patients allocated to the high PEEP group when both were ventilated using small to moderate tidal volumes.[137] Important considerations, however, were (a) neither group was exposed to plateau pressures that were clearly in a dangerous range; (b) recruitment potential was not stratified, so that patients who were not likely to benefit were assigned to both groups; and (c) no recruiting maneuver preceded PEEP application, nor was PEEP regulated as in conventional clinical practice. Unfortunately, there was also a failure of the randomization process, so that a disproportionate number of older patients were assigned to the high-PEEP limb. Two subsequent trials of high PEEP and small-to-moderate tidal volumes demonstrated some benefit of a higher PEEP strategy, but no overall mortality benefit.[138,139] The importance of PEEP is likely to depend on the severity of illness and the recruitability of lung units, which tend to track together, as well as the plateau pressure achieved.[140,141] A Spanish multicenter trial of modest size appears to confirm that PEEP is an integral part of a lung-protective approach,[131] an implication supported by an analysis of "real-world" ventilator practice and outcomes.[72] A meta-analysis of high PEEP strategy trials indicated that high PEEP exerts a mortality benefit for those with greatest disease severity.[142,143]

TABLE 29-6: COMMON EFFECTS OF PRONE POSITIONING IN EARLY ACUTE RESPIRATORY DISTRESS SYNDROME

More homogeneous transpulmonary pressure
Increased and sustained traction on dorsal lung units
Better $\dot{V}/\dot{Q}$ matching
Tendency for recruitment
Improved airway drainage
Improved lymphatic drainage
Modestly increased FRC
Reduced tidal tissue strain [V_T/FRC (and VILI?)]

Abbreviations: FRC, Functional residual capacity; $\dot{V}/\dot{Q}$, ventilation–perfusion ratio; V_T, tidal volume; *VILI*, ventilator-induced lung injury.

Recruitment maneuvers have also been examined in a clinical trials format as a substudy of the high-PEEP National Institutes of Health investigation.[144] The recruiting maneuvers were applied only in the high-PEEP limb, and the peak pressure achieved was limited to 35 cm H_2O. The small separation between plateau pressure and PEEP, the underlying disease characteristics of the study population, the relatively high level of PEEP at baseline, and the failure to augment PEEP after the recruiting maneuver undoubtedly biased the result against showing a significant benefit. Indeed, a meta-analysis of studies that employed recruiting maneuvers concluded that they have no routine place in ARDS management.[145] Again, however, it must be understood that most studies have used them as a supplement to the ventilator strategy, which remained unmodified, and not as a means for setting PEEP by decremental titration.

Finally, notwithstanding considerable theoretical appeal (Table 29-6), oxygenation benefit,[146] and suggestive experimental evidence,[57,58,147] four relatively large randomized trials[148–151] failed to demonstrate a statistically significant mortality benefit for prone positioning in broad samples of patients of varying severity with ARDS. A French study reported a lower incidence of ventilator-associated pneumonia in the prone cohort,[150] but this did not translate into a survival advantage for that trial limb. A large Italian trial utilized prone positioning for less than one-third of each day, and showed no overall mortality benefit.[149] Notably, however, patients who responded by improving CO_2 exchange and those with most severe physiologic disturbances fared better than nonprone patients.[152] Moreover, a prematurely truncated Spanish trial,[151] in which prone positioning was maintained for three-quarters of the day, showed an impressive separation (25% relative risk of death) between the supine and prone treatment arms. Unfortunately, neither study entered its targeted number of patients. The large follow-up Italian trial that entered only patients with moderate and severe illness strongly suggested that the most seriously affected patients, those exposed to higher ventilating pressures, and those who demonstrate improved ventilation efficiency are most likely to benefit (Fig. 29-21).[153,154] As with PEEP, a meta-analysis of prone studies that focused on the

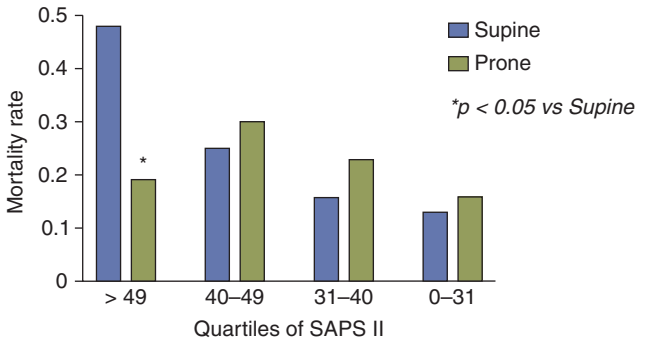

FIGURE 29-21 Effect of prone positioning on mortality as a function of illness severity. The cohort of most severely ill patients with acute lung injury by Simplified Acute Physiology Score (SAPS) II scoring benefit from proning. Less severely affected patients did not. (Data from first Italian multicenter clinical trial of prone vs. supine positioning in ARDS.[149])

most severely ill cohorts convincingly shows the benefit of the prone position in that specific patient category.[155]

Disappointingly, clinical trials of various other adjuncts to ventilation have also not demonstrated major outcome advantages.[156–160] From a physiologic perspective, this is hardly surprising. Precise numerical guidelines for selecting PEEP, tidal volume, and body position that are applicable to any given individual patient should not be expected from the results of studies conducted in a diverse sample population whose inclusion criteria are broadly inclusive and management details are unconstrained. In the end, the best that can be hoped for is a proof of principle—not a prescription for care. However internally valid such trials may be, they do not correspond to the "real-world" environment wherein comorbidities impinge and management of potentially influential variables (such as PEEP, Pa_{CO_2}, fluid management) is not protocolized. What follows is an approach to the care of the individual patient with ARDS based on an understanding of the physiologic principles that must be brought to bear in the complex clinical environment.

General Guidelines for Ventilatory Management

Key guiding principles include the following. First, adjust ventilator parameters empirically, rather than by formula-driven rules; prioritize patient comfort and safety. Second, assign the prevention of mechanical trauma precedence over maintenance of normocapnia and avoidance of oxygen toxicity. Although no exact upper limits for acceptable plateau pressure or fractional inspired oxygen concentration (FI_{O_2}) can be specified, very high FI_{O_2} pose a risk for absorption atelectasis as well as oxygen toxicity. Therefore, FI_{O_2} should be held to less than 0.7 whenever possible. Third, consider the impact of chest wall stiffness (including abdominal contents) on transpulmonary pressure and gas-exchange efficiency. In questionable situations, determine abdominal (bladder) and/or esophageal pressures to help estimate the transalveolar pressure.[49] Fourth, monitor hemodynamics as well as mechanics and gas exchange when regulating ventilatory therapy. Assess cardiac function by echocardiography and use reliable, noninvasive methods for tracking cardiac output if available. Although certainly not required for all, the much maligned pulmonary artery catheter is still quite useful in patients with complex cardiopulmonary problems.[161,162] Wide respiratory variation in the arterial pulse pressure, as well as other more precise echocardiographic indicators of vascular dimensions and heart preloading, suggest the need for additional intravascular volume.[163] A surrogate for measuring hemodynamics directly may be to monitor the central venous oxygen saturation. A value greater than 0% and a difference of 25% or less between arterial and mixed venous saturations strongly suggest an adequate cardiac index (>2.5 L/m^2/min).[164] Fifth, in severe cases, attempt to minimize ventilatory demands and thereby reduce needs for high airway pressures, high rates of gas flow, and increased cardiac output. Sixth, incorporate the "challenge" principle in making therapeutic decisions, regarding both the intensification and the withdrawal of therapeutic measures. Examples of such challenges include recruiting maneuvers to assess lung-unit instability and closely monitored (and preferably quickly reversible) challenges of fluid administration or removal (e.g., leg raising). Seventh, whereas aggressive fluid resuscitation is mandatory in the first phase of support, attempts should be made to avoid gross volume excess. Diuretic drips, repair of serious albumin deficits, and continuous hemofiltration hold important therapeutic potential once the resuscitation phase has been completed. Eighth, unless otherwise contraindicated, use prone positioning when high values for ventilatory pressure, PEEP, and FI_{O_2} are needed to maintain adequate supine arterial oxygen tension. Ninth, employ pressure limited forms of ventilation (e.g., pressure control, pressure support, or BIPAP/APRV) for evaluation of thoracic mechanics and ongoing management.

As a general rule, the desired goal is to use the least PEEP and tidal volume needed to achieve acceptable gas exchange while avoiding extensive tidal collapse and reopening of unstable lung units. Knowing that moderate hypercapnia generally is well tolerated, therapeutic targeting priorities are directed toward lung protection and maintenance of appropriate hemodynamics and oxygen delivery. Recruiting maneuvers help to characterize PEEP responsiveness, to determine the relative status of intravascular filling and response to altered cardiac loading conditions, and to set the PEEP–tidal volume combination (Fig. 29-22). Prone positioning is strongly considered in severe cases. On rare occasions, noninvasive mechanical ventilation using a comfortable full face mask (or a helmet, if available) may overcome short-lived deficits of oxygen exchange without the need for intubation. In practice, however, the needs to control the airway, to reduce ventilatory requirements, to apply high levels of PEEP, and to sustain support for extended periods usually preclude the use of noninvasive ventilation.

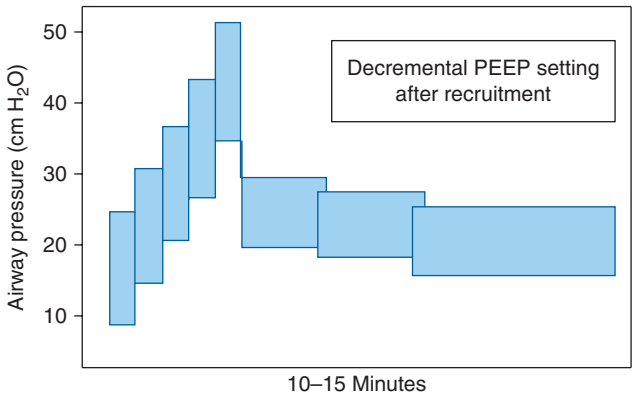

FIGURE 29-22 Procedure for setting decremental PEEP. Final PEEP is set after brief recruitment procedure, using progressive steps of PEEP with a fixed driving pressure. Note that PEEP is released abruptly from its highest level to a high tidal value, which is gradually reduced until deterioration of the monitored parameter (compliance or oxygenation) becomes apparent. After re-recruitment, tidal PEEP would then be set to the next higher step.

In the first phase of ventilatory support, patient comfort must be assured and ventilatory effort kept to a minimum. Existing data strongly suggest that muscle relaxing drugs are effective and well tolerated initially by many. Controlling ventilation for longer than 48 to 72 hours, however, is likely to contribute to muscle wasting and ventilator-induced diaphragmatic dysfunction.[165] Modes such as APRV, BIPAP, and high-frequency oscillation have persuasive advocates and considerable theoretical appeal.[109,166,167] The existing database and shared personal experience, however, have not provided convincing evidence that they offer a great deal beyond that which can be accomplished with carefully adjusted PCV in a well-sedated patient.

All patients should be assessed for severity of disease and for recruitment potential. After deficits of intravascular volume have been addressed and hemodynamics have been optimized, recruitment potential is gauged by applying high-level PCV: PEEP of 15 to 25 cm H_2O, driving pressure of 30 cm H_2O, and plateau pressure 50 to 60 cm H_2O for a maximum of 1 to 2 minutes, as tolerated. Even higher pressures may be appropriate for some severely affected patients and for patients with very stiff chest walls—for example, burn victims with chest wall edema or eschar. Although sustained inflation with high pressure has been traditionally used, widely employed, and selected for most reported research,[168] it is no more effective and tends to be less-well-tolerated hemodynamically than a recruiting method based on PCV that achieves lower average pressure but similar peak pressure during its inspiratory phase.[81,83] If oxygenation and lung mechanics do not improve substantially with high-level PCV as a recruiting technique, the patient is considered to have low recruiting potential *in that position and at that specific time*. Management goals in the "recruitable" group emphasize the maintenance of high-level PEEP, whereas in poorly recruitable patients, PEEP is maintained as low as feasible—generally in the range of 7 to 10 cm H_2O. In both groups end-inspiratory plateau pressure is kept less than 30 cm H_2O, except when chest wall compliance is very low. Periodic sighs may be advisable when very low tidal volumes (<5 to 6 mL/kg of predicted weight) are in use.[169,170]

ADJUSTING POSITIVE END-EXPIRATORY PRESSURE

Setting PEEP is an individualized empirical process that involves some degree of compromise (Table 29-7). Patients with an extensive "recruitable" population of lung units should respond to increased PEEP and recruiting maneuvers by demonstrating improved alveolar mechanics and improved gas exchange, reflected both by increased Pa_{O_2} and a reduction in the ration of minute ventilation to Pa_{CO_2}. These salutary changes are accompanied by only marginal effects on hemodynamics, as judged by systemic blood pressure and central venous oxygen saturation.[168] Assuming an unchanged rate of CO_2 production, the latter index—like a dead-space calculation—reflects the efficiency of CO_2 elimination, which is expected to improve with recruitment and deteriorate with overdistension. Inspiratory crackles (rales) audible over the dependent zones of the chest suggest that recruitment and derecruitment are occurring with each breath and indicate that recruitment maneuvers and higher levels of PEEP may be indicated to silence them.[171] Crackles occurring late in inspiration are of particular concern because they may originate in units opening under relatively high pressures. In gauging response to PEEP, it is important to consider CO_2 exchange as well as oxygenation response. With rare exception (e.g., when PEEP-impaired cardiac output causes mixed-venous O_2 content to fall), Pa_{O_2} tends to increase when PEEP is applied. This oxygenation improvement, however, may be accounted for either by recruitment of lung units or by reduced or redirected blood flow within the injured lung. In the latter circumstance, Pa_{CO_2} may also rise. When recruitment is the explanation for O_2 improvement, however, CO_2 exchange is not compromised and may even improve, reflecting increased alveolar ventilation. Similar principles apply during prone positioning.

The prone position should be considered in patients with severe gas-exchange impairment regardless of their

TABLE 29-7: HOW SHOULD POSITIVE END-EXPIRATORY PRESSURE BE ADJUSTED? A PRACTICAL COMPROMISE

Ensure adequate preload.
Use small to moderate tidal volume or driving pressure.
Recruit by increasing PEEP and/or pressure-controlled ventilation to plateau of approximately 50 to 60 cm H_2O for approximately 1 to 2 minutes.
Reduce driving pressure to 15 to 20 cm H_2O.
Reduce PEEP until arterial O_2 or compliance falls significantly.
Re-recruit and select next higher PEEP if hemodynamics are acceptable.
Ensure that plateau pressure remains below acceptable maximum (e.g., <30 cm H_2O).

"recruiting test" result in the supine position. Patients requiring more than 10 to 15 cm H_2O PEEP at FI_{O_2} equal to or greater than 0.7 to maintain oxygen saturation at 90% or greater should be considered for prone positioning unless there is a clear contraindication or the patient is improving rapidly. The prone position should be considered independently of supine recruiting potential because as prone positioning will help lymphatic drainage and secretion removal and release the lower lobes of the lungs from the need to support the weight of the heart. Although provocative experimental data have challenged the concept,[172] the preferred angle for head elevation in supine patients is 30 degrees to horizontal (Fowler) with frequent (at least every 2 to 4 hours) lateral turning. Similar rules apply in the prone position; reverse Trendelenburg at 15 to 30 degrees is preferred to flat (0 degrees) horizontal. Tidal volume is adjusted to the same value used in the supine position. An increase of plateau pressure strongly suggests that chest wall compliance has been altered by proning. In those instances, a proportional increase of PEEP may also be justified. (For example, if plateau pressure rises by 10%, PEEP would be increased by 10%.)

PREVENTION OF INJURY PROPAGATION

Patients in the first stage of localized lung inflammation, such as lobar pneumonia, may have mobile secretions and edema that are both initially contained regionally rich in inflammatory mediators and surfactant-inhibiting protein. These injurious biofluids temporarily have the potential to spread via the airways to other healthy regions, propagating tissue damage (Fig. 29-23). Measures to contain them include use of moderately high PEEP, small tidal volumes and modest gravitational inclination, as well as the avoidance of forceful expiratory efforts. Although currently unproven, it seems prudent to take such "lung protective" measures during the earliest phase of ventilation so as to avoid the blossoming of focal inflammation into ARDS.[173]

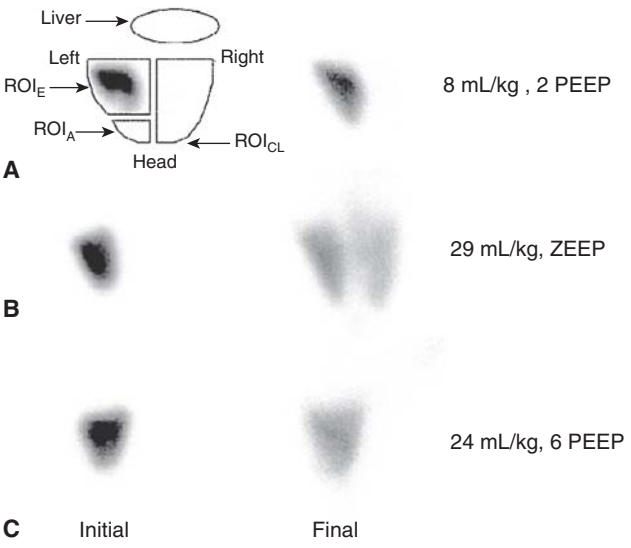

FIGURE 29-23 Propagation and limitation of intraalveolar biofluid via the airway network. In this experimental small-animal model, radiolabeled albumin can be spread from its initial lobar position throughout the lungs by high tidal volumes and low levels of PEEP. Conversely, moderate PEEP contains the fluid to the lung in which it was instilled. *ZEEP*, zero end-expiratory pressure. (Adapted, with permission, from de Prost N, Roux D, Dreyfuss D, Ricard JD, Le Guludec D, Saumon G Alveolar edema dispersion and alveolar protein permeability during high volume ventilation: effect of positive end-expiratory pressure. *Intensive Care Med.* 2007;33(4):711–717.)

Suggested Sequence of Management Decisions

Figure 29-24 is a suggested algorithm for decision making in ARDS ventilation.

INITIAL PHASE OF STABILIZATION AND SUPPORT

1. Determine whether the patient with oxygenation impairment has ALI, and if so, determine whether it is complicated by such reversible comorbidities as volume overload, pleural effusion, abdominal distension, or pneumothorax.
2. Initiate ventilation with face mask or intubate as severity warrants.
3. Decide on controlled versus spontaneous ventilation. Use controlled or nearly controlled ventilation to subdue respiratory efforts for the most severely involved patients during the early stage of support.[174]
4. Initial ventilator settings: FI_{O_2} 0.8, PEEP 5 to 8 cm H_2O (depending on concern regarding hemodynamic tolerance); tidal volume 6 to 10 mL/kg predicted body weight (depending on inspiratory plateau pressure and minute ventilation requirement).
5. Estimate volemic status initially from arterial blood pressure, respiratory variations of pulmonary and systemic arterial pulse pressure, central venous pressure, urinary output, and urinary electrolytes.
6. Confirm adequacy of intravascular volume using echocardiography, results from a volume challenge, and central venous and pulmonary artery catheter data (cardiac index, mixed venous O_2 saturation, and occlusion pressure), if available.
7. Replete any volume deficits and support the circulation with vasopressors and inotropes to the extent necessary to perform the ventilatory manipulations safely.
8. Determine the recruitment potential of the patient by using a recruiting maneuver and/or decremental PEEP trial.
9. Selected tidal volume should be inversely proportional to individual thoracic compliance and may range from 5 to 9 mL/kg of ideal body weight. During the PEEP trial, consider together the oxygenation change, the Pa_{CO_2} change, the alterations of mechanics, and the hemodynamic response. Adjust the PEEP and tidal volume combination to the lowest tolerated values that sustain the recruitment benefit.

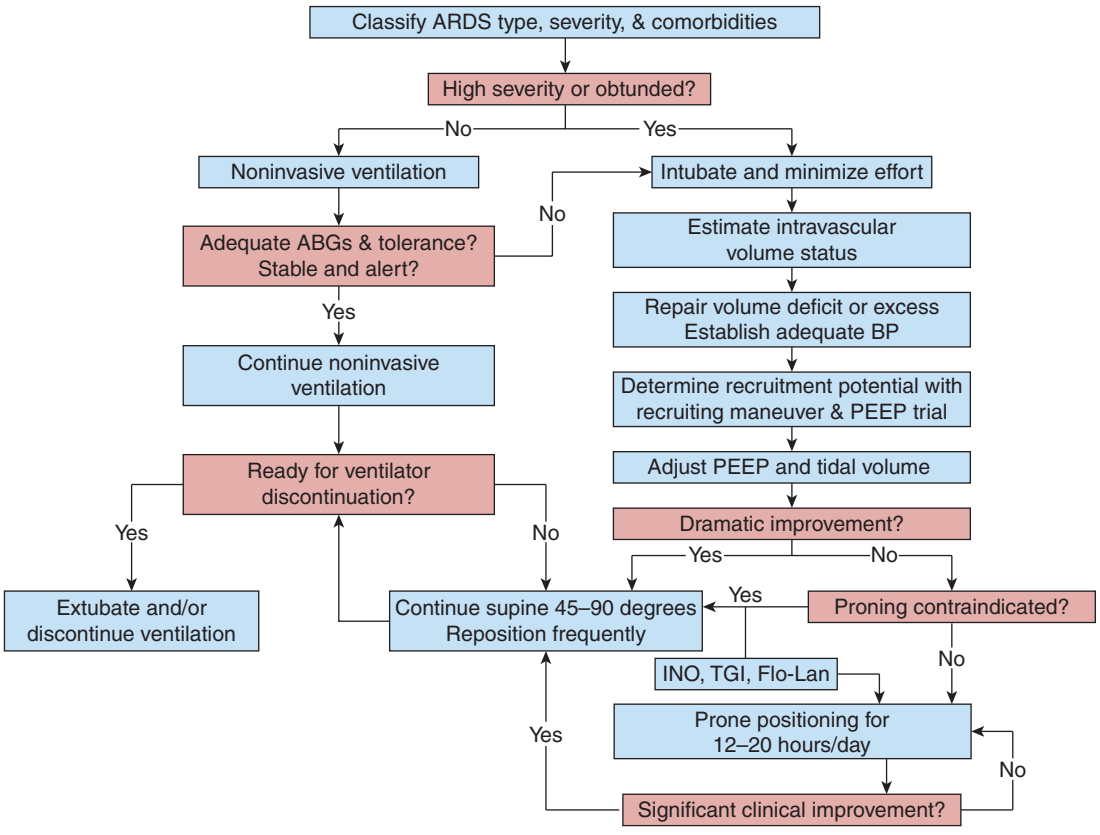

FIGURE 29-24 A suggested decision sequence for ventilation decisions in ARDS. *ABGs*, arterial blood gases; *BP*, blood pressure; *Flo-Lan*, proprietary name for prostacyclin; *INO*, inhaled nitric oxide; *PEEP*, positive end-expiratory pressure; *TGI*, tracheal gas insufflation. (Used, with permission, from Marini and Gattinoni.[5])

10. Proning is advisable in those with no contraindication and severe disease regardless of recruiting test, unless they are already improving rapidly. If the patient does not respond to the prone position, another recruiting maneuver is attempted while the patient is prone. The PEEP and tidal volume combination is readjusted as before.
11. When proning is used, scheduled reversion to the supine position is conducted at least once a day for cleanup, dressing changes, edema clearance, diagnostic procedures, transport to imaging, and so on, unless supine position is not physiologically tolerated. Many patients require almost continuous proning to maintain adequate gas exchange during the first several days of illness. Proning can be discontinued when it no longer makes an impressive contribution to oxygenation and plateau pressure can be kept in a "safe" range when the patient is supine.

SUBSEQUENT CARE

Recovery onset is recognized by improving Pa_{O_2}/FI_{O_2} and minute ventilation-to-Pa_{CO_2} ratios, clearing radiographic opacity, and rising compliance of the total respiratory system. Appropriate adjustments are then made to sedation and ventilating pressures and spontaneous breathing encouraged by conversion to pressure-support ventilation or to PCV with lower driving pressures as tolerated. Proning is discontinued when the alterations in Pa_{O_2} observed during position changes are less than 10%, status is clearly improved, or no obvious benefit has been achieved after a lengthy trial (>48 hours). Reductions in FI_{O_2} to an acceptable range are undertaken before cutbacks of PEEP.

PEEP weaning is initiated when FI_{O_2} is 40% or less and Pa_{O_2} is 80 mm Hg or greater.

FUTURE DIRECTIONS AND RESEARCH

Numerous questions related to the practical application of mechanical ventilation remain incompletely answered. These include the following.

Pathogenesis and Detection of Ventilator-Induced Lung Injury

Experimental data suggest that numerous intersecting variables can influence the severity of VILI. For a given combination of PEEP and tidal volume, vascular pressure, breathing frequency, and body temperature appear to be important

contributing variables in the expression of VILI. Although both mechanical and inflammatory disruption of the air–blood interface are likely to be in some part responsible, how mechanical forces causing structural alterations and signaling inflammation are not well elucidated. Markers for damaging patterns of ventilation are badly needed.

Long-Term Damage to Airways and Parenchyma

The determinants of alveolar and small-airway damage occurring in patients ventilated for ARDS are not clear—peak pressure, end-expiratory pressure, or both. Future outcome studies should target the incidence of obstructive, restrictive, and disordered gas exchange following recovery from ARDS.

Relationship of Ventilator-Induced Lung Injury to Multisystem Organ Dysfunction

Although laboratory studies have shown the release into the systemic circulation of gas, bacteria, and inflammatory mediators from injured lungs ventilated at high pressures with insufficient PEEP, the causative role of VILI in multiorgan failure must be investigated further for the clinical setting.

Ventilator-Associated Pneumonia

The incidence of ventilator-associated pneumonia is high in intubated patients, especially among those with ALI. Whether and how ventilator-related injury predisposes to ventilator-associated pneumonia needs to be clarified, and the measures necessary to reduce its incidence identified.

Environmental Modifications

Multiple factors have been shown in the laboratory to be important in the expression of VILI, including elevations of precapillary pressure, reduced left-atrial pressure, and elevated body temperature. Whether such factors play a role in the clinical setting is not clear. Do such cofactors as edema, FI_{O_2}, vasoactive and antiinflammatory drugs, and plasma protein concentrations determine the severity of expression of VILI? Are there additive or synergistic interactions among these variables?

Appropriate Patterns for Positive End-Expiratory Pressure, Tidal Volume, and Inspiratory Flow

How to select the most lung-protective combination of PEEP and tidal volume remains an area of active controversy. Although considerable progress has been made, the debate needs to be settled regarding the relative importance of limiting peak inflation pressure, optimizing PEEP, reducing driving pressure, or limiting tidal volume. Should arterial oxygenation, thoracic mechanics, or bedside imaging (as by electrical impedance tomography or acoustic mapping) be used to guide these selections? What are the added values of using strain ratio (tidal volume-to-functional residual capacity) and transpulmonary pressure calculations using the esophageal balloon to adjust ventilator parameters? The advisability of reducing inspiratory flow rate and minute ventilation to minimize VILI deserves to be studied carefully.

Recruitment Maneuvers

Sustained inflation with high airway pressure is an effective means of opening collapsed tissue and may be integral to selecting PEEP. The value of repeated recruiting maneuvers and the best means of doing so, however, have not been studied carefully. The effectiveness of recruitment maneuvers may well vary with the type or stage of ALI. Moreover, the incidence of lung rupture, hemodynamic compromise, and other complications requires documentation. How should such maneuvers be performed? In which patients? How often, and at what FI_{O_2}? Whether sighs help maintain recruitment in patients with low tidal volumes and unstable airways should be clarified.

Prone Positioning

The duration of proning (how long each day, when to cease proning in each patient) remains unsettled. Most investigators favor proning for most of each day, at least until there are clear improvements in mechanics and gas exchange, allowing adequate arterial oxygenation with FI_{O_2} less than 0.50 to 0.60 at tolerated levels of PEEP in the supine position. Whether proning confers an advantage on key outcomes other than oxygenation, at what stage of illness, and in which categories of patient, are other questions that merit further investigation. The advisability and appropriate intervals for body repositioning need further definition.

Noninvasive Ventilation

Noninvasive ventilation has been successfully applied to problems of acute respiratory failure, including some patients with ALI and ARDS.[95–97] Although vastly better than before, interfaces must be improved to ensure reliability and patient comfort. More information is needed to guide clinicians regarding optimal selection of patients, timing, equipment, and monitoring.

Therapeutic Value of Hypercapnia and Tolerance of Hypoxemia

Laboratory data suggest that hypercapnic intracellular acidosis protects against some forms of oxidant injury.[134–136]

Its therapeutic value for the clinical setting requires further investigation. Adaptation to hypoxemia occurs gradually in healthy individuals exposed to altitude and in many patients with chronically impaired oxygen exchange. Can patients who are acutely ill adapt to gradual imposition of hypoxemia? If so, how fast do they do so?

SPONTANEOUS VERSUS CONTROLLED VENTILATION

Strong arguments can be made for reducing ventilatory requirements and controlling ventilation in the first stages of ARDS management. The publication of a trial on use of paralytic agents[101] has energized debate as to the advisability of ceding control of the ventilatory pattern to the severely affected patient. The circumstances under which this is advisable or contraindicated as well as the most desirable ventilator mode need careful study.

Newer Modes of Ventilation

The physiologic rationale for high-frequency ventilation in ARDS is strong. It is not yet clear, however, that it confers benefits in beyond those achieved with conventional ventilator-based lung protective strategies. Definitive comparisons of high-frequency ventilation versus lung-protective strategies using a conventional ventilator are needed to identify possible benefits and hazards, as well as to learn the best approach to using this technology in the clinical setting. Certain less commonly introduced modes for ventilating ARDS, such as neurally adjusted ventilator assist,[110] proportional assist ventilation,[111] "noisy pressure support,"[86] APRV,[109] and high-frequency percussive ventilation,[118] are of strong interest, but their eventual place in ARDS ventilator management has not yet been settled.

Value of Adjunctive and Pharmacologic Measures

Tested as isolated interventions, nitric oxide, partial liquid ventilation, aerosolized surfactant, corticosteroids, almitrine, and prone positioning have not been demonstrated in multicenter trials to influence mortality except in highly selected patient cohorts.[156] The physiologic rationale for these measures, however, is strong for certain types of patients and for certain clinical conditions. Moreover, few of these adjuncts have been tested in combination. (Prone positioning, for example, adds to the oxygenation benefit of inhaled nitric oxide, but the impact of oxygenation of inhaled nitric oxide on survival has not been addressed.) The utility of such adjunctive measures—used alone and in combination—requires further study in populations most likely to benefit.

SUMMARY AND CONCLUSION

Injury to the alveolar–capillary membrane originates from diverse causes that may initially disrupt either the epithelial or endothelial surfaces. Managing the spectrum of conditions grouped together under the all-encompassing label of ARDS is a challenging assignment that must take into account the severity and stage of illness, as well as the interactions among the ventilatory and nonventilatory variables that influence the progress of this condition. Prevention of excessive tissue strain during the tidal cycle entails the avoidance of intolerable peak transalveolar and driving pressures, repetitive opening and closing of unstable lung units, as well as attention to pathogenetic cofactors that may initiate or exacerbate lung injury or retard healing. Because of the diversity of mechanical problems presented by different patients as well as the heterogeneity of mechanical properties among the lung units within the same individual, a logical approach requires mastery of key physiologic principles, awareness of the guidelines provided by well-conducted clinical trials, and integrated clinical judgment at the patient's bedside.

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30

MECHANICAL VENTILATION FOR SEVERE ASTHMA

James W. Leatherman

It is estimated that 6000 to 10,000 patients require mechanical ventilation for acute asthma in the United States each year.[1] Asthma exacerbations that lead to mechanical ventilation typically progress over 1 or more days, with viral infections being the most common etiology (Table 30-1).[2] Airways typically show extensive mucous plugging and eosinophilic infiltration with edema, explaining the often limited immediate response to bronchodilators.[3] Approximately 20% of patients experience a more explosive onset, with attacks occurring over minutes to hours.[2–4] The precise cause of "sudden asphyxial" asthma is not always apparent, but recognized triggers include aeroallergens, nonsteroidal antiinflammatory agents, airway irritants, and emotional distress.[2,4] Rapid-onset attacks are characterized by profound bronchospasm with minimal mucous plugging, explaining both their sudden onset and rapid resolution.[3]

Regardless of the mode of onset, life-threatening asthma is associated with a markedly increased airway resistance, pulmonary hyperinflation, and high physiologic dead space, which together lead to hypercapnia and risk of respiratory arrest.[5] Hypercapnia per se is not an indication for intubation, as most asthma exacerbations with hypercapnia do respond to bronchodilator therapy and others may be successfully managed with noninvasive ventilation (Fig. 30-1).[6–11] Inhalation of a helium–oxygen gas mixture (heliox) may also reduce work of breathing and might decrease the likelihood of intubation.[11,12]

Indications for intubation include respiratory arrest, depressed level of consciousness, or progressive fatigue and exhaustion. Rapid-sequence intubation has been advocated by some experts,[13] but a high degree of confidence in being able to intubate is a prerequisite before use of a paralytic because it may be difficult to achieve effective bag-mask ventilation in patients with markedly increased airway resistance. Regardless of the technique used, intubation should be performed by the most skilled operator present. Prolonged airway manipulation and repeated failed intubations in the setting of fulminant asthma may prove catastrophic.

Various drugs have been used to facilitate intubation. Ketamine does not cause respiratory depression or hypotension, but may increase laryngeal reflexes and predispose to laryngospasm with excessive upper airway manipulation.[14] Propofol decreases airways resistance after intubation as compared with etomidate or thiopental.[15] Etomidate, however, causes less hypotension than propofol and may be a better alternative in hemodynamically unstable patients.[14] Indeed, many of the drugs used to facilitate intubation reduce vascular tone, which, together with a sudden decrease in venous return secondary to pulmonary hyperinflation, may result in postintubation hypotension.[16] The latter should be anticipated and managed by rapid fluid administration and manual ventilation via an Ambu bag at a slow rate to limit the severity of hyperinflation.[17] Postintubation hypotension that is profound and refractory to these first-line interventions may be managed with a bolus dose of a rapidly acting vasopressor, such as phenylephrine, vasopressin, or epinephrine.

VENTILATOR MANAGEMENT

Controlled hypoventilation with permissive hypercapnia was first proposed as a ventilator strategy for severe asthma almost 30 years ago.[18] In brief, the rationale for this approach is that hypercapnia poses less risk than does markedly

TABLE 30-1: PATTERNS OF NEAR-FATAL ASTHMA

	Slow-Onset	Rapid-Onset
Time course (onset)	One or more days	Minutes to hours
Triggers	Virus, unknown	Aeroallergen, nonsteroid antiinflammatory drug, airway irritant, emotional stress, unknown
Frequency	~80%	~20%
Mechanisms of airflow obstruction	Mucous plugging and airway edema > bronchospasm	Bronchospasm ("dry airways")
Airway inflammation	Eosinophils	Neutrophils
Response to treatment	Slow: minimal response to initial bronchodilators	Rapid: good response to initial bronchodilators
Prevention	Steroids early in exacerbation	Avoid triggers
Duration intubation	Often several days	Often <24 hours

increased lung volume.[19,20] Although randomized studies of controlled hypoventilation in asthma are lacking, a retrospective analysis suggested that it is associated with better outcomes than a conventional ventilator strategy.[19] To apply controlled hypoventilation rationally, it is essential to understand methods for monitoring pulmonary hyperinflation and how the latter is influenced by the choice of ventilator settings.[21–25] Subsequent discussion of ventilator strategy and monitoring will be limited to use of volume-cycled ventilation, the preferred method for managing patients with severe airflow obstruction.[23]

Pulmonary Hyperinflation: Mechanism and Assessment

Patients with acute severe asthma breathe near their total lung capacity; with mechanical ventilation, lung volumes may increase further (Fig. 30-2).[23] During mechanical ventilation, dynamic hyperinflation is initiated when there is insufficient time during expiration for complete exhalation of delivered tidal volume, resulting in an increase in end-expiratory lung volume and auto–positive end-expiratory alveolar pressure (auto-PEEP). With subsequent breaths, a progressive increase in lung volume leads to improved expiratory gas flow because of higher elastic recoil pressure and an increase in airways diameter, permitting the entire tidal volume to be exhaled (Fig. 30-3). Although dynamic hyperinflation may be an adaptive process that enhances expiratory flow, it can result in severe hypotension and barotrauma, life-threatening complications that are a consequence of extreme alveolar overdistension.

The severity of hyperinflation in severe asthma varies among patients and within individual patients over time. Serial monitoring of dynamic hyperinflation is important for identifying an increased risk of hypotension and barotrauma and to assess changes in the severity of airflow obstruction in response to therapy.

Two methods of monitoring the severity of airflow obstruction in status asthmaticus have been used: measurement of total exhaled volume during a prolonged apnea beginning at end inspiration and assessment of airway pressure. Tuxen et al[21–24] used a prolonged apnea to assess dynamic hyperinflation in patients with severe asthma, with the total amount of gas exhaled during the apnea defined as the volume (above functional residual capacity) at end inspiration (V_{EI}). The volume at end expiration (V_{EE}) represents the increase in lung volume

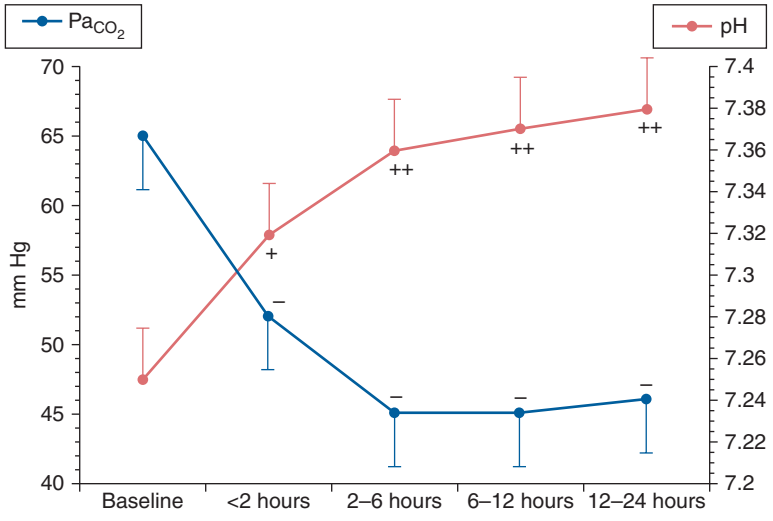

FIGURE 30-1 Change in partial pressure of arterial carbon dioxide (Pa_{CO_2}) and pH associated with the use of noninvasive positive-pressure ventilation by face mask in patients with severe asthma. (Used, with permission, from Meduri GU, Cook TR, Turner RE, et al. Noninvasive positive pressure ventilation in status asthmaticus. *Chest.* 1996;110:767–774.)

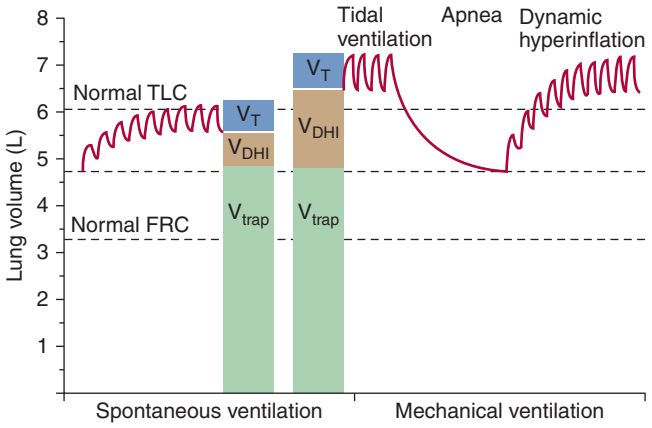

FIGURE 30-2 Lung volumes in severe asthma during spontaneous ventilation and with mechanical ventilation. Tidal breathing occurs near total lung capacity (*TLC*) during spontaneous ventilation and above TLC during mechanical ventilation. After delivery of tidal volume (V_T) during mechanical ventilation, a prolonged apnea permits exhalation of volume produced by dynamic hyperinflation (V_{DHI}); lung volume at the end of apnea, however, remains well above normal functional residual capacity (*FRC*) because of gas trapped behind occluded airways (*Vtrap*). (Adapted, with permission, from Tuxen et al.[23])

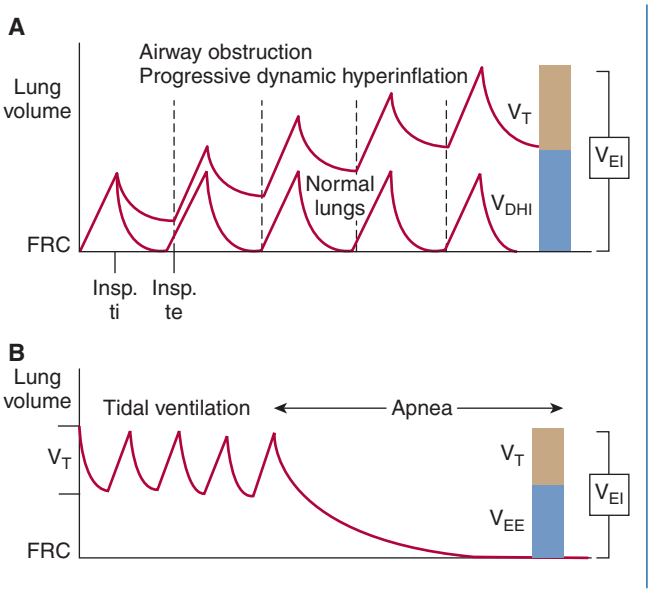

FIGURE 30-3 **A.** Dynamic hyperinflation. *FRC,* functional residual capacity; V_{DHI}, volume (above FRC) caused by dynamic hyperinflation; V_{EI}, volume (above FRC) at end inspiration; V_T, tidal volume. (Adapted, with permission, from Tuxen. *Am J Respir Crit Care Med.* 1994;150:1722–1737.) **B.** Measurement of V_{EI} and V_{EE} (volume above FRC at end expiration) by use of a prolonged apnea. V_{EE} (volume at end expiration) and V_{DHI} (volume produced by dynamic hyperinflation) are equivalent. (Used, with permission, from Tuxen DV, Lane S. The effects of ventilatory pattern on hyperinflation, airway pressures, and circulation in mechanical ventilation of patients with severe air-flow obstruction. *Am Rev Respir Dis.* 1987;136:872–879.)

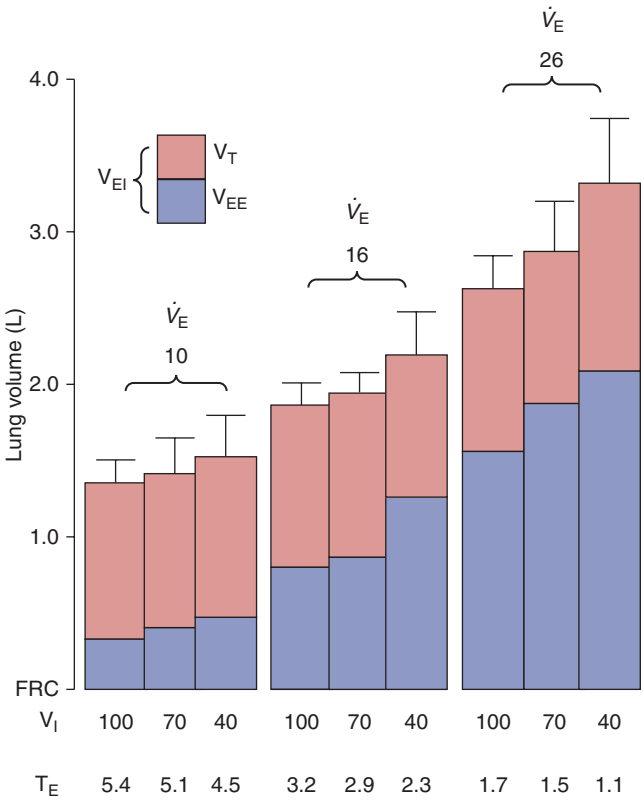

FIGURE 30-4 Effect of minute ventilation ($\dot{V}_E$) and inspiratory flow rate (V_I) on dynamic hyperinflation during mechanical ventilation for severe asthma. V_{EE}, volume at end expiration; V_{EI}, volume at end inspiration; V_T, tidal volume. (Used, with permission, from Tuxen DV, Lane S. The effects of ventilatory pattern on hyperinflation, airway pressures, and circulation in mechanical ventilation of patients with severe airflow obstruction. *Am Rev Respir Dis.* 1987;136:872–879.)

caused by dynamic hyperinflation and is calculated by subtracting tidal volume from V_{EI} (see Figs. 30-3 and 30-4). In one study, hypotension and barotrauma were more reliably predicted by V_{EI} than by airway pressures.[24] Nonetheless, measurement of V_{EI} and V_{EE} has not gained widespread clinical acceptance, in part because of the need for paralysis.[23]

A more commonly used monitoring method is assessment of airway pressures (Fig. 30-5). As described initially,[18] controlled hypoventilation in status asthmaticus targeted a peak airway pressure (P_{PEAK}) below 50 cm H_2O, a strategy used by others subsequently.[26] P_{PEAK}, however, is highly dependent on inspiratory flow-resistive properties and may not accurately reflect the degree of hyperinflation.[23,27] Patients with asthma often have a P_{PEAK} above 50 cm H_2O when managed with high inspiratory flow rate (see below), but their risk of barotrauma may be negligible.[27] Furthermore, P_{PEAK} may not consistently reflect the reduction in dynamic hyperinflation after expiratory time is prolonged, presumably because of an increase in airways resistance as lung volume decreases (Fig. 30-6).[25]

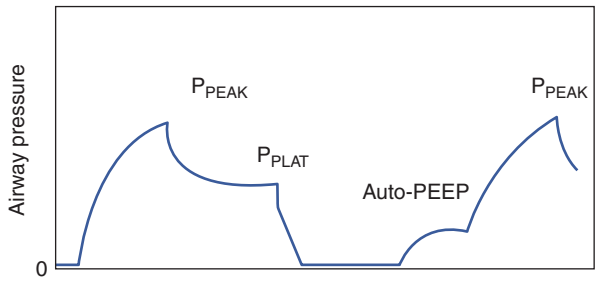

FIGURE 30-5 Proximal airway pressure during an end-inspiratory and end-expiratory airway occlusion. End-inspiratory occlusion is followed by an initial rapid fall in airway pressure, secondary to intrinsic airways resistance and then a more gradual fall in pressure secondary to gas redistribution and tissue resistance. P_{PEAK}, peak airway pressure; P_{PLAT}, plateau airway pressure; auto-PEEP, auto–positive end-expiratory pressure.

Plateau airway pressure (P_{PLAT}) may be a better parameter for monitoring lung hyperinflation in status asthmaticus (see Fig. 30-5).[23,27–31] Patients with severe airflow obstruction typically have near-normal respiratory system compliance and an increase in P_{PLAT} results from dynamic hyperinflation. At constant tidal volume, changes in the degree of dynamic hyperinflation in response to bronchodilators or manipulation of expiratory time can be inferred from changes in P_{PLAT}.[25] Because P_{PLAT} provides an estimate of maximal alveolar pressure, it might (in theory) help to predict risk of alveolar rupture. It should be noted, however, that P_{PLAT} represents the *average* end-inspiratory alveolar pressure and the maximal alveolar pressure in some units will be higher (Fig. 30-7).[31] The safe threshold for P_{PLAT} is not well defined in status asthmaticus, but an acceptable upper limit of 25 to 30 cm H_2O has been suggested most often (Table 30-2).[23,27,30,31]

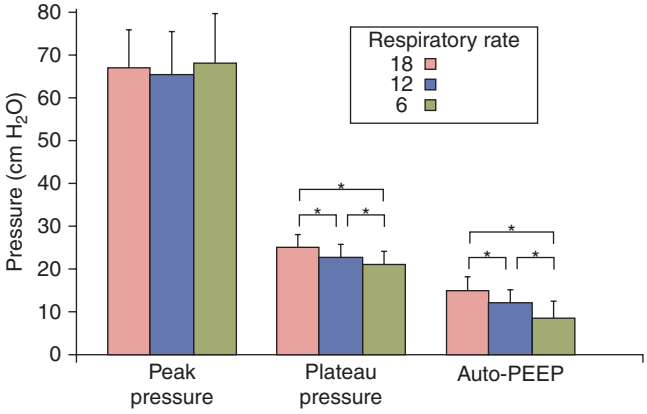

FIGURE 30-6 Peak airway pressure, plateau pressure, and auto-PEEP at respiratory rates of 18, 12, and 6 breaths/min during mechanical ventilation for severe asthma (n = 12). (Used, with permission, from Leatherman JW, McArthur C, Shapiro RS. Effect of prolongation of expiratory time on dynamic hyperinflation in mechanically ventilated patients with severe asthma. *Crit Care Med.* 2004;32:1542–1545.)

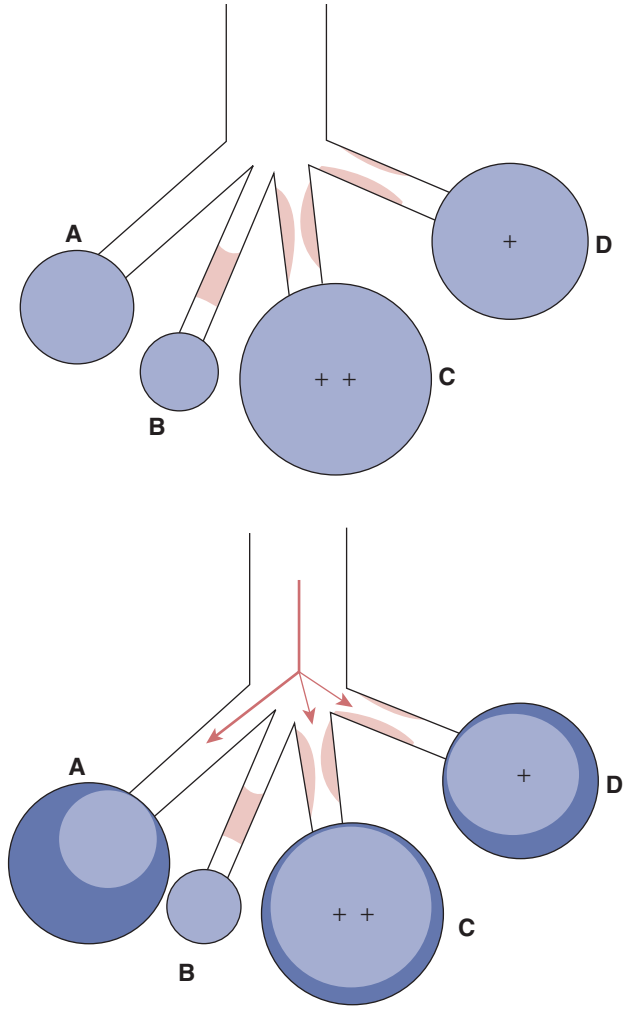

FIGURE 30-7 *Top.* Effect of varying degrees of airway obstruction on end-expiratory alveolar volumes and pressures. *Bottom.* Expected distribution of the tidal volume on application of pressure during mechanical ventilation in the setting of inhomogeneous obstruction (With kind permission from Springer Science and Business Media: Oddo et al. Management of mechanical ventilation in acute severe asthma: practical aspects. *Intensive Care Med.* 2006;27:1–10.)

When measured by end-expiratory airway occlusion, auto-PEEP provides an estimate of average end-expiratory alveolar pressure. The expected levels of auto-PEEP in status asthmaticus have been infrequently reported, but two studies found average values of 15 and 10 cm H_2O, respectively.[25,32] In general, changes in auto-PEEP track closely with changes in P_{PLAT}, and either (or both) may be helpful for following the degree of dynamic hyperinflation. On occasion, patients with status asthmaticus who have radiographic evidence of hyperinflation and elevated P_{PLAT} may have unexpectedly low values of measured auto-PEEP when ventilated at very low respiratory rates that encourage airway closure, preventing accurate assessment of end-expiratory alveolar pressure.[33] Auto-PEEP should always be measured during passive expiration, because forceful exhalation often leads to gross

TABLE 30-2: MECHANICAL VENTILATION FOR SEVERE ASTHMA: ONE APPROACH

Ventilator settings (initial)	
Mode	Assist-control
V_T	7 to 9 mL/kg
Rate	10 to 14 breaths/min
V_I	60 to 70 L/min
Waveform	Decelerating or square
PEEP	≤5 cm H_2O
FI_{O_2}	SaO_2 > 90%
Sedation/paralysis	
Propofol	2 to 5 mg/kg/h infusion
Fentanyl	50 to 200 µg/h infusion
Vecuronium	0.1 mg/kg bolus PRN
Therapy of airflow obstruction	
Albuterol-ipratropium MDI	6 puffs qh × 4, then q1-2h
Methylprednisolone	2 mg/kg/day
Ventilator adjustments	

Goals: P_{PLAT} < 30 cm H_2O (≤25 ideal) and pH ≥ 7.2
- P_{PLAT} > 30 cm H_2O → decrease $\dot{V}_E$ (rate)
- pH < 7.2 and P_{PLAT} < 25 → increase $\dot{V}_E$ (rate)
- pH < 7.2 and P_{PLAT} 25 to 30 → no change (consider buffer if adverse effects of acidosis suspected clinically)

Abbreviations: MDI, metered-dose inhaler; P_{PLAT}, plateau airway pressure; $\dot{V}_E$ minute ventilation; V_I, inspiratory flow rate; V_T, tidal volume.

overestimation of auto-PEEP and the severity of dynamic hyperinflation, potentially leading to unnecessary restriction of minute ventilation.[34]

Ventilator Settings

In severe asthma, three key factors determine the degree to which V_{EE} increases during mechanical ventilation: expiratory resistance, tidal volume, and expiratory time. The ventilator settings that most influence the severity of hyperinflation are tidal volume, respiratory rate, and inspiratory flow rate.

MINUTE VENTILATION: TIDAL VOLUME AND RESPIRATORY RATE

Tuxen and Lane[21] examined various ventilator settings in severe asthma and found that minute ventilation was the most important determinant of dynamic hyperinflation (see Fig. 30-4). For a given minute ventilation, the extent of dynamic hyperinflation was similar regardless of the specific combination of respiratory rate and tidal volume.[21] The degree of hyperinflation became quite marked when minute ventilation was increased from 10 to 16 and 26 L/min; at the highest minute ventilation, both hypotension and barotrauma were noted.[21]

Although these very high levels of minute ventilation clearly pose a risk in the ventilated patient with asthma, the benefit of extreme limitation of minute ventilation, as advocated by some authors,[35] is less certain. One study examined the effect of prolongation of expiratory time on dynamic hyperinflation—as assessed by P_{PLAT} and auto-PEEP—when the baseline minute ventilation approximated 10 L/min.[25] As expected, P_{PLAT} and auto-PEEP decreased when expiratory time was prolonged, but the magnitude of the reduction was not profound (see Fig. 30-6). For example, when respiratory rate was reduced from 12 to 6 breaths/min (adding 5 seconds to expiratory time), P_{PLAT} and auto-PEEP fell by only 2 to 3 cm H_2O.[25] The relatively modest effect on dynamic hyperinflation is understandable given the low expiratory flow rates after a few seconds of expiration (Fig. 30-8). Because flow decreases progressively throughout expiration, the reduction in hyperinflation that results from a given prolongation of expiratory time will depend on the baseline respiratory rate (i.e., less benefit at lower respiratory rates) (Fig. 30-8).

Another factor that may limit the degree to which prolongation of expiratory time lessens lung hyperinflation is the presence of gas trapped behind occluded airways. Total pulmonary hyperinflation has two components: a dynamic component that is amenable to ventilator manipulation and a second component caused by gas trapped behind occluded airways, with the latter being

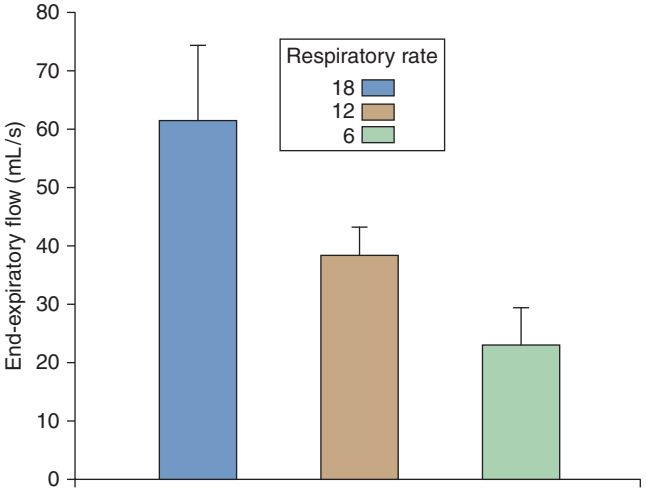

FIGURE 30-8 End-expiratory flow rates at respiratory rates of 18, 12, and 6 breaths/min during mechanical ventilation for severe asthma (n = 7). (Used, with permission, from Leatherman JW, McArthur C, Shapiro RS. Effect of prolongation of expiratory time on dynamic hyperinflation in mechanically ventilated patients with severe asthma. *Crit Care Med.* 2004;32:1542–1545.)

unaffected by expiratory time (see Fig. 30-2). One study suggested that trapped gas accounted for a greater percentage of total pulmonary hyperinflation than did dynamic hyperinflation.[22]

In essence, there is often little to be gained by reducing the respiratory rate below 10 to 14 breaths/min when a tidal volume of 7 to 9 mL/kg is used (see Table 30-2). An exception might be when hyperinflation is marked (e.g., P_{PLAT} >30 cm H_2O) or has resulted in complications, because even a small reduction in hyperinflation might have a meaningful clinical impact. Unfortunately, dramatic reductions in hyperinflation may not be easily achieved by ventilator manipulation alone and must await improvement in airflow obstruction.

INSPIRATORY FLOW RATE

It has been suggested that an inspiratory flow rate of 100 L/min and a square waveform be used in patients with status asthmaticus to shorten inspiratory time and lengthen time for expiration.[23,27,28] This strategy may yield a favorable inspiratory-to-expiratory timing (I:E) ratio, but the impact on dynamic hyperinflation will be modest (Table 30-3). Conventional flow rates (60 to 70 L/min) and a decelerating waveform are appropriate for patients whose minute ventilation has been limited (see Table 30-2).

TABLE 30-3: EFFECT OF INSPIRATORY FLOW RATE IN SEVERE ASTHMA

V_I and Waveform	T_I(s)	T_E(s)	I:E Ratio	Δ DHI (ml)	Δ auto-PEEP (cm H_2O)
60 L/min, decelerating	1.1	3.2	1:3	—	—
120 L/min, square	0.3	4.0	1:13	~−50	~−1

Note: Assume V_T 600 mL, respiratory rate 14 breaths/min, respiratory compliance 60 mL/cm H_2O, and end-expiratory flow rate approximately 60 mL/s.

Abbreviations: DHI, dynamic hyperinflation; I:E ratio, inspiratory-to-expiratory timing ratio; T_E, expiratory time; T_I, inspiratory time; V_I, inspiratory flow rate.

APPLIED POSITIVE END-EXPIRATORY PRESSURE

External PEEP has been used during mechanical ventilation of patients with chronic obstructive pulmonary disease (COPD) to decrease the effort required to trigger the ventilator without increasing lung volume.[36–38] There is less of a rationale for the use of external PEEP when a patient is undergoing controlled mechanical ventilation. In addition, the impact of applied PEEP on lung volume may be different in asthma and COPD (see Fig. 30-9).[36,38,39] One study found that external PEEP of 10 to 15 cm H_2O increased the lung

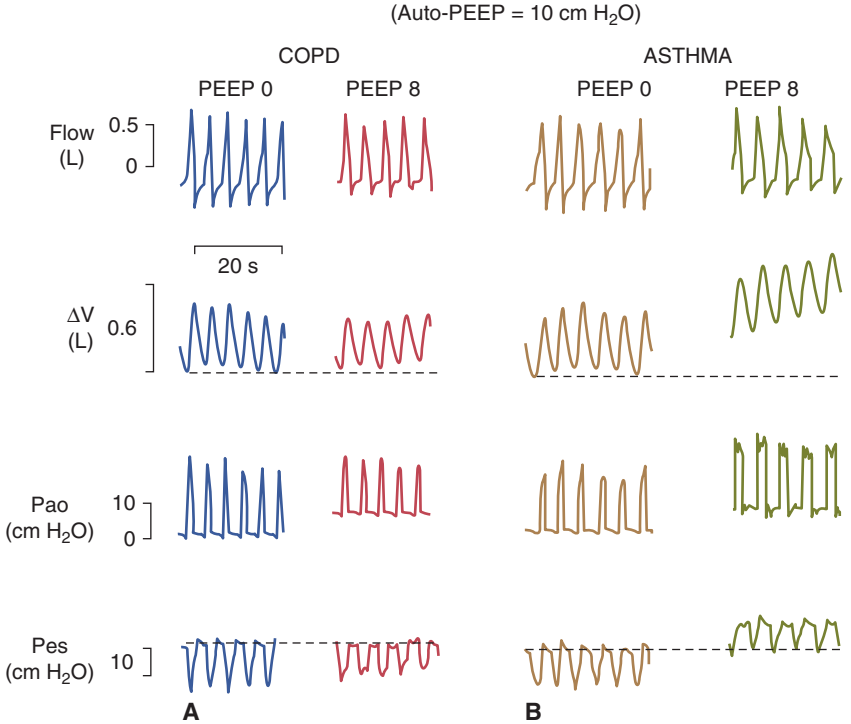

FIGURE 30-9 Response to 8 cm H_2O of PEEP in COPD and asthma during proportional-assist ventilation. Esophageal pressure (*Pes*) indicates a similar reduction in inspiratory effort in both patients. External PEEP did not affect lung volume (*V*) or airway opening pressure (*Pao*) in COPD, but both were increased by PEEP in asthma. (Adapted, with permission, from Ranieri VM, Grasso S, Fiore T, Giuliani R. Auto-positive end-expiratory pressure and dynamic hyperinflation. *Clin Chest Med.* 1996;17(3):379–394.)

volumes of ventilated patients with severe asthma, suggesting that minimal PEEP (≤5 cm H_2O) levels should be used in this setting[39] (see Table 30-2). A recent study claimed that the response to PEEP in patients with airflow obstruction is variable, with the effect being an increase, decrease, or no change in lung volume.[40] The likelihood of a beneficial effect of external PEEP in asthma would seem to be minimal, and if a trial of PEEP is attempted, it should be abandoned immediately if P_{PLAT} increases.

Gas Exchange: Hypercapnia

Hypercapnia is common during mechanical ventilation of patients with severe asthma, with an average partial pressure of arterial carbon dioxide (Pa_{CO_2}) of 68 mm Hg and pH of 7.18 in one study.[25] On occasion, the Pa_{CO_2} may exceed 100 mm Hg. Hypercapnia despite normal minute ventilation is a result of markedly increased physiologic dead space from alveolar overdistension. The impact of an increase in minute ventilation to lower Pa_{CO_2} is mitigated by further increase in dead space related to progressive hyperinflation. As such, hypercapnia in fulminant asthma may not be truly "permissive," because it may be impossible to normalize Pa_{CO_2} through ventilator manipulation.

Given the potential risks of excessive hyperinflation, a reasonable strategy may be to select ventilator settings that typically provide a safe level of dynamic hyperinflation (tidal volume of 7 to 9 mL/kg, respiratory rate of 10 to 14 breaths/min) and accept the resulting Pa_{CO_2} (see Table 30-2). Fortunately, hypercapnia in status asthmaticus is usually well tolerated, with serious adverse consequences being uncommon.[18,19] The most serious consequence of hypercapnia is an increased intracranial pressure in patients with acute neurologic pathology. Although rare, cerebral edema and subarachnoid hemorrhage attributed to hypercapnia has been reported in status asthmaticus.[41–43] Hypercapnia is of greatest concern when there has been cerebral anoxia secondary to respiratory arrest before intubation. Unfortunately, it may be difficult to achieve normocapnia in fulminant asthma without extracorporeal CO_2 removal unless the patient has rapidly reversible bronchospasm.

One approach to managing acute respiratory acidosis in status asthmaticus is to accept the elevated Pa_{CO_2} and administer buffering agents. Unfortunately, standard buffer therapy is relatively inefficient in acute respiratory acidosis. Even partial correction of severe respiratory acidosis will typically require a minimum of several hundred milliequivalents of sodium bicarbonate in an adult.[18] An animal study did find that administration of sufficient sodium bicarbonate (14 mEq/kg) to preserve a normal pH during induction of acute hypercapnia (Pa_{CO_2} = 80 mm Hg) prevented an increase in cerebral blood flow and intracranial pressure.[44] The effect on intracranial pressure is less certain if a smaller amount of bicarbonate is given slowly to raise the pH to 7.15 to 7.20, as has been recommended.[18,44] One problem with giving large amounts of bicarbonate is that once airflow obstruction and hypercapnia resolve, the patient will be left with a therapy-induced metabolic alkalosis.

As a general rule, unless there is some compelling reason to correct underlying respiratory acidosis (e.g., arrhythmia, hyperkalemia, or otherwise unexplained hemodynamic instability), it is probably reasonable to forego attempts to correct serum pH and wait for the Pa_{CO_2} to decrease as airflow obstruction improves. Fortunately, many patients experience substantial improvement in their hypercapnia during the first 12 hours of intubation.[45] If bicarbonate therapy is given, ideally it should be administered by slow infusion rather than by rapid bolus administration because the latter may lead to an acute increase in CO_2 production and a transient fall in intracellular pH as a consequence of rapid diffusion of CO_2 into cells. An alternative to sodium bicarbonate is tromethamine (THAM), a buffer that does not generate CO_2 during the buffering process.[18] Even though THAM may offer some theoretical advantages over sodium bicarbonate for buffering respiratory acidosis, its use may lead to the same problem of a posthypercapnic metabolic alkalosis.

NONVENTILATOR MANAGEMENT

All ventilated patients with severe asthma require inhaled bronchodilators, corticosteroids, and sedation. In rare instances, one or more unconventional approaches also may be considered.

Standard Therapy

BRONCHODILATORS AND GLUCOCORTICOIDS

The optimal dose of inhaled bronchodilators during mechanical ventilation of patients with severe asthma has not been defined. Based on studies of patients with COPD, the optimal dose of albuterol given by metered-dose inhaler is likely to be 4 to 6 puffs.[46–48] Hourly dosing is appropriate initially. Assessment of lung mechanics during incremental dosing of inhaled β_2 agonists may be useful to determine both the optimal number of puffs and dosing interval for individual patients, using an "n = 1" trial. Ipratropium might also be considered, given its benefit when added to albuterol therapy in nonintubated asthmatics with severe airflow obstruction.[49]

Glucocorticoids are an essential component of the treatment of severe asthma, with an effect being evident within 12 hours of administration.[50] An initial dose of 2 mg/kg/day of methylprednisolone or equivalent seems appropriate.[51]

SEDATION AND PARALYSIS

As with other causes of respiratory failure, minimal goals of sedation in status asthmaticus include provision of anxiolysis, analgesia, and prevention of patient–ventilator dyssynchrony. Patients with status asthmaticus present an additional challenge because of the need to enforce controlled hypoventilation despite acute respiratory acidosis that increases

respiratory drive.[8] A combination of propofol or a benzodiazepine (midazolam or lorazepam) with a narcotic (fentanyl or morphine) often proves optimal, and very large doses may be required (see Table 30-2).[8] Because airflow obstruction often improves within 24 to 48 hours,[27,45] residual sedation that delays extubation is undesirable. A major advantage of propofol over benzodiazepines is that propofol allows deep sedation that reverses promptly on its discontinuation. The maximal propofol dose should not exceed 5 mg/kg/hour, because prolonged infusion of very high doses of propofol can lead to life-threatening complications.[52]

Large doses of sedatives and narcotics in combination with marked lung hyperinflation may result in hypotension. When additional muscle relaxation is needed in the face of hemodynamic instability, it may be safer to administer a nondepolarizing neuromuscular blocking agent than increase the dose of sedatives and narcotics. Even when hypotension is not present, intermittent administration of one or more boluses of a neuromuscular blocking agent may help to provide a period of temporary muscle relaxation, during which time sedative doses can be escalated gradually to achieve target levels. Prolonged use of a neuromuscular blocking agent may increase the likelihood of myopathy in status asthmaticus (see the section Death and Complications), but short-term use likely does not carry significant risk.[53,54] The specific neuromuscular blocking agent selected is likely unimportant, although vecuronium, perhaps, should be avoided in patients with renal failure.[55] Intermittent bolusing is preferred to a continuous infusion because this permits ongoing assessment of the adequacy of sedation and lessens the likelihood that the patient will undergo unnecessarily prolonged neuromuscular paralysis. When sedatives and narcotics are used liberally, supplemented by short-term intermittent boluses of a neuromuscular blocking agent if needed, very few patients with status asthmaticus will require prolonged, continuous neuromuscular paralysis.

Alternative Therapies

Occasionally, one of several nontraditional approaches may be considered in patients with fulminant asthma. Strategies that have been reported anecdotally to be beneficial include the use of heliox, inhalational anesthetics, or ketamine, nitric oxide, mucolytic agents, bronchoscopy, and extracorporeal support.

HELIOX

The lower gas density of heliox reduces frictional resistance where gas flow is turbulent and, by lowering the Reynolds number, also encourages laminar flow.[11] One study reported that heliox produced a rapid fall in peak airway pressure and Pa_{CO_2} of ventilated patients with asthma.[56] The effects on P_{PLAT} and auto-PEEP, however, were not reported, and it is unclear whether changes in Pa_{CO_2} were at constant minute ventilation.[56] A second study of heliox in severe asthma found little change in Pa_{CO_2} when tidal volume and respiratory rate were held constant.[57] Two prospective studies found that a 70:30 mixture of heliox reduced auto-PEEP during mechanical ventilation of patients with COPD.[58,59] This suggests that heliox may have a measurable benefit in selected patients and might be considered for use when conventional management results in an unacceptable degree of dynamic hyperinflation in patients with status asthmaticus.[23] Continuous use of heliox is very expensive and can only be justified if it significantly improves indices of hyperinflation (P_{PLAT}, auto-PEEP) or hypercapnia.[60]

Before using heliox, it is crucial to fully understand how its use will affect performance of the ventilator.[61] Use of a density-independent spirometer in the expiratory limb of the ventilator circuit is advisable to ensure accurate setting of tidal volume.[11]

GENERAL ANESTHETICS

Inhalational anesthetics have potent bronchodilating properties, and several anecdotal reports have described their use in status asthmaticus.[62,63] In the only study to carefully assess lung mechanics, isoflurane resulted in a decrease in airways resistance and auto-PEEP in three patients with asthma, although only one had a marked response (Fig. 30-10).[64]

Isoflurane and sevoflurane are less arrhythmogenic than halothane and have equal or greater bronchodilator properties.[63] All these agents may cause hypotension secondary to their peripheral vascular effects, and an increase in venous capacitance may be particularly detrimental when marked dynamic hyperinflation already has compromised venous return. The adverse hemodynamic effects generally can be mitigated through liberal administration of fluid and with vasoactive support if necessary. It is mandatory, of course, that personnel highly skilled in the use of anesthetic agents be responsible for their administration. Some intensive care unit ventilators have a port to which the anesthesia vaporizer can be attached, and with appropriate scavenging

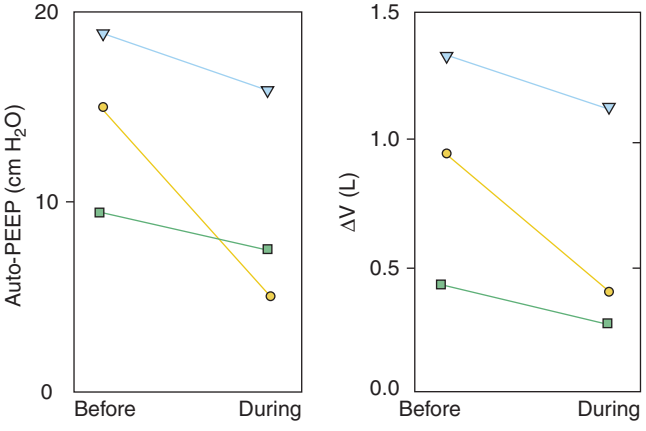

FIGURE 30-10 The effect of isoflurane on auto-PEEP and change in lung volume (ΔV) in three patients with severe asthma. (Adapted, with permission, from Maltais F, Sovilj M, Goldberg P, Gottfried SB. Respiratory mechanics in status asthmaticus. Effects of inhalational anesthesia. *Chest*. 1994;105:1401–1406.)

of anesthetic gases, the general anesthetic can be administered in the intensive care unit.[62]

Ketamine, an intravenous dissociative anesthetic, also has been advocated for use in severe asthma. This drug, however, can lead to significant increases in blood pressure, heart rate, and intracranial pressure. There seems little justification for the use of ketamine in ventilated patients with status asthmaticus.

MUCOLYTICS

The potential benefit of *N*-acetylcysteine as a mucolytic is unknown; in an anecdotal report, it seemed to enhance bronchoscopic extraction of mucous plugs.[65] Benefit from rhDNAse also has been reported.[66]

BRONCHOSCOPY

Patients with fatal asthma often have extensive mucoid impaction.[67] Removal of impacted mucus by bronchoscopy has been reported to lower airway pressures and improve gas exchange in ventilated patients with severe asthma.[65] However, there is a potential for worsening bronchospasm and several large series have reported good outcomes without use of bronchoscopy.[18,24,26,32,45] Patients who fail to improve after several days of mechanical ventilation might be considered for diagnostic bronchoscopy to inspect the airways for mucous plugs that might be extracted, the goal being to reduce the duration of ventilator support.

EXTRACORPOREAL LIFE SUPPORT

Both pump-driven and pump-less extracorporeal life support has been used in severe asthma.[68–70] Because severe asthma is fully reversible, this approach clearly would be justified if there were an imminently lethal impairment in gas exchange. Refractory hypoxemia, however, is unusual in asthma and hypercapnia generally is well tolerated (see the section Gas Exchange:Hypercapnia, above). Extracorporeal life support might be considered if there is profound hypercapnia and extreme hyperinflation, especially if accompanied by barotrauma or hemodynamic instability.[69,70] Besides correcting hypercapnia and avoiding complications related to hyperinflation, extracorporeal life support could also permit safe use of bronchoscopy to treat mucoid impaction.

DEATH AND COMPLICATIONS

Mortality

Published mortality rates for patients undergoing mechanical ventilation for severe asthma have varied greatly, ranging from 0% to 38%.[32,45,71–74] A literature review of more than 1220 patients reported an average mortality of 12.4%.[23] Although the outcome seems to have improved over the last two decades, perhaps because of more widespread use of controlled hypoventilation, mortality rates as high as 15% to 20% have been reported in series published during the last decade.[72,73] Most fatalities result from cerebral anoxia secondary to cardiorespiratory arrest before intubation. Indeed, in a recent analysis of 1223 patients who underwent mechanical ventilation for severe asthma, 80% of in-hospital deaths were preceded by cardiorespiratory arrest before admission to the intensive care unit.[73]

Complications

Patients with severe asthma are at risk for many of the same complications affecting other ventilated patients, including atelectasis, nosocomial pneumonia, sinusitis, pulmonary embolism, and gastrointestinal bleeding. Additional complications may result directly from the asthma exacerbation or from medications used to treat airflow obstruction and provide muscle relaxation; these include ventilator-associated hypotension, barotrauma, myocardial injury, rhabdomyolysis, lactic acidosis, neurologic injury, and acute myopathy (Table 30-4).

HYPOTENSION

Hypotension during mechanical ventilation for status asthmaticus is most often a result of the combined effects of sedatives and the excessive pulmonary hyperinflation that impedes venous return. In one series, mild-to-moderate hypotension was documented at some point during the course of mechanical ventilation in 35% of patients, with risk being greatest in patients whose V_{EI} exceeded approximately 20 mL/kg (Fig. 30-11).[24] Extreme hyperinflation can lead

TABLE 30-4: COMPLICATIONS OF MECHANICAL VENTILATION FOR SEVERE ASTHMA

Complications	Likely Mechanism
Hypotension	Primary: excessive hyperinflation, sedatives Secondary: pneumothorax, myocardial depression
Barotrauma	Excessive hyperinflation
Myocardial dysfunction	Primary: stress cardiomyopathy secondary to massive catecholamine release Secondary: severe myocardial hypoxia and/or acidosis
Rhabdomyolysis	Primary: extreme muscle exertion with or without hypoxia Secondary: high-dose propofol
Lactic acidosis	Primary: excessive β_2 agonists Secondary: extreme muscle exertion and/or hypoxia
CNS injury	Primary: cerebral anoxia secondary to respiratory arrest Secondary: hypercapnia-related cerebral edema, subarachnoid hemorrhage
Acute myopathy	Glucocorticoids plus prolonged paralysis or deep sedation

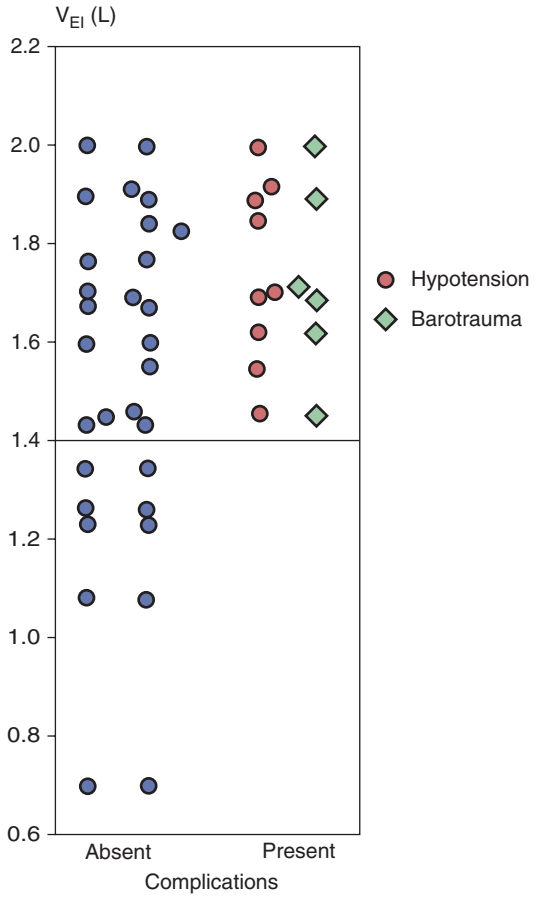

FIGURE 30-11 Relationship between hypotension, barotrauma, and lung volume at end inspiration (V_{EI}). (Used, with permission, from Williams TJ, Tuxen DV, Scheinkestel CD, et al. Risk factors for morbidity in mechanically ventilated patients with acute severe asthma. *Am Rev Respir Dis.* 1992;146:607–615.)

to cardiac arrest with pulseless electrical activity.[17] When a ventilated patient with severe asthma develops significant hypotension, a 1-minute apnea trial is recommended.[23] If the apnea trial and a rapid infusion of fluid do not restore blood pressure, then less-common causes of hypotension (e.g., pneumothorax, myocardial depression) must be considered.

BAROTRAUMA

Pneumothorax also occurs most often in patients with the highest end-inspiratory lung volume (see Fig. 30-11).[24] The incidence of pneumothorax was as high as 30% in some early series,[71] but is relatively infrequent (<10%) when a strategy of controlled hypoventilation is used.[8,26,27,32,45,74] In an analysis of barotrauma in various types of respiratory failure, pneumothorax was documented in only 6% of patient with status asthmaticus.[75] A pneumothorax may be particularly dangerous in patients with severe asthma because the hyperinflated lungs resist collapse and allow even a small pneumothorax to be under tension, resulting in rapid deterioration and sometimes death.[23] For this reason, clinical (and radiographic) diagnosis of tension pneumothorax may be challenging.[23] Chest tubes always should be placed by blunt dissection rather than by the blind trocar method to avoid injuring the hyperinflated lungs.[23]

CARDIAC COMPLICATIONS

A reported cardiac complication of status asthmaticus is stress cardiomyopathy, typically manifested as decreased myocardial contractility with reversible segmental myocardial wall-motion abnormalities and deep T-wave inversions in the electrocardiogram, simulating myocardial ischemia (Fig. 30-12).[76,77] Stress cardiomyopathy in status

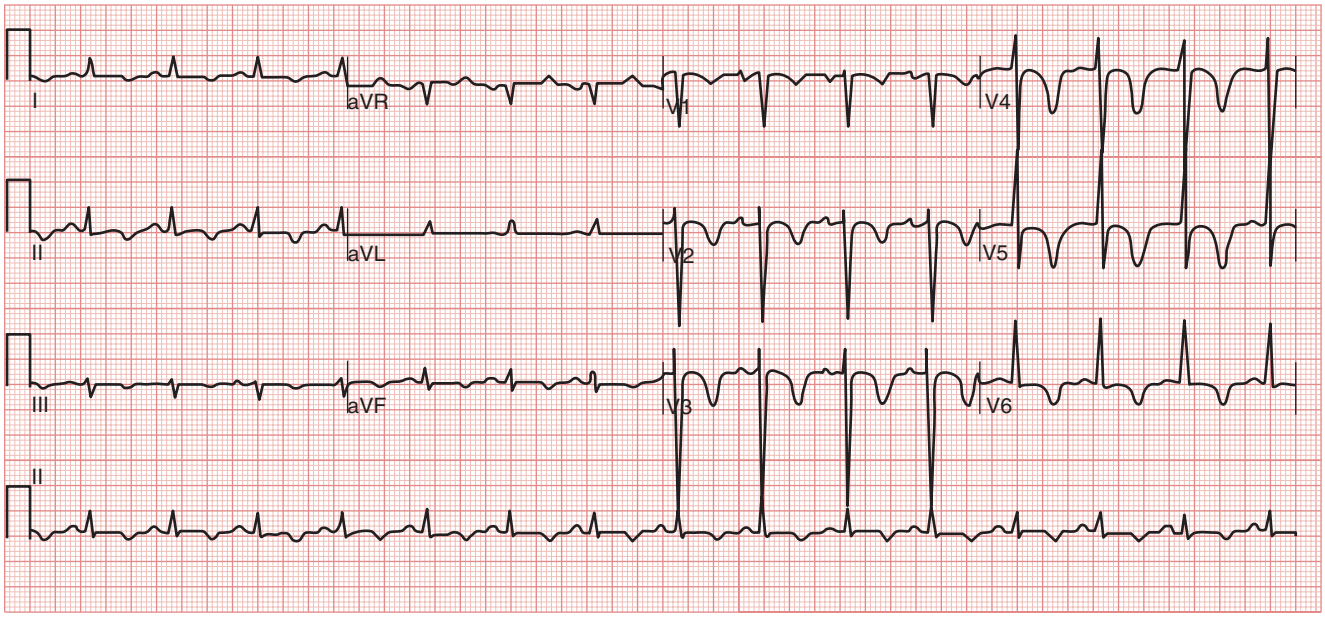

FIGURE 30-12 Electrocardiogram of a patient with acute reversible left-ventricular dysfunction caused by status asthmaticus. Deep inverted T-waves in anterior precordial leads are seen commonly in this condition.

asthmaticus is similar to that seen after subarachnoid hemorrhage, severe psychological stress, and other conditions associated with massive endogenous sympathetic activation. It often follows a benign course with no long-term cardiac sequelae, but may be associated with significant hypotension.[77]

RHABDOMYOLYSIS

Rhabdomyolysis has been reported in patients with status asthmaticus, presumably as a result of extreme muscular exertion coupled with hypoxia.[78] Rhabdomyolysis also has been noted in patients who had received prolonged infusions of propofol in very high doses.[52]

LACTIC ACIDOSIS

Mild lactic acidosis is relatively common in status asthmaticus and has been attributed to lactate production by respiratory muscles.[79–81] Lactic acidosis can also occur as a result of excessive use of β_2 agonists. Although more common when the latter are given intravenously, lactic acidosis also can follow high-dose inhalational therapy with albuterol.[82] Even a moderate degree of lactic acidosis may be problematic in patients with significant hypercapnia.

CENTRAL NERVOUS SYSTEM INJURY

As noted earlier, cerebral anoxia is the most common cause of death in patients with status asthmaticus.[73] Rarely, cerebral edema or subarachnoid hemorrhage in status asthmaticus can occur in the absence of prior cerebral anoxia and have been attributed to hypercapnia.[41–43]

MYOPATHY

Acute myopathy probably is the most common cause of morbidity affecting patients with asthma who undergo mechanical ventilation. The pathogenesis of myopathy is incompletely understood, but has been attributed to the combined effects of glucocorticoids and prolonged neuromuscular paralysis (Fig. 30-13).[53,54] Myopathy also occurs in patients with asthma who have undergone prolonged (>5 to 7 days) mechanical ventilation under deep sedation without paralysis.[83,84] It is possible that prolonged near-total muscle inactivity, whether induced by neuromuscular paralysis or by deep sedation, may increase the risk of this complication.[84] Recent studies show that daily physical therapy during scheduled awakening significantly reduces the incidence of intensive care unit-acquired weakness.[85] When patients with asthma are unable to be extubated within a few days of intubation, daily scheduled awakening for physical therapy should be strongly considered, provided airflow obstruction is not so severe that withdrawal of sedation is deemed unsafe.

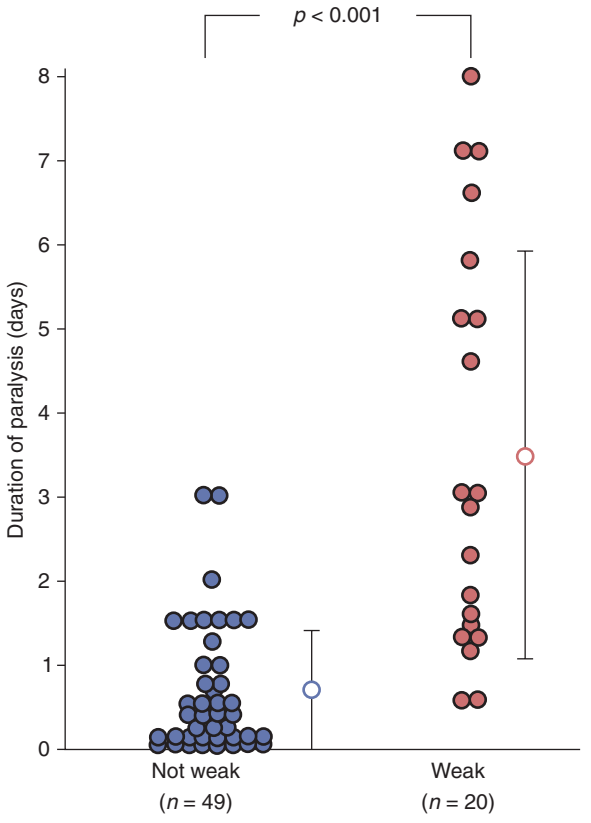

FIGURE 30-13 Duration of paralysis in patients with and without weakness (defined clinically) after undergoing mechanical ventilation for severe asthma. (Used, with permission, from Leatherman JW, Fluegel WL, David WS, et al. Muscle weakness in mechanically ventilated patients with severe asthma. *Am J Respir Crit Care Med.* 1996;153:1686–1690.)

POSTHOSPITALIZATION PROGNOSIS

Although in-hospital mortality of patients who receive mechanical ventilation for severe asthma is relatively low, one study reported that seventeen of 121 (14%) patients died of a recurrent asthma attack during a follow-up period of 6 years, with most deaths occurring in the first year after hospital discharge.[86] Another study identified prior intubation as the strongest risk factor for death from asthma.[1] These data emphasize the crucial importance of outpatient management—including regular use of inhaled glucocorticoids, avoidance of smoking and other factors known to increase airway responsiveness, close supervision, and intensive education—following hospital discharge of patients with asthma who undergo mechanical ventilation.

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31

MECHANICAL VENTILATION IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Franco Laghi

Acute exacerbation of chronic obstructive pulmonary disease (COPD) is defined as an increase in dyspnea, cough, or sputum production that requires therapy. The annual rate of exacerbations is 0.5 to 3.5 per patient.[1] Hospitalization rates range from 0.1 to 2.4 per patient per year.[1] Most exacerbations are caused by viral infections, such as *Rhinovirus* or influenza species or bacterial infections, such as *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, or *Pseudomonas* species.[2] Occasionally, exacerbations are caused by air pollution and other environmental factors.[2] When evaluating a patient suspected of having an exacerbation, concurrent conditions such as pulmonary emboli, pneumothorax, and congestive heart failure should be clinically excluded.[2] In about one-third of cases, no underlying etiology is identified.[3]

The clinical presentation of exacerbations of COPD is highly variable. Most patients require only an increase of maintenance medications, while others develop frank respiratory failure and require ventilator assistance.[4,5] The goals of ventilator assistance are to decrease respiratory distress and dynamic hyperinflation, to improve gas exchange, and to buy time for resolution of the processes that triggered the episode of acute respiratory failure.

This chapter focuses on the aspects of ventilator management that are unique for patients with COPD. General principles of ventilator management are covered in other chapters—such as ventilator modes, bronchodilator therapy, weaning, and so on—and only the aspects specific to COPD are discussed in the present chapter. More than is the case with any other group of patients, clinical decision making and ventilator management in COPD is predicated on a detailed knowledge of the underlying pathophysiology.

PATHOPHYSIOLOGIC FEATURES RELEVANT TO VENTILATOR SUPPORT

The basic physiologic abnormalities of patients who experience acute respiratory failure in COPD include deteriorations in respiratory mechanics, respiratory muscle function, and gas exchange.

Deterioration of Respiratory Mechanics

INCREASED INSPIRATORY AIRWAY RESISTANCE

In stable patients with COPD, inspiratory flow resistance is approximately 6 cm H_2O/L/s above normal.[6] During an episode of acute respiratory failure, resistance can increase by

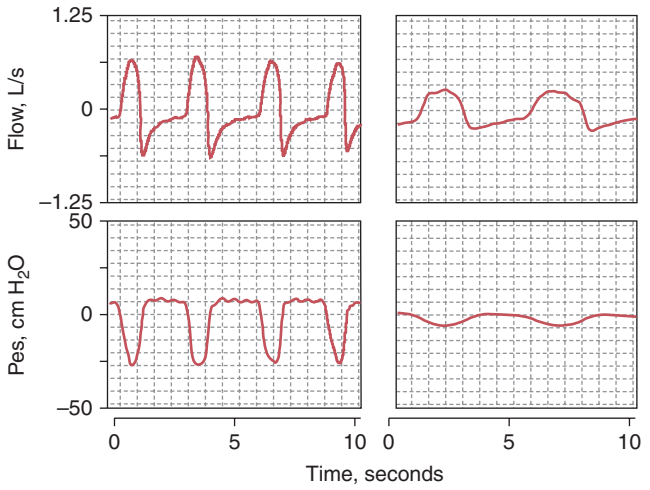

FIGURE 31-1 Respiratory effort during spontaneous respiration. Recordings of flow (*inspiration upward*) and esophageal pressure (*Pes*) in a patient with chronic obstructive pulmonary disease (COPD) in respiratory failure (*left panel*) and in a stable patient with COPD (*right panel*). The patient in respiratory failure exhibits a steeper fall and greater excursion in esophageal pressure than does the stable patient, signifying greater respiratory motor output. Despite the fivefold larger excursion in Pes in the patient in respiratory failure, peak inspiratory flow is only two times more than in the stable patient, signifying more abnormal mechanics in the former than in the latter patient. The patient in respiratory failure exhibits tachypnea, reflected by the shorter respiratory cycle, and exhibits a supramaximal flow transient at the beginning of exhalation, which is typical of expiratory flow limitation.

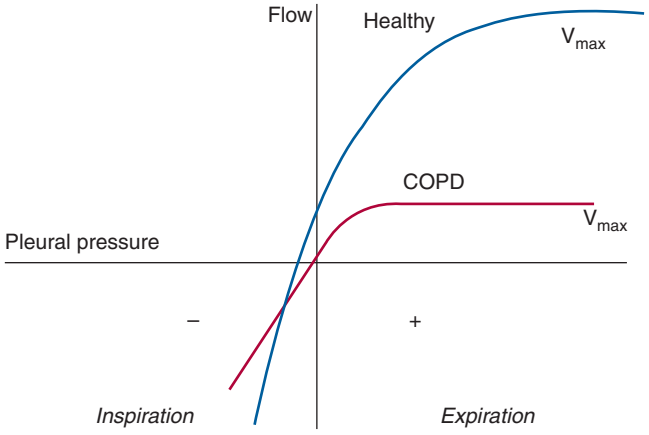

FIGURE 31-2 Schematic of the isovolume pressure–flow relationship. Patients with chronic obstructive pulmonary disease (COPD) exhibit an initial diagonal segment, where increases in pressure produce increases in airflow (the effort-dependent region on the *left*), followed by a flat portion, where increases in pressure do not produce increases in flow (the effort-independent region on the *right*). Compared with a healthy subject, the slope of the initial diagonal segment is decreased, indicating an increase in airway resistance, and maximum flow is much reduced in the remaining portion secondary to expiratory flow limitation. (Used, with permission, from Tobin et al.[16])

an additional 6 cm H_2O/L/s or more.[7,8] Mechanisms responsible for the increase include bronchospasm, airway inflammation, and mucus production.[9]

Increases in inspiratory resistance and respiratory motor output lead to increased inspiratory effort (Fig. 31-1).[7] In patients with severe COPD, the pressure output of the inspiratory muscles during resting breathing is three times higher than in healthy subjects: average pressure-time products of 259 to 341 versus 94 cm H_2O • second per minute.[8,10] Values are five times higher when patients are in respiratory distress.[8,11]

INCREASED EXPIRATORY AIRWAY RESISTANCE

In healthy subjects, inspiratory and expiratory airway resistance are of similar magnitude.[6,12] In contrast, patients with COPD have greatly increased expiratory resistance.[12–14] In ventilated patients with COPD, the ratio of expiratory to inspiratory flow resistance ranges from 3.8 at low lung volumes to 1.6 at high lung volumes.[14] The increased resistance at low lung volumes is related to dynamic narrowing of the small airways during exhalation.[15] This narrowing is thought to result from damage to the elastic scaffold surrounding the airways[16] and as well as to the "wave speed limitation" of the expiratory flow—the tracheobronchial tree cannot adjust an airflow more rapidly than the velocity at which pressure travels along the airways.[15] Small-airway narrowing and wave-speed limitation reduce maximum flow during exhalation with the development of expiratory flow limitation (Fig. 31-2). Expiratory flow limitation occurs in 60% of stable patients during resting breathing,[17] and universally during episodes of acute respiratory failure.[18]

Patients with expiratory flow limitation experience air trapping whereby activation of the expiratory muscles increases alveolar pressure without decreasing the end-expiratory lung volume below the relaxation volume of the respiratory system (Vrel).[15] The inability to decrease end-expiratory lung volume below Vrel has several negative consequences. First, expiratory muscle contraction—a constrained response of the respiratory centers to increased ventilatory demands—does not achieve storage of elastic energy in the respiratory system at end exhalation.[4] Second, relaxation of the expiratory muscles at the onset of inhalation cannot assist the inspiratory muscles in expanding the respiratory system during inhalation. Third, the entire burden of breathing is borne by the inspiratory muscles. Fourth, recruitment of the expiratory muscles dissipates precious energy substrates. That is, expiratory muscle recruitment in COPD is harmful,[19] and it can account for 66% of the variation in Borg scale ratings of difficulty in breathing.[20]

DYNAMIC HYPERINFLATION AND INTRINSIC POSITIVE END-EXPIRATORY PRESSURE

The minimum time required to exhale from a given lung volume to Vrel is determined by the maximum expiratory flow.[15] When the time for exhalation (T_E) is less than this minimum time, inhalation will begin before the respiratory system has returned to Vrel—a state known as dynamic hyperinflation (Fig. 31-3).[16] Dynamic hyperinflation (a "volume"

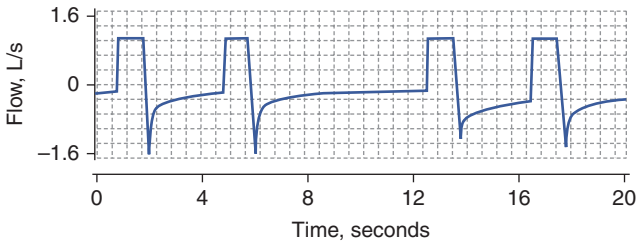

FIGURE 31-3 Persistent expiratory flow at end-exhalation. Recording of flow (*inspiration upward*) in a patient with chronic obstructive pulmonary disease (COPD) and respiratory failure receiving controlled mechanical ventilation. Whether the duration of exhalation is 3 seconds (first and third breaths) or 6 seconds (second breath), expiratory flow at end-exhalation is always present. Persistent expiratory flow at end-exhalation signifies that inhalation begins before the respiratory system has returned to its relaxation volume—dynamic hyperinflation.

phenomenon) is almost invariably associated with an increase in end-expiratory elastic recoil of the respiratory system (a "pressure" phenomenon).[15] This increase in end-expiratory elastic recoil has been called auto–positive end-expiratory pressure (auto-PEEP)[21] or intrinsic PEEP (PEEPi).[22] Dynamic hyperinflation and PEEPi have been reported in all ventilated patients with COPD.[23] Increases in dynamic hyperinflation during exacerbations are proportionally greater than increases in airflow obstruction.[24]

Dynamic hyperinflation and PEEPi can fluctuate widely as a result of several factors.[15] First, bronchospasm, mucosal edema, and sputum inspissation can abruptly worsen expiratory flow limitation. Second, patients are often tachypneic and, thus, T_E is shortened.[25] Finally, ventilatory demands can fluctuate because of sudden episodes of anxiety or deterioration of gas exchange.[15]

Acute worsening in dynamic hyperinflation is beneficial because it optimizes expiratory flow by limiting dynamic airway narrowing during exhalation[26] and by increasing the elastic recoil of the lung and, less so, of the chest wall.[18] It is detrimental because it decreases the effectiveness of the respiratory system through several mechanisms. First, at the start of inhalation patients have to first generate negative inspiratory pressure equal in magnitude to the value of PEEPi before inspiratory flow can be initiated (threshold inspiratory load).[8,27] In patients with COPD recovering from an episode of respiratory failure necessitating mechanical ventilation, Jubran and Tobin[8] reported that, during a spontaneous breathing trial, approximately 20% to 25% of the inspiratory muscle effort was required to overcome PEEPi. Second, dynamic hyperinflation impairs respiratory muscle function by worsening the length–tension relationship of the muscles (Fig. 31-4), by decreasing the zone of apposition,[28] and by interfering with inspiratory muscle perfusion.[29] Finally, dynamic hyperinflation increases end-inspiratory lung volume.[18] When excessive, increases in end-inspiratory lung volume can reduce lung compliance, increase the elastic work of breathing, and can cause alveolar overdistension. Alveolar overdistension can lead to hemodynamic compromise through several mechanisms. First, it can reduce right-ventricular preload as a result of impaired venous return.[21] Second, it can raise right-ventricular afterload by increasing pulmonary vascular resistance.[21] The increased right-ventricular afterload can increase the right ventricular end-diastolic volume and shift the interventricular septum toward the left ventricle. This shift can impair left-ventricular filling (ventricular interdependence). Finally, the threshold load imposed on the inspiratory muscles can increase left-ventricular afterload secondary to increased negative intrapleural pressure during inhalation.[21] All these phenomena can severely decrease cardiac output, effects exaggerated in COPD because the abnormally compliant lungs transmit a high fraction of alveolar pressure to intrathoracic vessels.[30]

Deterioration of Respiratory Muscle Function

RESPIRATORY MUSCLE WEAKNESS

Patients with COPD do not generate as much negative maximal inspiratory pressures as do healthy subjects.[4] This decrease in respiratory muscle strength may result from several factors, including greater protein degradation of muscle fibers,[31,32] malnutrition, sepsis, systemic steroids, and ventilator mode.[4,28] In some patients, however, the inspiratory weakness can be completely explained by hyperinflation-induced muscle shortening.[33] In addition, diaphragmatic myofibers of patients with COPD are also more susceptible to sarcomere disruption when subjected to an acute inspiratory load than are the diaphragms of healthy controls.[34]

Patients with COPD have an increased risk of coronary artery disease, and 20% to 30% have chronic heart failure.[35] Increased stress on the myocardium during acute respiratory failure could overwhelm an already impaired cardiac reserve.[36,37] An increased load resulting from interstitial edema secondary to acute left-ventricular failure together with decreased blood flow to the respiratory muscles may markedly impair respiratory muscle performance.[38]

RESPIRATORY MUSCLE FATIGUE

Contractile fatigue occurs when a sufficiently large respiratory load is applied over a sufficiently long period of time. Contractile fatigue can be brief or prolonged.[28] Short-lasting fatigue results from accumulation of inorganic phosphate, failure of the membrane electrical potential to propagate beyond T-tubules, and to a much lesser extent intramuscular acidosis.[28] In nine patients who developed acute respiratory failure during a weaning trial (four of whom had COPD), Brochard et al[39] reported electromyographic signs suggestive of incipient short-lasting diaphragmatic fatigue. Short-lasting fatigue appears to have a protective function, because it can prevent injury to the sarcolemma caused by forceful muscle contractions.[40] Long-lasting fatigue[41] is consistent with the development of, and recovery from, muscle injury.[28,40]

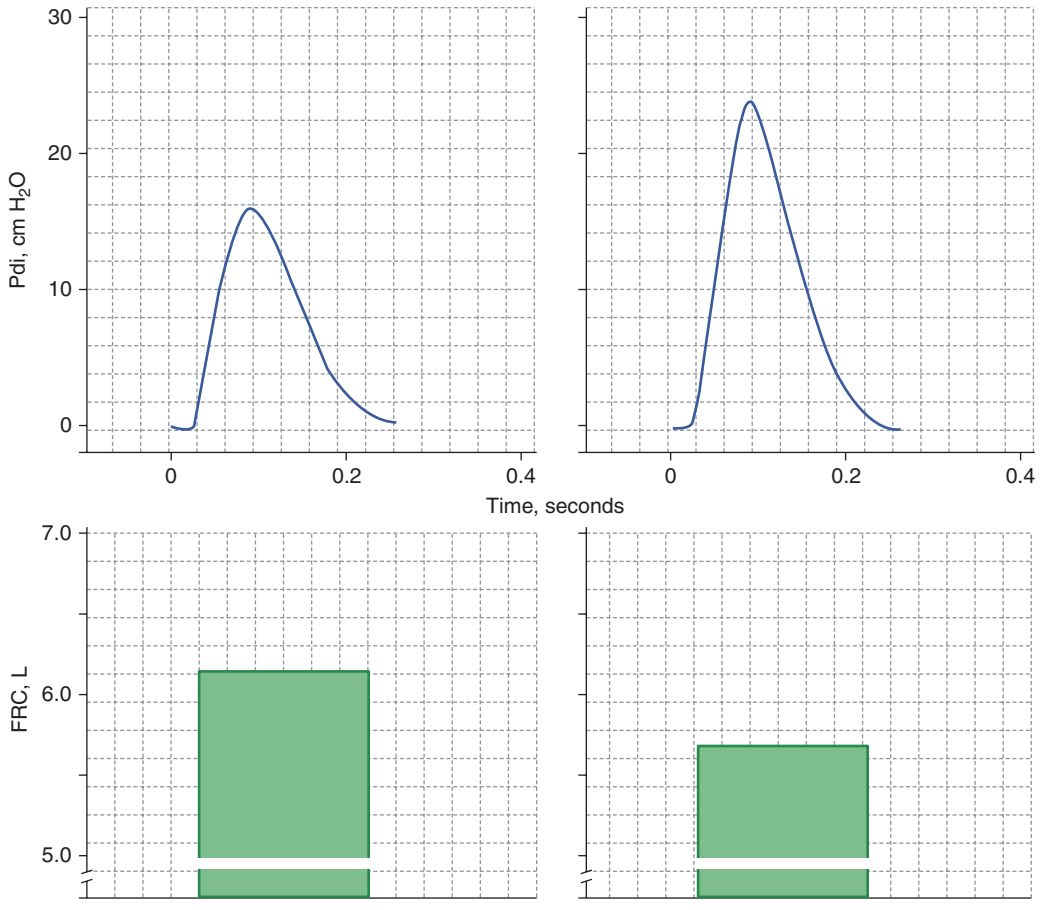

FIGURE 31-4 Twitch transdiaphragmatic pressure (*Pdi*) elicited by phrenic nerve stimulation (*upper panels*) and functional residual capacity (*FRC*; *lower panels*) in a patient with chronic obstructive pulmonary disease (COPD) before (*left*) and after (*right*) lung volume reduction surgery. The higher twitch Pdi after surgery was in part caused by decrease in operating lung volume as demonstrated by decrease in FRC. (Data from Laghi et al.[10])

To assess whether patients in acute respiratory failure develop long-lasting fatigue, Laghi et al[11] measured the contractile response of the diaphragm to phrenic nerve stimulation in sixteen patients being weaned from mechanical ventilation. In that study, no patient developed long-lasting fatigue of the diaphragm. The investigators concluded that patients displayed clinical manifestations of severe respiratory distress for a substantial time before they would develop fatigue.

Deterioration of Gas Exchange

Abnormal distribution of ventilation–perfusion ($\dot{V}_A/\dot{Q}$) ratios[42] and decreased mixed venous oxygen tension are common causes of hypoxemia during exacerbations.[43,44] In patients without alveolar pathologies (pneumonia, pulmonary edema) shunt is almost negligible.[43]

Hypercapnia is present in nearly half of patients admitted to a hospital with an acute exacerbation of COPD.[45] Hypercapnia plus respiratory acidosis is almost universal in patients with COPD requiring mechanical ventilation.[45]

Excluding patients who are on the verge of respiratory arrest, most patients with COPD in respiratory failure who develop hypercapnia experience a decrease in alveolar ventilation ($\dot{V}_A$) as a result of a change in the pattern of breathing and not as a result of decreased respiratory drive.[25] The dominant finding of this pattern of breathing is a shortening of inspiratory time (T_I) and T_E.[25] These combined changes lead to a marked increase in respiratory frequency and decrease in tidal volume (V_T)—rapid shallow breathing. The decrease in V_T results in increased dead-space-to-tidal-volume ratio (V_D/V_T) or dead space ventilation that is not compensated by the increase in minute ventilation. In a study of seventeen patients with COPD requiring mechanical ventilation, Tobin et al[25] reported that the combined changes in V_T and respiratory frequency accounted for 81% of increase in partial pressure of arterial carbon dioxide (Pa_{CO_2}) in the ten patients who developed respiratory distress when disconnected from mechanical ventilation. Whether rapid shallow breathing is an adaptive response to the mechanical constraints of acute dynamic hyperinflation that minimizes dyspnea and lessens the risk of respiratory muscle fatigue remains to be determined.

In some patients with COPD, hypercapnia can be worsened by the administration of supplemental oxygen.[45] This risk is significant when the inspired oxygen concentration exceeds 30%. Mechanisms that may contribute to CO_2 retention include a decrease in hypoxic ventilatory response consequent to the administration of oxygen; an increase in dead space consequent to release of hypoxic vasoconstriction and, thus, worsening of $\dot{V}_A/\dot{Q}$ relationships; and the Haldane effect (for any given amount of CO_2 bound to hemoglobin, Pa_{CO_2} is considerably higher in the presence of a high versus a low oxygen saturation).[16]

VENTILATOR ASSISTANCE

The many pathophysiologic defects considered above have direct bearing to the judicious administration of mechanical assistance in patients with COPD in respiratory failure. Physicians considering the need to implement mechanical ventilation in these patients have to answer five basic questions:

1. When should mechanical ventilation be started, and which goals should be pursued?
2. How should mechanical ventilation be delivered—noninvasive versus invasive?
3. What setting and mode of mechanical ventilation should be used?
4. When—and how—should mechanical ventilation be discontinued?
5. What can be done when weaning is difficult or impossible?

Ventilator Assistance: Indications

Most patients with mild exacerbations of COPD (70% to 90% of those hospitalized for an exacerbations)[5,45,46] can be cared for with oxygen and pharmacotherapy alone. The remaining 10% to 30% require ventilator assistance.[5,45–47]

INDICATIONS FOR NONINVASIVE POSITIVE-PRESSURE VENTILATION

Noninvasive positive-pressure ventilation (NIPPV) has become the first line intervention for most patients with COPD in acute respiratory failure (Table 31-1).[5] NIPPV decreases the need for endotracheal intubation and the rate of ventilator-related complications, intensive care unit (ICU) admissions, and in-hospital and 1-year mortality.[47–49]

In most studies, the rate of failure with NIPPV is inversely related to the severity of respiratory acidosis. When pH is 7.30 to 7.34 on admission, the rate of NIPPV failure is 10% to 20%;[47,50] when pH is 7.25 to 7.30, NIPPV failure is 30% to 40%;[51,52] and when pH is less than 7.25, failure is 50% to 60%.[53,54] These rates, however, have to be interpreted with caution. In some series, NIPPV failure in patients with very low pH (7.13 to 7.20) on admission was only 14% to 35%.[55–57]

TABLE 31-1: INDICATIONS AND CONTRAINDICATIONS FOR NONINVASIVE VENTILATION IN EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Indications
Clinical observations
Moderate to severe dyspnea
Tachypnea
Accessory muscle use, abdominal paradox
Impaired gas exchange
Acute or acute-on-chronic hypercapnic respiratory failure (Pa_{CO_2} > 45 mm Hg, pH < 7.35)
Hypoxemia ($Pa_{O_2}/FI_{O_2} \leq 200$)[a]
Contraindications
Absolute
Bradypnea, respiratory arrest, immediate need for intubation
Life-threatening hypoxemia
Unable to fit mask
Upper airway obstruction
Undrained pneumothorax
Vomiting/severe upper gastrointestinal bleeding
Relative
Agitated, uncooperative
Severe hypercapnic encephalopathy (Glasgow Coma Scale score < 10)
Inability to protect the airway
Impaired swallowing or cough
Excessive secretions
Recent upper airway or upper gastrointestinal surgery
Multiorgan failure
Medically unstable
Uncontrolled cardiac ischemia or arrhythmia
Hypotensive shock

Abbreviations: FI_{O_2}, fractional inspired oxygen concentration; Pa_{CO_2}, partial pressure of arterial carbon dioxide; Pa_{O_2} partial pressure of arterial oxygen.

[a]Noninvasive ventilation should be used with caution in exacerbations of chronic obstructive pulmonary disease (COPD) accompanied with hypoxemia.

Failure with NIPPV usually occurs in the first hours of ventilator support.[58] Mask intolerance, uncontrollable leaks, and lack of improvement in gas exchange are the most common causes of failure.[59,60] Early improvement should not lull the physician into a false sense of security: Approximately 20% of initial responders (first 48 hours) experience a second episode of acute respiratory failure.[60] Late-onset deterioration is more likely in patients with worse clinical condition before admission, and more complications at admission.[60] Patients who experience late failure have a poor inhospital prognosis, particularly if they are not promptly intubated.[60]

INDICATIONS FOR NONINVASIVE NEGATIVE PRESSURE VENTILATION

Negative pressure ventilation (iron lung ventilation) has been successfully used in patients with COPD and severe respiratory acidosis (pH < 7.25).[61–63] (See Chapter 16.)

INDICATIONS FOR INVASIVE VENTILATION

NIPPV and negative pressure ventilation do not protect the upper airway in patients who are gasping, have respiratory arrest or have lost consciousness.[47] NIPPV and negative pressure ventilation are also unsafe and poorly tolerated in patients requiring high levels of inspiratory airway pressure (>25 to 30 cm H_2O) and inspired oxygen (FI_{O_2} > 0.60). These patients, as well as those who are hemodynamicaly unstable despite fluid resuscitation and vasopressors, and those who are agitated, uncooperative, or who fail noninvasive ventilation, require endotracheal intubation and invasive ventilation (see Table 31-1). Despite earlier concerns, severe hypercapnic encephalopathy (Glasgow Coma Scale score ≤8 to 10) should not—a priori—be considered an absolute contraindication to NIPPV.[55,57,64,65] If NIPPV is used in encephalopathic patients, opinions vary as to the advisability of inserting a nasogastric tube to decrease the risk of aspiration of gastric contents.[55,57,64]

Goals of Ventilator Assistance

The primary goals of ventilator assistance are to decrease inspiratory effort and respiratory distress, to minimize dynamic hyperinflation and PEEPi, to lessen respiratory acidosis, and to improve hypoxemia.

Most patients with COPD in respiratory failure are dyspneic and have clinical signs of increased work of breathing: nasal flaring, vigorous activity of the sternomastoid muscles, tracheal tug, recession of the suprasternal, supraclavicular and intercostal spaces, paradoxical motion of the abdomen, and pulsus paradoxus.[66] In these patients, invasive[67,68] and noninvasive[69–71] ventilation can decrease inspiratory effort and respiratory distress (Fig. 31-5).

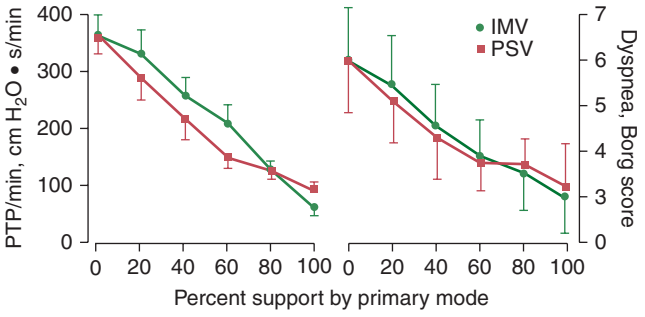

FIGURE 31-5 Inspiratory effort, quantitated as by esophageal pressure-time product per minute (*PTP/min*), and dyspnea, quantitated by Borg score in eleven ventilator-dependent patients with chronic obstructive pulmonary disease (COPD) while receiving pressure-support ventilation (*PSV*) and intermittent mandatory ventilation (*IMV*). *Left panel:* PTP decreased as the level of PSV or IMV was increased. At proportional levels of ventilatory assistance, PTP/min was not different during PSV and IMV ($p < 0.0005$ in both instances). *Right panel:* Dyspnea decreased with increasing levels of PSV or IMV ($p < 0.05$ in both instances). Bars represent ± standard error (SE). (Modified, with permission, from Leung et al.[67])

Mechanical ventilation can both worsen or improve dynamic hyperinflation and PEEPi.[15] Dynamic hyperinflation and PEEPi should be suspected in any patient with persistent expiratory flow (see Fig. 31-3) at end-exhalation.[15] The magnitude of end-expiratory flow, however, bears little relation to the magnitude of PEEPi.[30]

Mechanical ventilation improves hypercapnia by decreasing CO_2 production and, more importantly, by increasing $\dot{V}_A$. Vigorous increases in minute ventilation should be avoided, because of risk of iatrogenic dynamic hyperinflation. When dynamic hyperinflation is a concern, and provided that intracranial hypertension and overt hemodynamic instability do not exist, acceptance of acidemia (pH > 7.2) may be reasonable.[72]

In addition to worsening dynamic hyperinflation, overzealous ventilation can cause life-threatening alkalosis.[66] Severe alkalosis can cause coronary artery spasm, central nervous system hypoperfusion, myoclonus, asterixis, and seizures. Other effects of alkalosis include increase in hemoglobin affinity for oxygen, and, in the presence of increased shunt, a possible worsening of the $\dot{V}_A/\dot{Q}$ relationship (secondary to a decrease in hypoxic pulmonary vasoconstriction).[66] Excessive ventilation, over time, causes bicarbonate wasting by the kidney. In patients who retain CO_2 when clinically stable, this renal wasting of bicarbonate will increase ventilatory demands during weaning.

Choice of Ventilator Mode

A wide variety of ventilator modes are used in COPD. These include pressure-support ventilation (PSV), assist-control ventilation (ACV) that can be either volume-cycled or pressure-cycled (PCV), intermittent mandatory ventilation, and, more recently, proportional-assist ventilation and neurally adjusted ventilatory assist. Each of these modes is covered in detail in other chapters.

It is unknown whether one ventilator mode is superior to another in patients with COPD. I summarize here my own preferences, and the physiologic rationale behind my choices. In patients requiring NIPPV, I usually use PSV[5,73] based on two considerations. First, unlike volume-cycled modes (ACV, intermittent mandatory ventilation), PSV allows breath-by-breath titration of support. The hope is to improve patient comfort and thus achieve greater success with NIPPV. Second, PSV is equally as effective as volume-cycled modes in decreasing inspiratory effort (see Fig. 31-5). I add a moderate amount of external PEEP to counterbalance PEEPi—a combination that lowers inspiratory work more than the use of PSV or PEEP alone.[74,75] Persistent respiratory distress despite high levels of support can result from expiratory muscle recruitment.[76] This recruitment can be caused by inadequate "cycling-off" criteria of PSV: In patients with COPD the decay in inspiratory flow during PSV is less steep than in patients with normal respiratory mechanics.[76,77] When expiratory muscle recruitment does occur an increase in the threshold of peak

inspiratory flow to cycle off PSV can improve patient–ventilator interaction.[77,78]

Persistent respiratory distress despite high levels of support can result from excessive load on the respiratory muscles. In this situation, an increase in inspiratory pressurization rate—the time needed to reach the target inspiratory pressure—can decrease inspiratory effort.[79] Unfortunately, increases in pressurization rate during NIPPV are associated with increased air leaks and decreases a patient's tolerance of NIPPV.[79] When respiratory distress persists despite high levels of support, it may be more prudent to intubate a patient.

In intubated patients, I mostly use ACV[80] and, occasionally, PCV. I prefer ACV and PCV over PSV in intubated patients because these patients commonly receive sedation. Sedation can decrease respiratory motor output and thus promote alveolar hypoventilation. When using ACV I usually set the inspiratory flow waveform in the square pattern to facilitate monitoring of mechanics. When intubated patients with COPD display a high drive, I may use PCV. With this mode, patients have more control over the peak flow than with ACV. I avoid controlled mechanical ventilation because it is associated with the early development of respiratory muscle atrophy and damage.[81,82]

Proportional-assist ventilation and neurally adjusted ventilatory assist are two novel modes, but it is not known whether they will prove superior to traditional ventilator modes.

Intrinsic and External Positive End-Expiratory Pressure

The most valuable approach to reduce or eliminate PEEPi is to diminish minute ventilation,[30] even if this means development of alveolar hypoventilation—permissive hypercapnia.[83] In patients with PEEPi ventilated with volume-cycled modes, clinicians often increase inspiratory flow to decrease T_I. This is done hoping to prolong T_E. Increases in inspiratory flow, however, commonly lead to an increase in respiratory rate[84,85] and the anticipated reduction in T_E could increase PEEPi. Laghi et al[85] studied this phenomenon in ten patients with COPD while they were receiving ACV with a backup rate of 1 breath/min. As expected, an increase in flow from 30 to 90 L/min increased the respiratory rate from 16 ± 1 to 21 ± 2 breaths/min. Despite the rise in rate, PEEPi decreased from 7 ± 1 to 6 ± 1 cm H_2O. The decrease in PEEPi was the result of a paradoxical increase in T_E, which permitted extra time for lung deflation. The investigators reasoned that the shortened T_I secondary to the increase inspiratory flow combined with time-constant inhomogeneity of COPD caused overinflation of some lung units to persist into neural exhalation. Continued inflation during neural exhalation could stimulate the vagus, which prolongs expiratory time.[84,85]

In patients with COPD and flow-limited physiology, low levels of external PEEP can maintain a patent (or nearly patent) channel between the central airway and the alveolar compartment at the start of inhalation. In these patients, application of low-level external PEEP reduces the effort to trigger the ventilator,[14,86] improves patient–ventilator interaction,[14] and reduces the effort to start inspiratory flow during weaning from mechanical ventilation.[87] External PEEP of 5 cm H_2O or less often suffices to reach these goals.[88] In patients with PEEPi, intravascular fluid expansion can increase blood pressure and cardiac output.[21] Prompt disconnection from the ventilator can resolve hypotension secondary to PEEPi. If that is the case, mechanical ventilation should be restarted with lower minute ventilation.

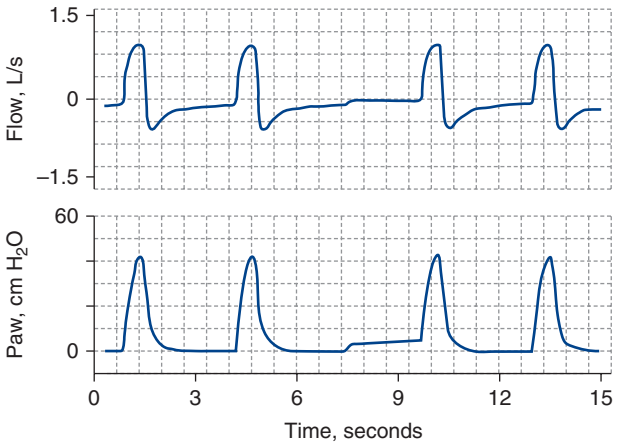

FIGURE 31-6 Measurement of static intrinsic positive end-expiratory pressure (PEEPi) by single-breath end-expiratory airway occlusion in a patient with chronic obstructive pulmonary disease (COPD) during controlled mechanical ventilation. End-expiratory airway occlusion is carried out at the time when the third ventilator breath should have taken place. The end of occlusion to preocclusion difference in airway pressure (Paw) is the static PEEPi. In this example, static PEEPi is 6 cm H_2O.

The selection of external PEEP should be guided by measurement of static PEEPi (Fig. 31-6).[15] When PEEPi is present, the rise in airway pressure during the occlusion maneuver should be maintained until a plateau is reached, usually in less than 4 seconds.[18] The delayed plateau in the airway pressure signal is caused by stress adaptation phenomena and by time-constant inequalities.[18] During controlled mechanical ventilation, application of a value of external PEEP at or above 50% of the static PEEPi improved ventilation–perfusion matching (Fig. 31-7)[89] and oxygenation without causing a decrease in cardiac output.[90]

When measuring static PEEPi with the occlusion method, it is impossible to detect any increased alveolar pressure distal to airways that are completely occluded during exhalation.[91] In other words, the occlusion method estimates only the end-expiratory alveolar pressure that is measurable in the upper airway during tidal breathing.[30] Consequently, some experts advocate the measurement of end-inspiratory plateau airway pressure as external PEEP is titrated as a more sensitive tool to monitor the potential perils of dynamic hyperinflation.[15,30,91]

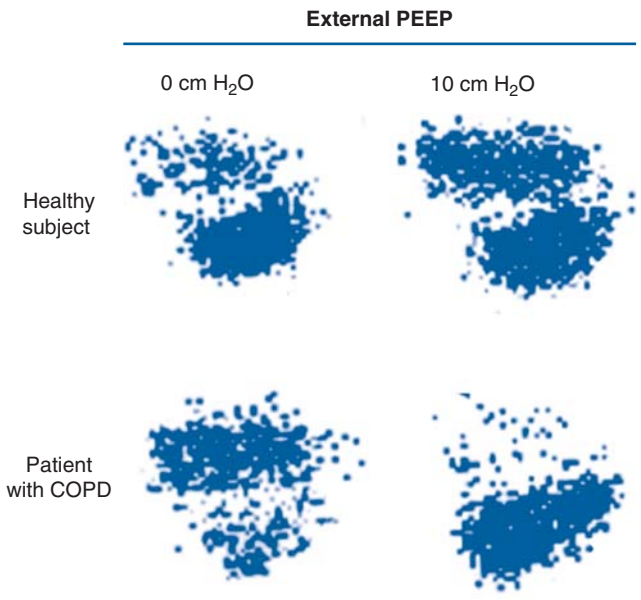

FIGURE 31-7 Ventilation scans (radioactive krypton) in a healthy subject (*upper panels*) and in a patient with chronic obstructive pulmonary disease (*COPD*) (*lower panels*) resting in the left lateral decubitus position while receiving positive end-expiratory pressure (*PEEP*) of 0 cm H_2O (*left panels*) and 10 cm H_2O (*right panels*). At a PEEP of 0 cm H_2O, ventilation was distributed predominantly to the dependent regions in the healthy subject (*left upper panel*) and in the nondependent regions in the patient (*left lower panel*). PEEP 10 cm H_2O restored ventilation to the dependent regions in the patient probably because it prevented collapse of the dependent airways. (Modified, with permission, from Shim et al.[89])

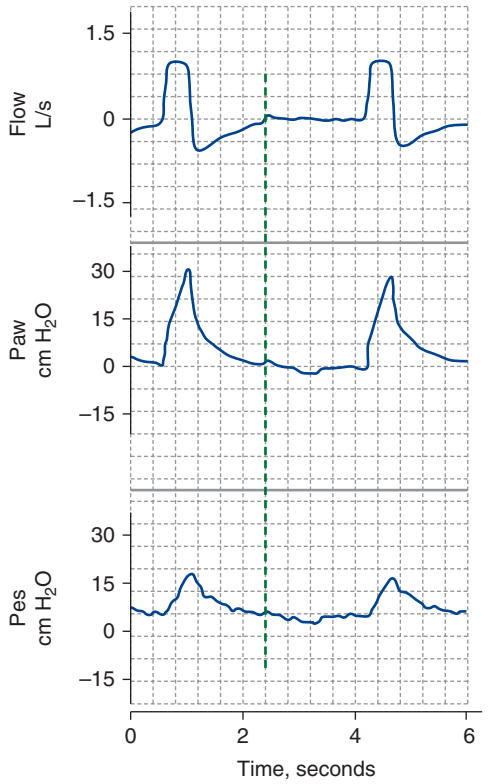

FIGURE 31-8 Inspiratory effort during end-expiratory airway occlusion maneuver. Recordings of flow (*inspiration upward*), airway pressure (*Paw*) and esophageal pressure (*Pes*) in a patient with chronic obstructive pulmonary disease (COPD) in respiratory failure receiving mechanical ventilation. Shortly after the start of airway occlusion (*green vertical line*), the patient exhibits an inspiratory effort (negative deflection in the Paw and Pes signals). Measurement of static intrinsic positive end-expiratory pressure during active inhalation is inaccurate.

The occlusion method is impractical and potentially inaccurate in patients who trigger most breaths during assisted ventilation (Fig. 31-8).[15] These patients can be instrumented with an esophageal balloon catheter system to measure the deflection in esophageal pressure from the beginning of inspiratory effort to the onset of inspiratory flow (counterbalance method) (Fig. 31-9).[15] This deflection is the so-called dynamic PEEPi. The counterbalance method is based on several assumptions.[27] First, the end-expiratory alveolar pressure represents the elastic recoil pressure of the relaxed respiratory system. Second, the change in esophageal pressure from the beginning of inspiratory effort to the onset of inspiratory flow reflects the inspiratory muscle pressure required to counterbalance the elastic recoil of the respiratory system at end-exhalation. Because of time constant inequalities between lung units, the end-expiratory elastic recoil may not be distributed homogeneously.[92] It follows that PEEPi measured with the counterbalance method represents the pressure required to start inspiratory flow in lung units with a short time constant and fast exhalation (minimum PEEPi). This characteristic of dynamic PEEPi raises several points. First, dynamic PEEPi underestimates the magnitude of static PEEPi, at times by as much as 90%.[93] Second, the true clinical impact of PEEPi can be misjudged if only dynamic PEEPi is considered.[15] Third, the difference between dynamic and static PEEPi—often reported as the ratio of dynamic to static PEEPi or "inequality index"[15]—can estimate the severity of time constant inequalities of the respiratory system.[93] In a study of paralyzed, ventilated patients, Maltais et al[93] reported a lower inequality index in patients with airway obstruction, 0.36 ± 0.06, than in patients without airway obstruction, 0.87 ± 0.05.

A final assumption with the counterbalance method is that exhalation is passive. If expiratory muscle contraction is present at end-exhalation, the decrease in esophageal pressure at the start of inhalation will reflect, in part, the relaxation of the expiratory muscles rather than inspiratory muscle contraction alone.[27] Several techniques to correct for this confounder have been proposed[74,94] with various success.[95,96] An additional confounding factor when measuring dynamic PEEPi is breath-to-breath variability in the duration of neural T_E.[94] This phenomenon causes a variable duration of lung emptying, which, in turn, can cause large fluctuations of PEEPi, even over short periods of time.[67,94] Systematic investigations of the effect of this additional confounder on the determination of dynamic PEEPi are not available.

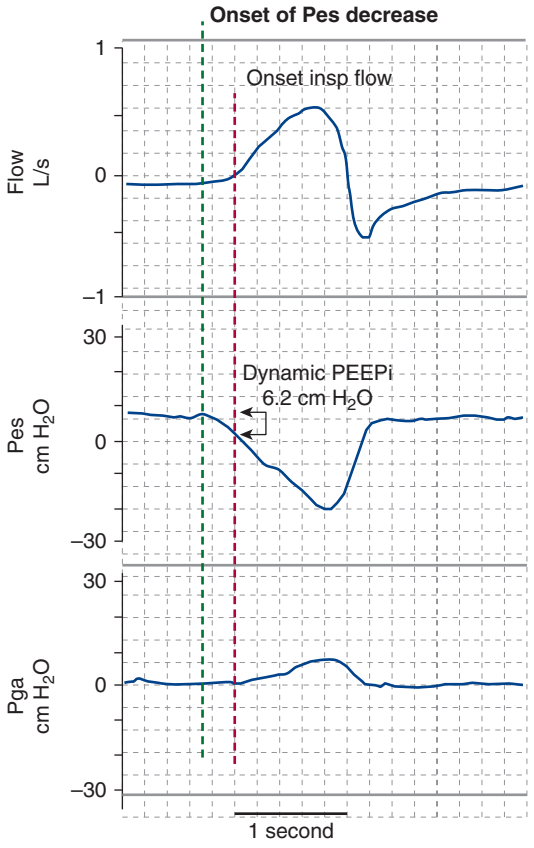

FIGURE 31-9 Recordings of flow (*inspiration upward*), esophageal pressure (*Pes*) and gastric pressure (*Pga*) illustrating the counterbalance method for measuring dynamic intrinsic positive end-expiratory pressure (*PEEPi*) during spontaneous respiration. The *green vertical line* indicates the onset of inspiratory effort and the *purple vertical line* indicates the onset of inspiratory flow. Dynamic PEEPi is measured as the negative deflection in Pes from the start of inspiratory effort to the onset of inspiratory flow. The Pga signal is flat during exhalation suggesting absent expiratory muscle recruitment.

In summary, the major goal of using external PEEP in patients with airflow obstruction who are triggering the ventilator is to decrease workload[14] and dyspnea[87] and to improve patient–ventilator synchrony.[67] Titration of external PEEP should continue until dyspnea has improved, respiratory motor output has decreased,[97] or until peak and plateau airway pressure demonstrate a sizeable increase (volume-cycled ventilation) (Fig. 31-10)[98] or tidal volume starts to decrease (PCV).[15]

Susceptibility to Ventilator Complications

Patients with COPD are particularly susceptible to ventilator complications. This susceptibility results from several mechanisms, including the pathophysiologic derangements that contribute to the need for mechanical ventilation in COPD (dynamic hyperinflation), side effects of medications, and complications that arise from the underlying lung disease (tissue destruction of the emphysematous lung).

DYSSYNCHRONIES

The complex abnormalities of lung mechanics in patients with COPD and respiratory failure make them particularly susceptible to develop patient–ventilator dyssynchrony. Dyssynchronies occur when there is inadequate matching between patient demand and ventilator support in terms of timing, volume, and flow. Dyssynchronies can occur at the onset of neural inhalation (ineffective trigger, trigger delay), during neural inhalation (double triggering, inadequate pressurization, inadequate flow or volume), at the offset of neural inhalation (premature or prolonged assist), and during neural exhalation (autotriggering) (Fig. 31-11).[16]

Ineffective triggering attempts occur in a quarter to a third of inspiratory efforts of patients with COPD receiving high levels of PSV or ACV (Fig. 31-12).[67] The number of ineffective triggering attempts increases in direct proportion to the level of ventilator assistance and result from premature inspiratory efforts that are insufficient to overcome the increased elastic recoil associated with dynamic hyperinflation.[67] Because there is no lung inflation during a failed triggering attempt, mechanical exhalation continues for a longer time and end-expiratory volume continues to fall until triggering becomes successful.

Trigger delays can be caused by factors intrinsic to the ventilator and factors intrinsic to the patient. Ventilator factors include the algorithms that control cycling and the electrical and mechanical processes in the machine.[99] Patients' factors include respiratory mechanics, respiratory drive, and inspiratory pressure output.[67,100–102]

A mismatch of the timing between a relatively long neural inhalation and a relatively short mechanical inflation (double triggering) (Fig. 31-13), or as a mismatch between patient flow demand and the flow delivered by the ventilator, can produce dyssynchronies during neural inhalation. Flow mismatch can be either in excess or in defect of the patient's demand. Excessive flow delivered by the ventilator will always raise peak airway pressure. If the patient is receiving NIPPV, an increase in peak airway pressure can cause air leaks around the mask. These leaks are uncomfortable and they diminish the patient's acceptance of NIPPV.[79] In addition, air leaks can decrease alveolar ventilation and worsen patient–ventilation interaction.

When the ventilator's inspiratory flow is insufficient for the patient's flow demands, two types of dyssynchrony can occur. First, the ventilator unloads the respiratory muscles unsatisfactorily or it may even impose an external elastic load on the respiratory muscles.[103,104] Second, the time required to deliver a given V_T will exceed the duration of neural T_I. In this case, mechanical inflation will continue during neural T_E. The sense of being unable to empty the lungs may cause patients to activate the expiratory muscles. This uncomfortable activation will cause a positive spike in the airway pressure signal at end-inhalation.

During ACV or PCV, when a patient's neural T_I is short, ventilator inflation may continue into neural exhalation and thus decrease the time available for lung emptying. This phenomenon increases the likelihood for dynamic

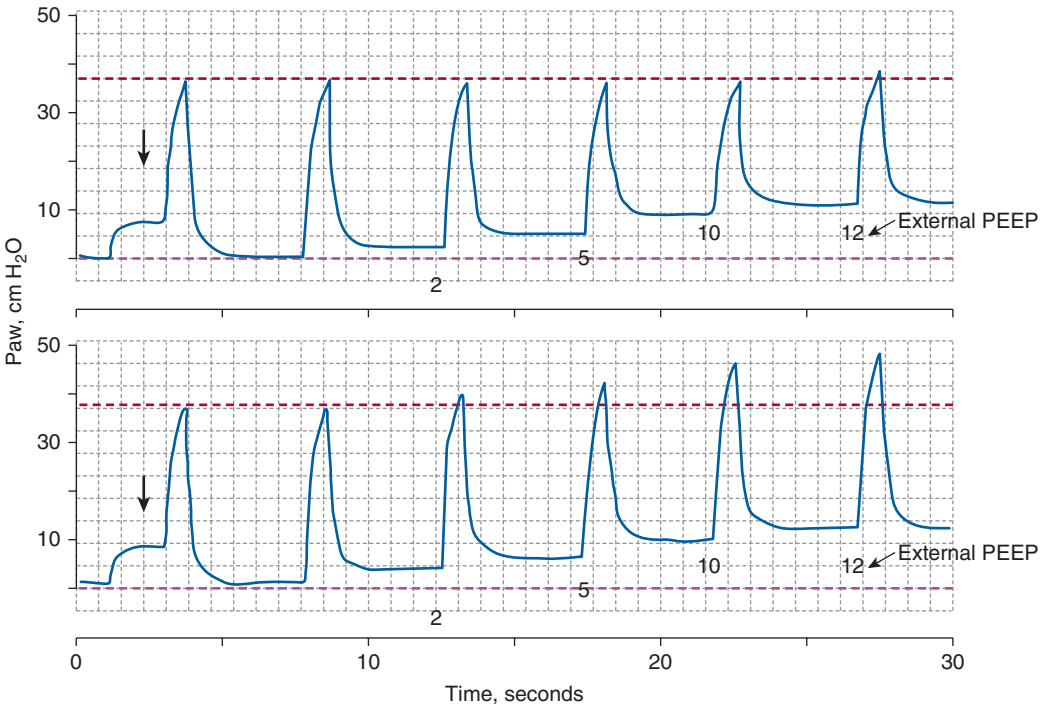

FIGURE 31-10 Schematic of airway pressure (*Paw*) versus time during controlled mechanical ventilation as external positive end-expiratory pressure (PEEP) is increased from 0 to 12 cm H_2O in a patient with expiratory flow limitation (*upper panel*) and in a patient without expiratory flow limitation (*lower panel*). In both patients, static intrinsic PEEP (PEEPi), determined by the end-expiratory airway occlusion technique (↓), is 10 cm H_2O. In the presence of expiratory flow limitation (*upper panel*), peak airway pressure increases only when external PEEP is 12 cm H_2O (*dotted red line*). In the absence of expiratory flow limitation (such as in patients with asthma; *lower panel*), application of external PEEP causes a proportional increase in peak airway pressure. The qualitative responses to external PEEP, seen with peak airway pressure, are expected to occur also with plateau pressure.

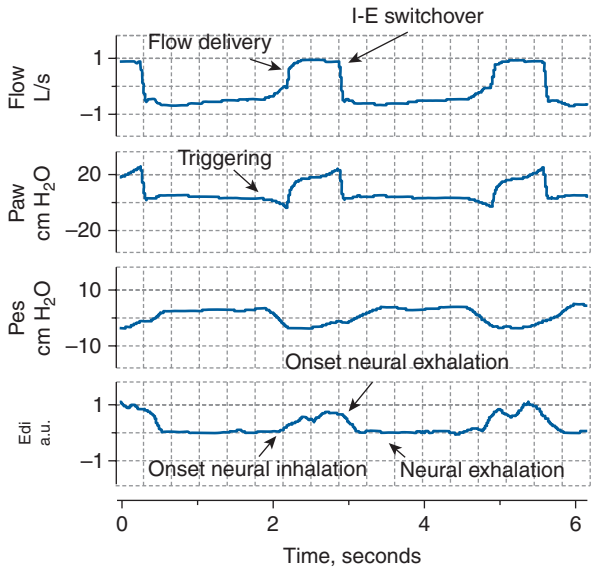

FIGURE 31-11 Points at which patient–ventilator dyssynchrony may arise: onset of neural inhalation (point of triggering, cycling-on function), during neural inhalation (inspiratory flow delivery, posttrigger inflation), onset of neural exhalation (switchover between inspiration and expiration, cycling-off function), and during neural exhalation (autocycling). *a.u.*, arbitrary units; *Edi*, electrical activity of the diaphragm; *Paw*, airway pressure; *Pes*, esophageal pressure.

hyperinflation (with attendant ineffective triggering) and activation of the expiratory muscles.

During PSV, dyssynchronies at the offset of neural inhalation are caused by the algorithm for "cycling-off" of mechanical inflation (see section Choice of Ventilator Mode above).[76,77,105] Air leaks between the mask and the patient's face and increased dead space make the synchronization between the offset of neural inhalation and the offset of mechanical inflation particularly tenuous when delivering PSV with NIPPV.[106,107] Strategies designed to improve synchronization include the use of a time-cycled expiratory trigger[107] and neurally adjusted ventilatory assist.[101,102,108]

Occasionally a ventilator delivers an assisted breath during neural exaltation. This phenomenon, known as *autotriggering* or *autocycling*, can cause severe respiratory alkalosis.[109] Autotriggering is relatively common when there is water in the ventilator circuit or when air leaks are present.[99,110] These leaks can occur around the endotracheal tube cuff,[111] around NIPPV masks,[99,112] and from chest tubes.[109] Oscillation of gas in the airways caused by cardiac contractions can also result in autotriggering (Fig. 31-14). Elimination of water from the ventilator circuit,[110] reduction of inspiratory trigger sensitivity, and minimization of leaks can reduce autotriggering.[99,109] An additional cause of autotriggering occurs when a stiff nasogastric tube placed on suction is erroneously passed into the airway rather than into the esophagus.[113]

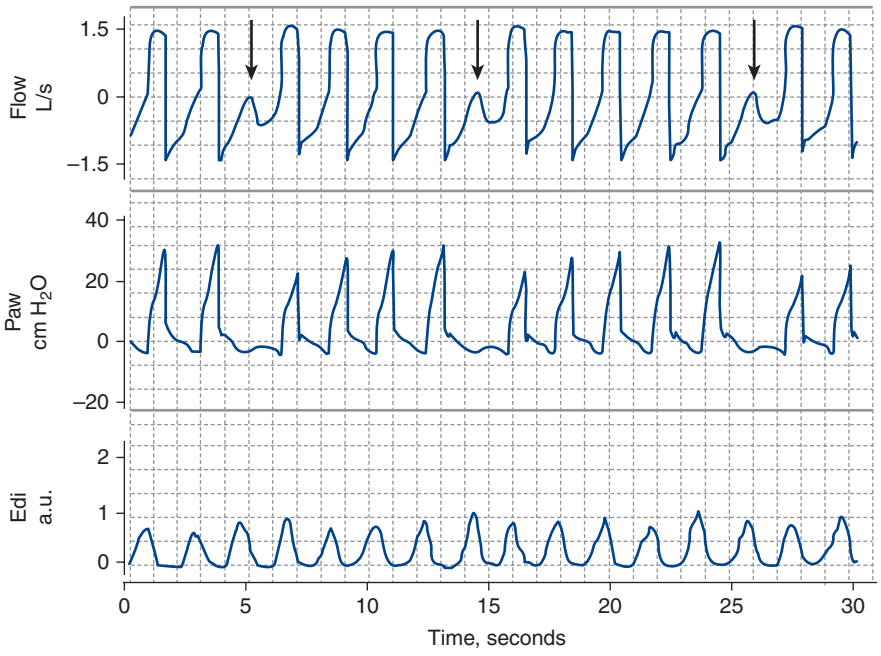

FIGURE 31-12 Failure to trigger the ventilator. Flow, airway pressure (*Paw*) and electrical activity of the diaphragm (*Edi*) in a patient with COPD who is receiving assist-control ventilation. Contractions of the inspiratory muscles during the failed triggering attempts (↓) cause brief deceleration of expiratory flow and decreases in Paw. The brief decelerations in flow are followed by brief accelerations of expiratory flow that coincide with the termination of the unsuccessful inspiratory effort. Of note, the peak airway pressure increases following each episode of failure to trigger the ventilator. This finding is caused by progressive air trapping. *a.u.*, arbitrary units.

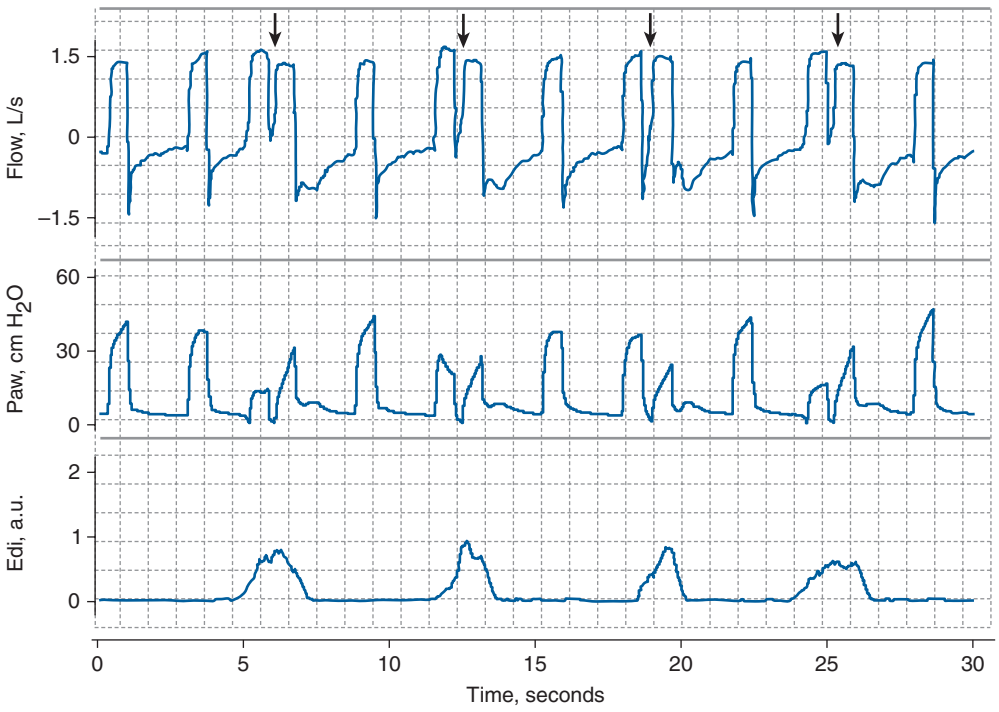

FIGURE 31-13 Double triggering caused by long duration of inspiratory effort. Four incidents of double triggering, each indicated by an arrowhead (↓). Flow, airway pressure (*Paw*) and electrical activity of the diaphragm (*Edi*) in a patient with chronic obstructive pulmonary disease (COPD) and pneumonia who was receiving assist-control ventilation. The patient generates only four neural inhalations (positive deflection in the Edi signal). The duration of each neural inhalation was substantially longer than the duration of mechanical inflation. This mismatch is responsible for double triggering. *a.u.*, arbitrary units.

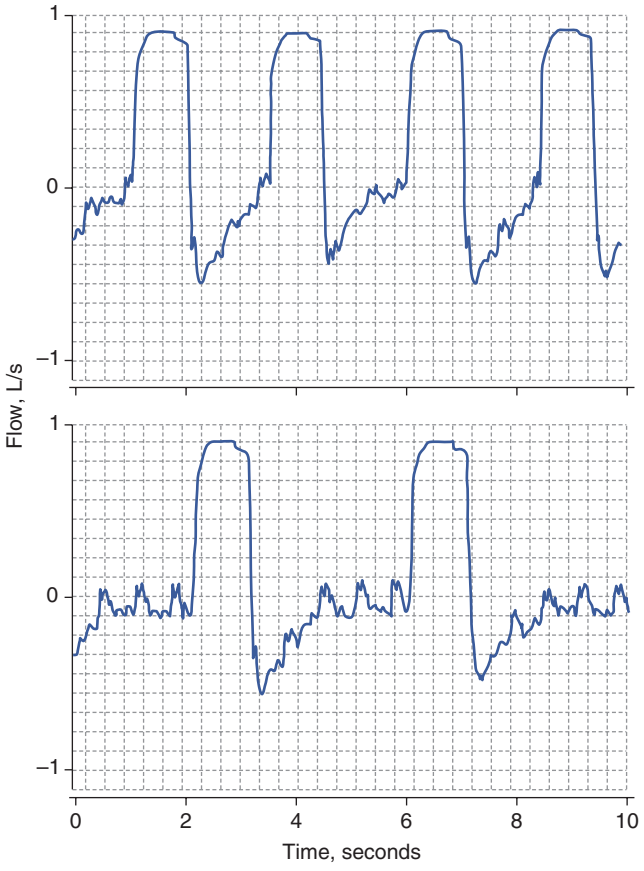

FIGURE 31-14 Autotriggering caused by cardiac oscillations. Recording of flow (*inspiration upward*) in a patient with chronic obstructive pulmonary disease (COPD) and aortic insufficiency. The patient was maintained on assist-control ventilation with a rate of 15 breaths/min and flow-triggering. *Upper panel:* The triggering sensitivity was set at 1 L/min. Despite the absence of clinically detectable inspiratory efforts, the ventilator rate was 24 breaths/min. *Lower panel:* When the triggering sensitivity was changed to 4 L/min, the ventilator rate decreased to 15 breaths/min, and large cardiac oscillations could be appreciated on the flow signal.

VENTILATOR-INDUCED HYPERINFLATION

In patients with COPD, mechanical ventilation itself increases the risk of dynamic hyperinflation through several mechanisms. First, ventilator settings (excessive minute ventilation, V_T, short time available for exhalation) can be unsuitable for the respiratory system resistance, elastance, and flow limitation of a given patient.[15] Second, the ventilator's circuit increases flow resistance. This increase in (external) resistance is caused by the combination of resistance of the endotracheal tube (particularly if the tube has concretions or is partially bent),[114] ventilator tubing, exhalation valves, and external PEEP.[15] Even in an intubated patient with healthy lungs, total expiratory resistance (across lungs, endotracheal tube, and exhalation valves) can exceed 10 cm H_2O/L/s (normal: <4 cm H_2O/L/s), enough to cause measurable PEEPi when the minute ventilation exceeds 20 L/min.[98]

VENTILATOR-ASSOCIATED PNEUMONIA

Ventilator-associated pneumonia is a common and potentially lethal complication of invasive ventilation. Factors that directly contribute the development of pneumonia include the presence of the endotracheal tube, contamination of the ventilator circuit and respiratory-therapy equipment with bacteria, ineffective cough, need of sedation, and development of acute sinusitis (see Chapter 46).

STEROID MYOPATHY

Most patients with exacerbations of COPD receive corticosteroids.[115,116] Administration of corticosteroids—with or without concomitant use of muscle relaxants—can trigger development of an acute myopathy characterized by loss of myosin heavy chains within muscle fibers.[28] Occasionally, corticosteroids cause acute rhabdomyolysis or myonecrosis.[28] In a prospective study of twenty-six patients with COPD exacerbation requiring invasive ventilation, Amaya-Villar et al[117] reported development of myopathy in nine patients (35%). Severity of illness (admission Acute Physiology and Chronic Health Evaluation [APACHE] II score), occurrence of sepsis and total dose of corticosteroids were higher in patients who develop myopathy than in those who did not develop it. Myopathy was associated with an increase in the duration of ventilation and lengths of ICU and hospital stay. An association between corticosteroid administration and development of myopathy in the ICU[118] or between myopathy and duration of mechanical ventilation[119] has been reported by other investigators.

In patients with steroid myopathy, acute weakness is likely caused by impaired muscle membrane excitability.[120] In contrast, prolonged weakness is more likely caused by proteolysis of myosin filaments, reduced myosin transcription, and decreased expression of the sarcoendoplasmic reticulum calcium-adenosine triphosphatase (SERCA)-type pumps (key protein pumps for calcium kinetics during muscle relaxation following contraction, which scavenge calcium from the cytosol).[28]

Two recent observations raise questions on the negative impact of (short-term) administration of corticosteroids during mechanical ventilation. In a study conducted in rats, Maes et al[121] reported that a single high dose of methylprednisolone protected diaphragmatic muscle function from the deleterious effects of controlled mechanical ventilation. According to the investigators, the most likely mechanism for this protective effect was a corticosteroid-dependent inhibition of the calpain proteolytic system. The second investigation was conducted in 340 patients with severe acute respiratory distress syndrome.[122] Patients were randomly assigned to receive, for 48 hours, either the neuromuscular blocking agent cisatracurium besylate (178 patients) or placebo (162 patients); 42% of all patients received corticosteroids for sepsis. Early administration of cisatracurium besylate—with or without corticosteroids—improved adjusted 90-day survival and increased the time off the ventilator without increasing muscle weakness.

Weaning from Noninvasive Positive-Pressure Ventilation

Most investigators decrease NIPPV when respiratory distress and tachypnea have resolved and FI_{O_2} requirement is less than 0.40.[55] At that point, inspiratory and expiratory pressures are decreased by 2 to 3 cm H_2O each hour as tolerated. When gas exchange is adequate and patients are comfortable with inspiratory pressure of 10 to 12 cm H_2O and external PEEP of 3 to 5 cm H_2O, clinicians can temporarily discontinue NIPPV. Periods of unassisted breathing are maintained until patients develop some degree of respiratory deterioration (tachypnea, dyspnea, increased use of accessory muscles).[123] Ideally, NIPPV is interrupted for progressively longer periods until patients can sustain unassisted breathing indefinitely.[51,55,123] In patients with exacerbations of COPD with an initial pH of 7.13 to 7.29 and who respond successfully to NIPPV, the mean duration of ventilator assistance—plus periods of interruption—can range from 2 to 9 days.[55,57,59,123,124] Occasionally patients require nocturnal noninvasive ventilation.

Weaning from Invasive Ventilation

Chapter 58 discusses ventilator weaning. In brief, my personal approach is to screen for early weanability with use of the ratio of respiratory frequency to tidal volume (f/VT).[125,126] When the result predicts weaning success, I proceed to a T-tube trial, usually lasting no more than 30 minutes. If a patient tolerates this trial without undue distress, I proceed to extubation.

ADJUNCTIVE THERAPIES

Several adjunctive therapies are administered in ventilated patients with COPD. These include therapies aimed at improving airflow (bronchodilators, helium–oxygen mixtures), decreasing inflammation (corticosteroids), and controlling infections (antibiotics).

Improvement in Airflow: Helium–Oxygen

Gas mixtures of helium and oxygen have lower density and slightly higher viscosity than standard air–oxygen mixtures.[127] This lower density decreases the Reynolds number of helium–oxygen mixtures.[127] A smaller Reynolds number can decrease resistance to gas flow through several mechanisms.[127] First, it will make flow laminar over a larger number of (medium-to-large) airway generations, over a greater fraction of the respiratory cycle, and over higher flow rates.[127] Second, when gas enters a bifurcated airway, laminar flow results in a lower airway resistance than does turbulent flow.[127] Third, for a given rate of laminar flow, a lighter gas mixture (smaller Reynolds number) results in a shorter entrance length. Entrance length is the length of a tube (bronchial tube) required to reestablish laminar flow after gas enters a bifurcated airway. For the portion of a tube over which laminar flow is becoming established, resistance will be higher as compared with when laminar flow has already been established.[127]

Several investigators have assessed the possibility to use those mixtures in patients with COPD.[44,51,128–132] In stable patients with severe COPD, Hussain et al[128] reported that patients who exercised while breathing helium–oxygen experienced less inspiratory muscle load, dyspnea, and dynamic hyperinflation, and could exercise for longer than when breathing air–oxygen alone (Fig. 31-15).[128] In patients with COPD and respiratory failure, NIPPV plus helium–oxygen decreases work of breathing and dyspnea and improves CO_2 clearance more than NIPPV alone.[129,130]

Two prospective trials have been conducted to assess whether NIPPV plus helium–oxygen could reduce the intubation rate and improve the clinical outcome of patients with COPD in respiratory failure.[51,131] In 123 patients, Jolliet et al[131] used a mixture of 78% helium and 22% oxygen. Intubation rates and ICU length of stay were comparable. In 204 patients, Maggiore et al[51] used a 65% helium and 35% oxygen mixture and found no differences in arterial blood gases, dyspnea, duration of NIPPV, ICU and hospital length of stay, and 28-day mortality.

At least two mechanisms may have contributed to the these negative results.[51,131] First, the trials were underpowered because of lower-than-expected intubation rates in the control groups. Second, helium–oxygen can improve gas dynamics by promoting the transition of flow from turbulent to laminar and by decreasing the driving pressure in areas where flow remains turbulent.[132] Turbulent flow is more likely when the increased resistance to airflow is located in the central airways than in the peripheral airways. If the increased resistance was mainly located in the peripheral airways of the patients in these two trials,[51,131] it would have been impossible for helium–oxygen to improve clinical outcomes.

Improvement in Airflow: Bronchodilators

Chapter 63 discusses bronchodilator therapy. My personal approach in patients receiving either NIPPV or invasive ventilation is to administer short-acting bronchodilators (albuterol and ipratropium) with a metered-dose inhaler and spacer. Occasionally I use nebulizers in patients receiving NIPPV.[133]

Corticosteroids

Administration of systemic corticosteroids in patients with exacerbations of COPD reduces dyspnea, treatment failure, and hospital stay.[115] Systemic corticosteroids are also associated with improvement of forced expiratory volume in 1 second and arterial blood-gases during the early treatment phase (to 72 hours) and at the end of treatment

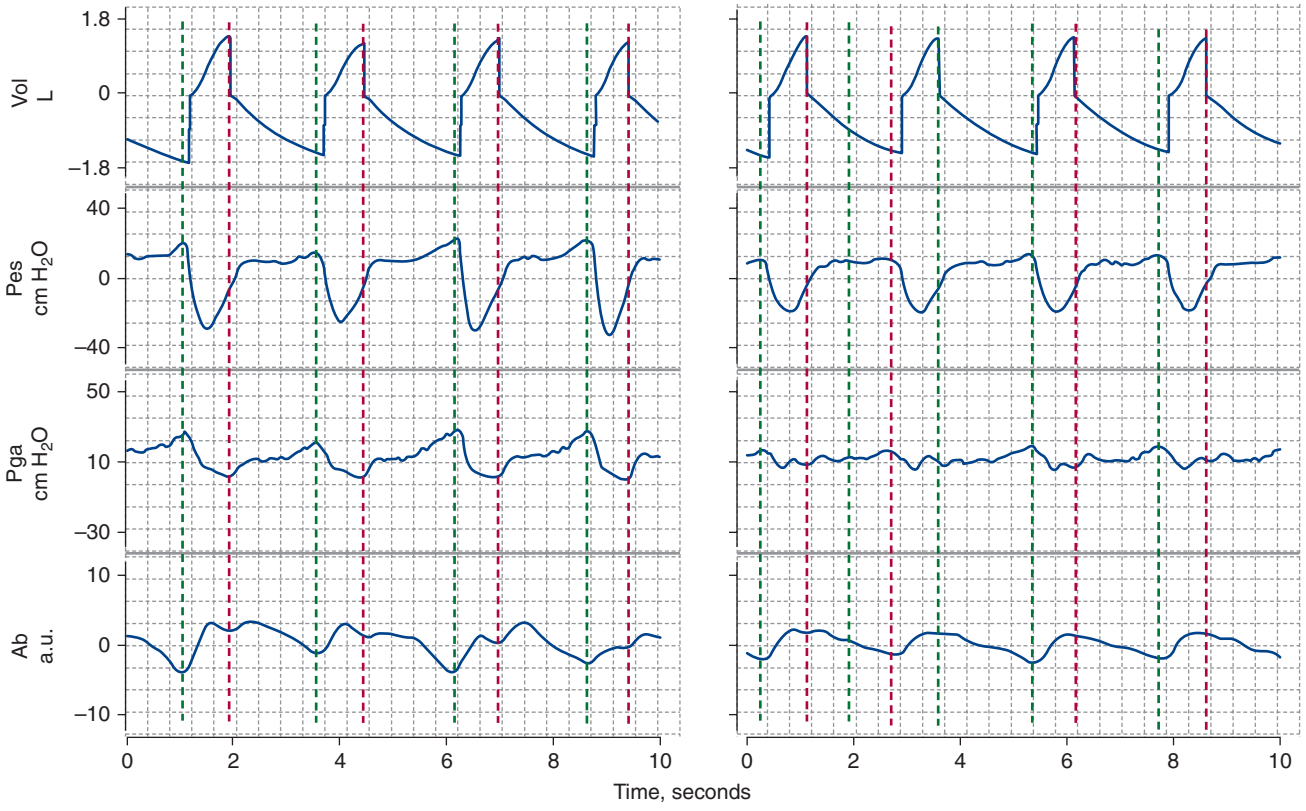

FIGURE 31-15 Helium–oxygen decreases inspiratory effort during exercise. Tracings of volume, esophageal (*Pes*) and gastric (*Pga*) pressures, and cross-sectional area of the abdomen (*Ab*) in a patient with severe chronic obstructive pulmonary disease (COPD) and severe hyperinflation during submaximal constant-load exercise test (cycle ergometer). The *green vertical lines* indicate the onset of inspiratory effort and the *red vertical lines* indicate the end of tidal inspiration. The patient exercised while breathing 30% oxygen (*left panel*) or a mixture of 70% helium plus 30% oxygen (*right panel*). Tidal volume was similar in the two conditions but tidal swings in Pes were decreased by almost half during helium–oxygen as contrasted with oxygen alone. In addition, expiratory muscle recruitment, reflected by positive deflection in the Pga signal and negative deflection in the Ab signal during exhalation, was less with helium–oxygen (*right panel*) than with oxygen alone (*left panel*). *a.u.*, arbitrary units. (Data from Hussain et al.[128])

(up to 15 days).[115] Systemic corticosteroids, however, predispose to hyperglycemia and do not decrease mortality.[115] Dose and duration of corticosteroid therapy continues to be debated.[115] In this regard, Lindenauer et al[116] compared the outcomes of nearly 80,000 exacerbations of COPD treated with low doses of corticosteroids administered orally (20 to 80 mg of prednisone) versus higher doses administered intravenously (120 to 800 mg prednisone equivalent). The risk of treatment failure, inpatient mortality, readmission for acute exacerbation of COPD was equivalent in the two groups. No benefit is derived by prolonging therapy beyond 2 weeks.[134] In patients with exacerbations of COPD, high-dose nebulized budesonide (1.5 to 2 mg every 6 hours) can be as effective as systemic corticosteroids, although much more expensive.[135]

Antibiotics

The use of antibiotics in the treatment of acute exacerbation of COPD is largely accepted.[136] In patients without pneumonia, inexpensive broad-spectrum antibiotics, such as ampicillin, doxycycline, and trimethoprim-sulfamethoxazole, are usually effective.[134] In a randomized, double-blind trial of 170 patients with an acute exacerbation of COPD requiring mechanical ventilation, trimethoprim-sulfamethoxazole was equivalent to a more expensive agent (ciprofloxacin).[136] In a recent review of eleven trials involving 917 patients, antibiotic administration in exacerbations of COPD was shown to reduce short-term mortality by 77% and the risk of treatment failure by 53%.[137]

Patients with COPD who have community-acquired pneumonia and who do not require ICU admission should be treated with a respiratory fluoroquinolone alone (levofloxacin, gemifloxacin, moxifloxacin) or with a β-lactam plus a macrolide.[138] Macrolides are attractive because they possess additional antiinflammatory and mucoregulatory properties.[139] Patients with COPD and pneumonia who require ICU admission should be treated with a β-lactam (cefotaxime, ceftriaxone, ampicillin-sulbactam) plus azithromycin or with a β-lactam plus a respiratory fluoroquinolone.[138]

Patients with recurrent exacerbations leading to frequent use of steroids and antibiotics are at increased risk of *Pseudomonas* pneumonia.[138] When these patients develop pneumonia, they should be treated with a β-lactam with

antipseudomonas and antipneumococcal properties (piperacillin-tazobactam, cefepime, imipenem or meropenem) plus ciprofloxacin or levofloxacin. An aminoglicoside plus azithromycin can be used as a alternative to ciprofloxacin or levofloxacin.[138] When community acquired methicillin-resistant *Staphylococcus aureus* is a consideration, vancomycin or linezolid should also be administered.[138]

Other Adjunctive Therapies

In patients with COPD and respiratory failure, mucolytics agents, respiratory stimulants, and methylxanthines are of uncertain benefit or no benefit or even harmful.[140,141] Chest physiotherapy is ineffective or even detrimental in patients with exacerbations of COPD requiring medical treatment alone or medical treatment plus invasive ventilation.[141] In patients treated with NIPPV, intrapulmonary percussive ventilation[56] and exhalation under positive-pressure (PEP mask)[142] may improve gas exchange, enhance removal of airway secretions and reduce duration of ventilator support and ICU length of stay.

Patients with COPD and acute respiratory failure often experience anxiety and agitation.[110] These symptoms can be caused by many factors including dyspnea, hypoxia, infection, fever, fear, and sleep deprivation. Identification and treatment of the underlying cause of anxiety does not always result in a satisfactory control of these symptoms. Anxiety and agitation can be sufficiently severe to interfere with the patient's adaptation to noninvasive or invasive ventilation. In these patients, the physician should consider the judicious use of sedatives.[110] The use of sedatives during NIPPV, however, is potentially dangerous and thus controversial.[110]

LONG-TERM OUTCOME FOLLOWING ACUTE RESPIRATORY FAILURE TREATED WITH MECHANICAL VENTILATION IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Patients with COPD who survive an episode of acute respiratory failure treated with NIPPV have significant morbidity and mortality following hospital discharge.[124,143] Chu et al[124] undertook a prospective study to assess the long-term outcome of 110 patients with COPD who survived an episode of acute respiratory failure treated with NIPPV. One year later, nearly half of the patients were dead, mostly because of respiratory failure. It is uncertain whether domiciliary nighttime NIPPV could improve the long-term outcome of these patients.[144]

Long-term use of nocturnal NIPPV has also been proposed for stable patients with severe COPD and chronic ventilatory failure,[145–147] including those with recurrent admissions for acute respiratory failure.[148] In two Italian studies, long-term nocturnal NIPPV plus oxygen was associated with small improvements in dyspnea,[146,147] daytime hypercapnia, and health-related quality of life.[147] More recently, the investigators of the Australian trial of noninvasive Ventilation in Chronic Airflow Limitation (AVCAL)[145] concluded that nocturnal NIPPV in stable oxygen-dependent patients with hypercapnic COPD may improve survival while worsening quality of life (see Chapters 18 and 68).

In a recent multicenter study conducted in France and Tunisia, Girault et al[149] reported the outcome of more than 200 patients with COPD who had been intubated for an episode of acute respiratory failure. In the study, 76% of patients survived hospitalization. At discharge, 81% of the survivors were able to maintain spontaneous respiration completely unassisted, 12% were discharged on noninvasive ventilation, and 4% required invasive ventilation through a tracheostomy.

Tracheostomized patients discharged from an ICU may be transferred to a long-term weaning facility.[150,151] In approximately one-third of patients transferred to these facilities, mechanical ventilation can be successfully discontinued after early trials of spontaneous respiration.[151] In the remaining patients, the weaning process is slow (average of 33 to 44 days).[150,151] Eventually, 55% to 75% of patients in whom the weaning process is slow are successfully weaned and decannulated.[150,151] The remaining 18% to 45%, however, die during the admission to the weaning facility or remain ventilator dependent.[150,151]

The long-term outcome of patients with COPD who are ventilator dependent is poor.[150] In a small series of patients with COPD who required prolonged mechanical ventilation, Nava et al[150] reported death rates of 50% at 6 months and 78% at 2 years in patients who could not be weaned. In contrast, death rates in patients who were weaned were 20% at 6 months and 32% at 2 years ($p < 0.01$).

CONCLUSION

Few groups of patients have benefitted more from the intelligent use of mechanical ventilation than have patients with COPD. Forty years ago, pulmonologists commonly employed little more than palliative care in the management of patients with COPD who had developed acute respiratory failure. Pulmonologists were reluctant to intubate such patients because of their increased susceptibility to complications and the fear that subsequent extubation would be well-nigh impossible. All that has changed. Expert use of mechanical ventilation helps the vast majority of patients with COPD to successfully battle an episode of acute respiratory failure, and patients are typically weaned and extubated without undue difficulty. Indeed, ventilator assistance is mostly achieved noninvasively, without recourse to intubation. Success with use of NIPPV has not been achieved to the same extent with any other group of patients.

The successes achieved by mechanical ventilation are the consequences of major advances in understanding of respiratory pathophysiology that began during World War II and continued in the subsequent decades. Harnessing this knowledge to better engineering of ventilator machinery

combined with more sophisticated methods of patient monitoring has resulted in more intelligent use of mechanical ventilation and fewer complications. Selecting the most appropriate mode of ventilator assistance and settings in a given patient with COPD is predicated on careful evaluation of that patient's pathophysiology. Few other illnesses managed in an ICU depend on the same level of physiologic understanding as does the management of a patient with COPD in acute respiratory failure—the reason why I have devoted the bulk of this chapter to discussion of the pathophysiology of COPD.

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32 MECHANICAL VENTILATION IN NEUROMUSCULAR DISEASE

Ahmet Baydur

The earliest application of assisted ventilation in patients with neuromuscular disease was with the iron lung during the poliomyelitis epidemic in the 1940s and 1950s, which enabled patients with severe respiratory insufficiency to recover, become ventilator-free, and go on to lead productive lives.[1] In most cases, the device was used for a few weeks to up to 2 years, with eventual recovery of ventilatory function. Many polio patients with disability continue to reside in iron lungs in the community after several decades.[2] Others have converted to tracheostomy-assisted positive-pressure ventilation, achieving mobility and the ability to clear airway secretions. With appropriate weaning techniques, some have switched to noninvasive positive-pressure ventilation (NIPPV).[3] NIPPV is now preferred to support most patients with chronic neuromuscular disorders and is used increasingly to support patients with acute ventilatory insufficiency, such as with Guillain-Barré syndrome and myasthenia gravis. Table 32-1 lists neuromuscular conditions associated with respiratory impairment and failure.

OVERVIEW OF PERTINENT PATHOPHYSIOLOGY

The primary muscle of inspiration is the diaphragm, which is innervated by the third through fifth cervical nerves. In addition, the external intercostal muscles provide stability to the rib cage during inspiration. With ascending paralysis, such as with Guillain-Barré syndrome or traumatic quadriplegia above the T10 level (Fig. 32-1),[4] there are reductions in vital capacity and other volume subdivisions, as well as rib cage distortion with inspiratory effort. These changes result in regional ventilation–perfusion mismatching, particularly in the dependent portions of the lungs. An early increase in the alveolar-arterial oxygen (O_2) difference can be found in some patients with neuromuscular impairment long before hypercapnia develops.[5,6] Gas exchange worsens during sleep secondary to alveolar hypoventilation, inhibited intercostal and accessory muscle activity, and dead space ventilation induced by rapid shallow breathing.[6–8] Long-term episodic hypoxia in dystrophic mice leads to dysfunction of myofibrillar contractility as there is no change in diaphragmatic collagen content and dry-to-wet ratio.[9] Expiratory muscles in muscular dystrophies are more impaired than inspiratory muscles.[10] Despite this finding, cough effort can still be preserved if inspiratory volume and respiratory elastic recoil are maintained.[11]

Patients with Duchenne muscular dystrophy with a vital capacity above 1.8 L remain normocapnic.[12] Below this value, nocturnal hypercapnia is likely to ensue. Many factors contribute to hypercapnia including respiratory muscle weakness,[13] central hypopneas during rapid-eye movement sleep,[14] upper airways obstruction,[15] sleep fragmentation,[16]

TABLE 32-1: NEUROMUSCULAR DISEASES ASSOCIATED WITH RESPIRATORY IMPAIRMENT OR FAILURE

1. Muscle diseases
   a. Dystrophies (Duchenne, fascioscapulohumeral, limb girdle)
   b. Myotonias
   c. Autoimmune/inflammatory myopathies (dermatomyositis, polymyositis)
   d. Metabolic myopathies (hypophosphatemia, glycogen-storage disorders, disturbed lipid metabolism)
   e. Endocrine myopathies (hypothyroidism, hyperthyroidism)
   f. Periodic paralysis
   g. Toxic myopathies (alcohol)
2. Peripheral neuropathies
   a. Autoimmune/inflammatory (Guillain-Barré, Chronic demyelinating inflammatory polyneuropathy)
   b. Toxic (heavy metal, organophosphates, nitrofurantoin, hexacarbons)
   c. Acute intermittent porphyria
   d. Tick paralysis
   e. Shellfish poisoning
   f. Hereditary (Charcot-Marie-Tooth)
   g. Endocrine (hypothyroidism, hyperthyroidism, diabetic)
3. Neuromuscular junction (myasthenia gravis, botulism)
4. Motor neuron disease
   a. Poliomyelitis
   b. Amyotrophic lateral sclerosis
   c. Spinal muscle atrophies
5. Intensive care unit-related weakness
   a. Critical illness polyneuropathy (sepsis, multisystem organ failure)
   b. Neuromuscular blocking agent-related neuropathy
   c. Status asthmaticus-associated neuromyopathy (high-dose steroids, aminoglycosides, paralytic agents)
6. Spinal cord injury

obesity,[14] respiratory muscle asynchrony,[17] and decrease in respiratory compliance.[18,19] Thoracic scoliosis, often associated with disorders such as poliomyelitis and muscular dystrophy (Fig. 32-2), further reduces respiratory compliance, resulting in an increase in inspiratory drive, altered force-length and force-velocity relationships,[20,21] and, ultimately, diaphragmatic fatigue.

Body position influences regional ventilation in individuals with neuromuscular disease. Furthermore, use of positive-pressure ventilation and an abdominal belt results in greater global and regional ventilation in the supine position than in the right and left lateral positions.[22] Intermittent positive-pressure breathing sessions (30 consecutive deep breaths at pressures up to 30 cm H_2O) improve regional ventilation by approximately 30%, more so in the anterior regions.[22,23]

Measurement of maximal static mouth pressures (Pmax) provides a guide to the degree of respiratory muscle weakness and is an adjunct in assessing the need for assisted ventilation. In stable neuromuscular disease, maximal expiratory mouth pressures are lower in myopathy than in polyneuropathy and in proximal than in distal muscle weakness.[10,24]

Weakened abdominal muscles reduce the ability to cough, as reflected by decreased peak expiratory flow rates. Patients with peak expiratory flows of less than 160 L/min need cough assistance to prevent accumulation of airway secretions.[25,26] Cough impairment is worsened by inspiratory muscle weakness and glottic dysfunction. Bulbar muscle involvement impairs swallowing and speech and increases risk of aspiration and upper airway collapse.

Dysregulation of breathing in muscular dystrophy and myotonic dystrophy has been attributed to abnormal feedback from respiratory muscle receptors and abnormal central ventilatory control, respectively.[27,28] Sleep-disordered breathing can be related to respiratory muscle weakness, chest wall deformities, obesity, craniofacial abnormalities, bulbar dysfunction, and abnormalities in control of ventilation.[14,29] Loss of rib cage and bulbar muscle tone, particularly during rapid-eye movement sleep, results in hypoventilation, decreased inspiratory flow, fragmented sleep, and daytime symptoms, well described in myotonic dystrophy, diaphragmatic paralysis, Duchenne muscular dystrophy, and amyotrophic lateral sclerosis.[30–34] Despite muscle weakness, central drive in patients with neuromuscular and chest wall disorders is often increased.[35]

CLINICAL AND PHYSIOLOGIC INDICATIONS TO INITIATE ASSISTED VENTILATION

Altered mental status, cardiac or respiratory arrest, shock, arrhythmias, gas-exchange abnormalities, and bulbar dysfunction are absolute indications for endotracheal intubation. Such acute changes are frequently seen in patients with Guillain-Barré syndrome, myasthenia gravis, and almost always in cervical spinal cord injury. Lawn and Wijdicks[36] advocated the use of a pulmonary function score, the sum of the vital capacity, maximum inspiratory pressure ($P_I$max), and maximum expiratory pressure ($P_E$max), to predict prolonged ventilation and the need for tracheostomy in patients with Guillain-Barré syndrome.

The patient developing slowly progressive respiratory impairment will experience dyspnea, increased use of accessory neck muscles, paradoxical breathing, cough after swallowing (indicative of aspiration), tachycardia, sweating, and inability to say more than a few words in a row. Some patients may complain of headaches or sleep disturbances or exhibit cognitive impairment associated with daytime hypercapnia with partial compensation. Those with generalized muscle weakness often experience orthopnea whereas patients with quadriplegia prefer the supine position because the diaphragm assumes a greater resting length and force generation.[4]

Serial measurements of forced vital capacity provide a simple and reliable means of assessing disease progression, and may predict difficulties with cough and secretion clearance[37] although as much as 50% reduction in respiratory

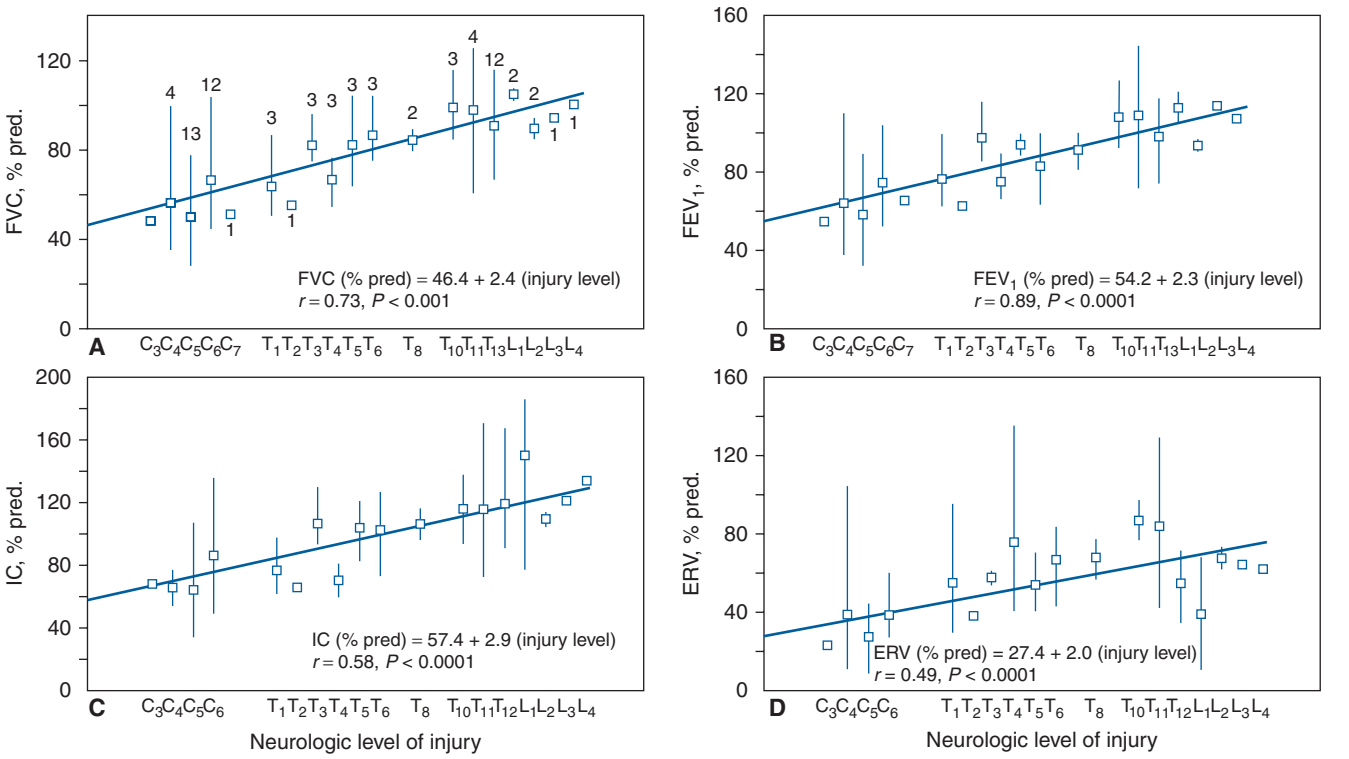

FIGURE 32-1 Spirometric variables in seated spinal cord-injured subjects distributed according to lesion level. **A.** Forced vital capacity (*FVC; n* = 74). **B.** Forced expiratory volume in 1 second (FEV_1; *n* = 74). **C.** Inspiratory capacity (*IC; n* = 73). **D.** Expiratory reserve volume (*ERV; n* = 73). Values are means and ranges of percent predicted (*% pred*) values for healthy persons. Numbers above squares in A are numbers of subjects at each injury level and are the same for B to D. (Used, with permission, from Baydur et al.[4])

muscle strength occurs before these values are reduced.[38] In general, patients with less than 10% of predicted (or <1 L) vital capacity have little tolerance off assisted ventilation.[2,3] In patients with bulbar involvement who have difficulty holding a mouthpiece in place, a full face mask can be used to perform spirometry. Facemask measurements tend to produce vital capacity values larger than those recorded by mouthpiece, in some cases by as much as 1.2 L in the seated position.[39] A more useful guide to diaphragmatic weakness is the comparison of the vital capacity measured in the seated and supine positions. Reductions in vital capacity of 12% to 65% have been recorded in patients with neuromuscular disease[3,4,40,41] (except in those with traumatic quadriplegia[4,42,43]) on assuming the supine position.

Measurements of $P_I$max and $P_E$max are noninvasive and have established normal values for adults and children. They require, however, maximal effort and coordination, and are uncomfortable to perform. Low values may be difficult to interpret.[44,45] Poor effort or air leaks around the mouthpiece give rise to submaximal measurements. Sniff esophageal pressure (Pes-sniff) and twitch transdiaphragmatic pressure (Pdi) tests are more precise but somewhat invasive (Fig. 32-3).[46–48] Sniff nasal inspiratory force avoids the need for use of a mouthpiece and is easily performed by most patients, but may be tiring because of the need for repetition.[49,50] A sniff nasal inspiratory force less than

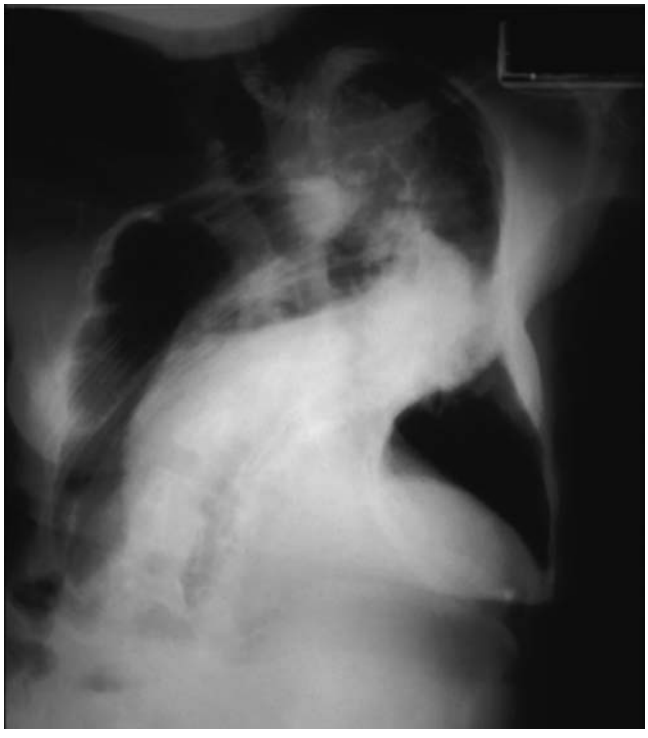

FIGURE 32-2 Patient with Duchenne muscular dystrophy and severe scoliosis.

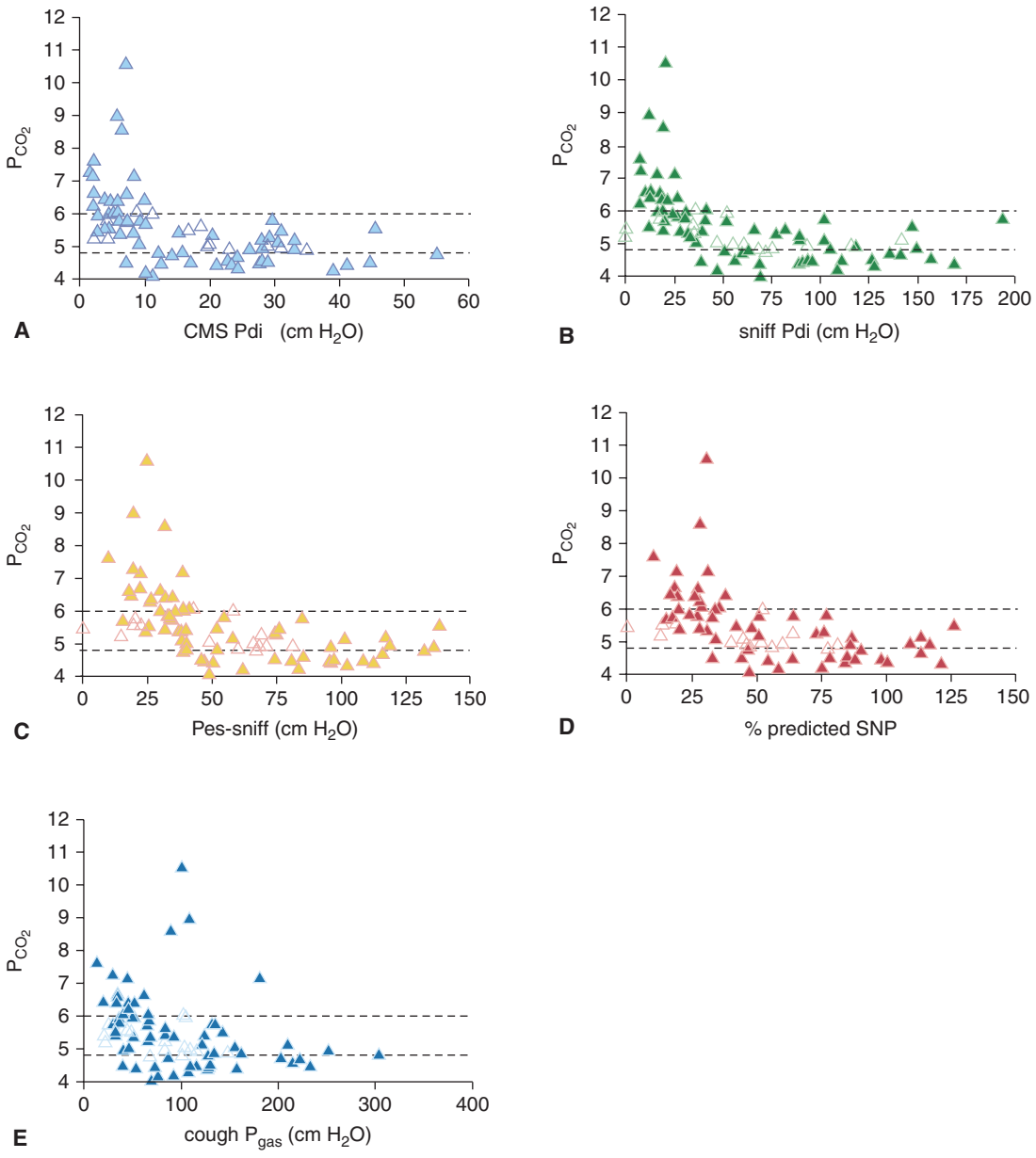

FIGURE 32-3 Relationship between tests of respiratory muscle strength (RMS) and P_{CO_2}. Each graph shows earlobe blood gas P_{CO_2} in kPa on the *y*-axis and RMS on the *x*-axis. *Open symbols* represent the bulbar patients and *closed symbols* the limb patients. The *dotted lines* represent the lower and upper limits of normal for earlobe blood gas P_{CO_2} (4.8 to 6.0 kPa). *CMS Pdi,* transdiaphragmatic pressure after bilateral cervical magnetic phrenic nerve stimulation; *cough* P_{gas}, cough gastric pressure; *sniff Pdi,* maximal sniff transdiaphragmatic pressure; *Pes-sniff,* maximal sniff esophageal pressure; *SNP,* maximal sniff nasal pressure. (Used, with permission, from Lyall A, Donaldson N, Polkey MI, Leigh PN, Moxham J. Respiratory muscle strength and ventilatory failure in amyotrophic lateral sclerosis. *Brain.* 2001;124:2000–2013, with permission of Oxford University Press.)

40 cm H_2O_2 has a sensitivity of 97% and specificity of 79% for predicting 6-month mortality in amyotrophic lateral sclerosis.[51] The use of individual tests tends to overdiagnose respiratory muscle weakness by approximately 27%, while the combination of tests increases precision and reduces the diagnosis of respiratory muscle weakness by 19% to 56% (Fig. 32-4).[52] Supine forced vital capacity, upright forced vital capacity, $P_I$max, $P_E$max, and Pdi-sniff are associated with tracheostomy-free survival, more so than Pa_{CO_2} (Fig. 32-5).[41]

Table 32-2 lists physical and functional findings used in the evaluation of patients with impending respiratory failure secondary to neuromuscular disease.

VENTILATOR TARGETS IN NEUROMUSCULAR DISEASE

The chief goals are to reverse altered mental status, correct gas exchange, and improve quality of life (see Table 32-2). With the use of nighttime NIPPV, daytime hypercapnia in

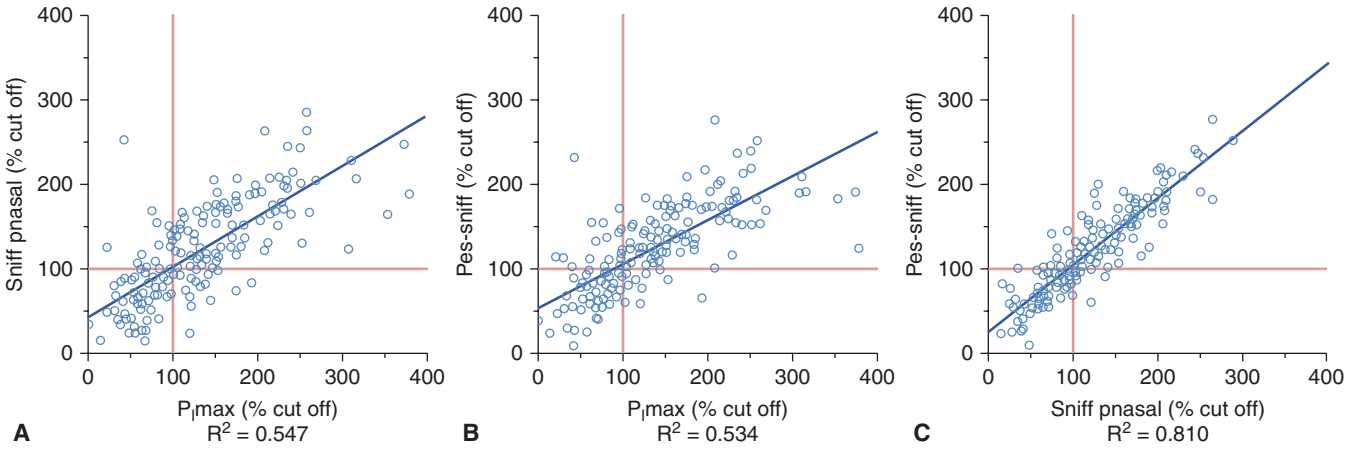

FIGURE 32-4 Correlation between (**A**) maximum inspiratory pressure ($P_I max$) and sniff nasal pressure (*Pnasal*), (**B**) $P_I max$ and sniff esophageal pressure (*Pes*), and (**C**) *Sniff Pnasal* and *Pes-sniff*. (Reproduced from Steier J, Kaul S, Seymour J, Jolley C, Rafferty G, Man W, Luo YM, Roughton M, Polkey MI, Moxham J. The value of multiple tests of respiratory muscle strength. *Thorax.* 2007;62;975–980, copyright 2007 with permission from BMJ Publishing Group Ltd.)

Duchenne muscular dystrophy is delayed by 4 to 5 years[53] and survival improves by 5 to 10 years.[54,55] Application of a few hours of daytime NIPPV reduces breathlessness and increases endurance capacity in Duchenne muscular dystrophy more effectively than nocturnal NIPPV alone (Fig. 32-6).[55] Similarly, NIPPV improves survival and quality of life in amyotrophic lateral sclerosis, even in those with bulbar dysfunction.[56,57]

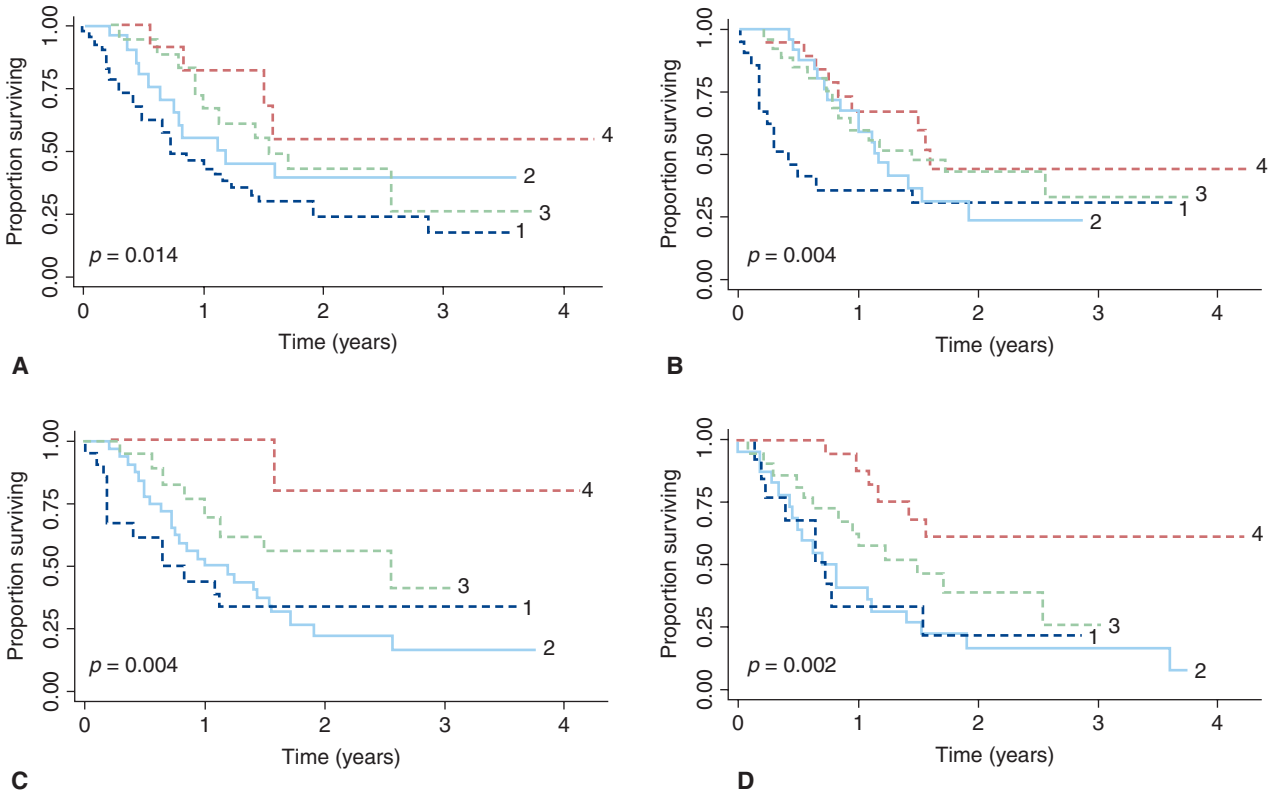

FIGURE 32-5 Kaplan-Meier curves showing differences in survival based on values of supine forced vital capacity (FVC) (**A**), upright FVC (**B**), maximal inspiratory pressure ($P_I max$) (**C**), and maximal expiratory pressure ($P_E max$) (**D**). The categories of FVC are as follows: FVC ≤50% (line 1); FVC = 51% to 65% (line 2); FVC = 66% to 80% (line 3); FVC >80% (line 4). The $P_I max$ categories are as follows: $P_I max$ greater than −25 cm H_2O (line 1); $P_I max$ = −25 to −50 cm H_2O (line 2); $P_I max$ = −51 to −70 cm H_2O (line 3); $P_I max$ less than −70 cm H_2O (line 4). The $P_E max$ categories are as follows: $P_E max$ <25 cm H_2O (line 1); $P_E max$ = 25 to 50 cm H_2O (line 2); $P_E max$ = 51 to 70 cm H_2O (line 3); $P_E max$ >70 cm H_2O (line 4). The *p* values compare differences in survival between the four categories of each pulmonary test by the Wilcoxon test. (Used, with permission, from Schmidt et al.[41])

TABLE 32-2: INDICATIONS FOR INITIATING MECHANICAL VENTILATION IN NEUROMUSCULAR DISEASES

- Relative subjective symptoms (orthopnea, frequent arousals from sleep, morning headaches, daytime somnolence/napping, impaired cognitive function [memory, concentration], fatigue)
- Cor pulmonale
- Vital capacity <25% of predicted
- Maximal inspiratory mouth pressure <25 cm H_2O
- Nasal "sniff" pressure <25 cm H_2O
- Changes in gas exchange indicating progressive respiratory failure:
  - Daytime Pa_{CO_2} >45 mm Hg
  - Sustained nocturnal hemoglobin desaturation (>5 minutes or >10% of total study time)
- Recurrent acute respiratory failure episodes requiring intervention
- Failure to respond to continuous positive pressure alone in patients with documented sleep apnea syndrome before neuromuscular weakness is detected

EXPERIENCE WITH TRADITIONAL MODES OF VENTILATION

Many patients with poliomyelitis were supported with negative-pressure devices such as oscillating beds (Fig. 32-7), iron lungs (Fig. 32-8), cuirasses, and "ponchos" (Figs. 32-9A and B). Subsequently, individuals with other neuromuscular disorders received tracheostomies for positive-pressure support (Fig. 32-10). Disadvantages of tracheostomies include the necessity of teaching the patient and caregivers how to maintain the tracheostomy, and complications such as stomal infections, airway erosions (from repeated suctioning), tracheal stenosis, and difficulty with speech and swallowing (that can be overcome with proper speech and bulbar training and use of a one-way speaking valve). Airway-vascular fistulas (with fatal hemorrhage) and tracheobronchomalacia are infrequent but devastating complications that can occur even with uncuffed tracheostomies.[58] Tracheostomies can be performed with local anesthesia during NIPPV support in hypercarbic patients with neuromuscular disease (vital capacity <20% predicted).[59]

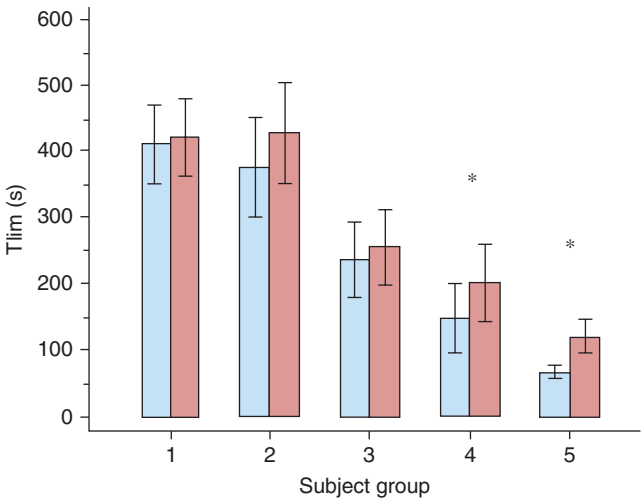

FIGURE 32-6 Endurance capacity (*Tlim*) in the five groups of patients with Duchenne muscular dystrophy. Columns represent mean values; errors bars represent 1 standard error of the mean (SEM). *Blue columns:* Evening Tlim; *red columns:* morning Tlim; $*p < 0.05$ (paired t test, evening vs. morning). Group 1, no assisted ventilation and 24/24 hours normocapnia; group 2, nocturnal hypercapnia before the start of noninvasive positive-pressure ventilation (NIPPV) implementation; group 3, nocturnal NIPPV with no breathlessness; group 4, nocturnal NIPPV with breathlessness; group 5, full-time NIPPV. (Used, with permission, from Toussaint M, Soudon P, Kinnear W. Effect of non-invasive ventilation on respiratory muscle loading and endurance in patients with Duchenne muscular dystrophy. *Thorax.* 2008;63: 430–434. Adapted by permission from BMJ Publishing Group Limited.)

FIGURE 32-7 An oscillating bed used in patients with mild to moderate respiratory impairment.

NONINVASIVE POSITIVE-PRESSURE VENTILATION

Not all patients elect to undergo tracheostomy for ventilation. The use of oral, lip (Fig. 32-11), nasal, or full-face (Figs. 32-12 to 32-14) interfaces in neuromuscular disorders

FIGURE 32-8 An iron lung (negative-pressure) ventilator.

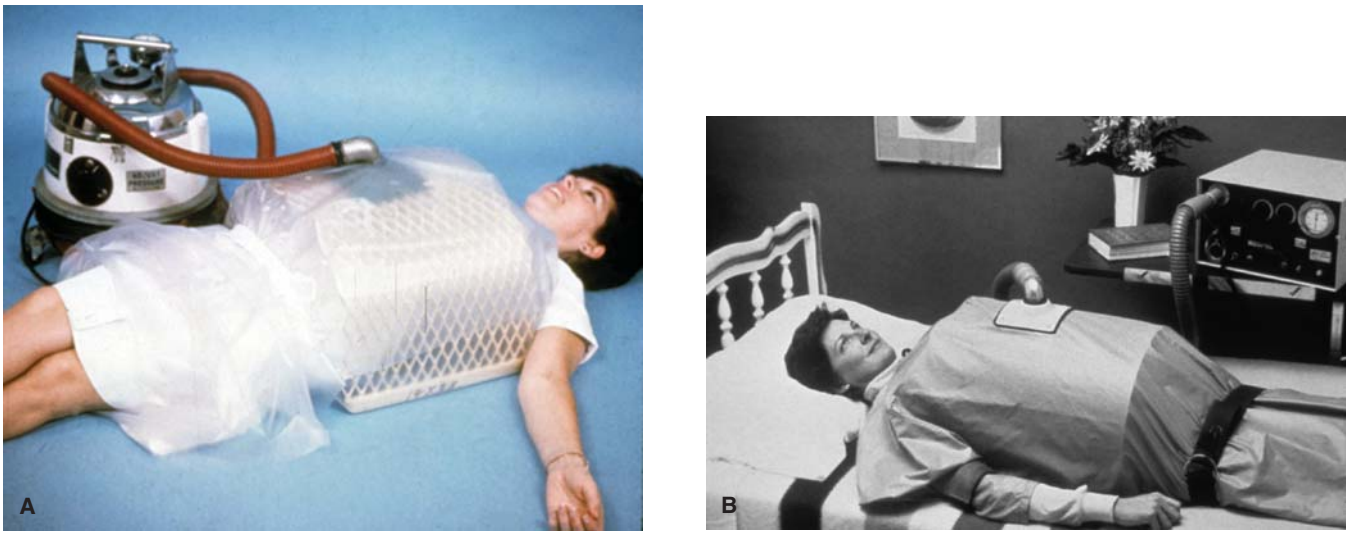

FIGURE 32-9 Two smaller negative-pressure ventilators. (**A**) Cuirass; (**B**) poncho type. (Used, with permission, from Respironics Inc., Murrysville, PA.)

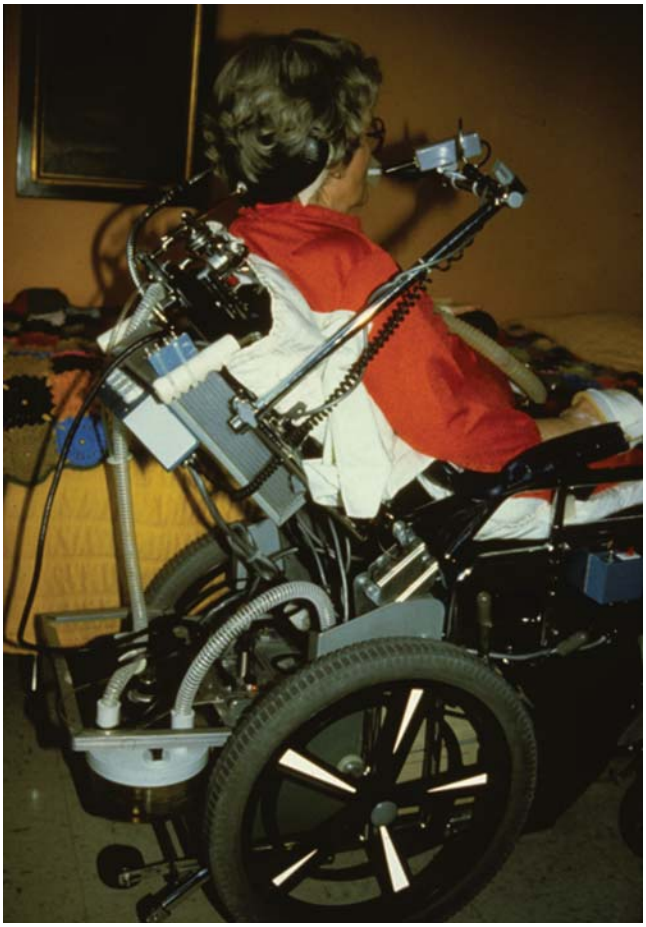

FIGURE 32-10 A poliomyelitis survivor receiving tracheostomy positive ventilation.

enables avoiding tracheostomies. They also have been used to wean patients off tracheostomy-assisted ventilation.[3] An open mouthpiece circuit can be used in respiratory-dependent neuromuscular patients with a portable volume ventilator. Only volume-cycled ventilators with negative-pressure triggering should be used, however, because flow-triggered volume ventilators autocycle when used with an open-circuit mouth-positive system.[3,60]

Delivery of effective ventilation is dependent on many factors, including ventilator type, mode, settings, presence of leaks (Fig. 32-15), upper airway resistance, expiratory valve, type of triggering (Fig. 32-16), pressurization rate, cycling pattern, and positive end-expiratory pressure (PEEP) level.[60] Patients with increased respiratory elastance (e.g., scoliosis) are likely to benefit more from a volume-cycled ventilator than from a bilevel positive airway pressure machine.

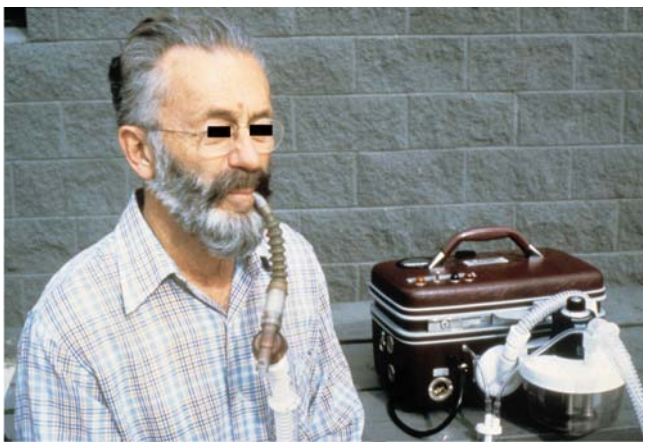

FIGURE 32-11 An individual with late effects of poliomyelitis receiving mouth positive ventilation through a mouthpiece.

FIGURE 32-12 A full-face mask used in noninvasive ventilation. (With permission from Hans Rudolph, Inc.)

FIGURE 32-14 Nasal adaptor ("pillows") used with noninvasive ventilation. (Used, with permission, from Swift™FX © ResMed 2012.)

Volume-cycled ventilators have the advantage of delivering higher volumes and can provide air "stacking" to maximum insufflations via an oral interface.[3,26] Leaks are best handled with pressure-targeted ventilators.[60]

With a close working relationship between the patient and caregivers, machine tolerance can be achieved in virtually all patients with neuromuscular diseases, including those with hypercapnic amyotrophic lateral sclerosis.[61] The prognosis in the latter group is particularly poor if they do not accept mask ventilation (death usually within less than a year). One study found a survival disadvantage in patients treated early with NIPPV for Duchenne muscular dystrophy,[62] but this finding may have resulted from the exclusion of hypercapnic patients.

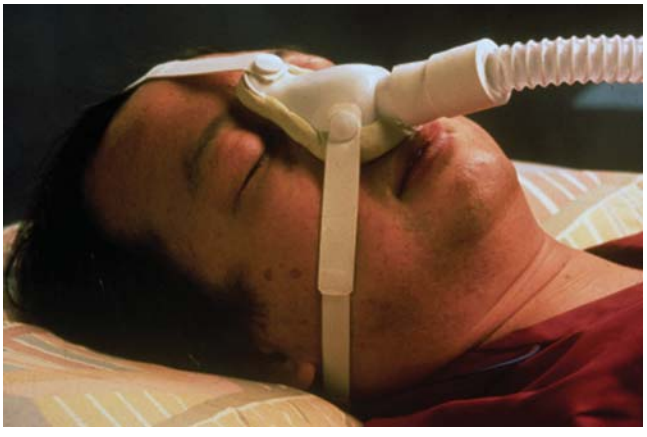

FIGURE 32-13 A silicone nasal interface used with noninvasive positive-pressure ventilation.

Current evidence concerning the benefits of NIPPV is consistent, suggesting relief of symptoms of hypoventilation in the short-term and, for the most part, improvement in survival[56,57] and quality of life.[47,56] Development of a home protocol in which oxygen desaturations are prevented or reversed using NIPPV and manual and mechanically assisted coughing techniques results in fewer and shorter hospitalizations than if such a protocol were not used.[3] Early respiratory evaluation improves patient outcomes, particularly in patients without bulbar dysfunction, and increases survival time.[57] Bulbar involvement worsens survival and increases intolerance of NIPPV.[56,57,61] Initiation of NIPPV in the hospital also improves tolerance through nocturnal adaption, and increases the likelihood of adhering to the home-ventilation program following discharge[57,61]

ROLE FOR NEWER MODES OF VENTILATION

Although pressure-cycled ventilation is the most common mode of providing ventilatory assistance in the long-term setting, patient–ventilation asynchrony sometimes occurs.[63] Proportional-assist ventilation improves patient–ventilatory synchrony by providing inspiratory flow and pressure in proportion to the patient's effort.[64] In a crossover study of fourteen patients with chronic ventilatory insufficiency (ten with restrictive thoracic disorders) comparing pressure-cycled with proportional-assist ventilation, both modes were shown to result in similar tolerance and were equally effective in reducing daytime

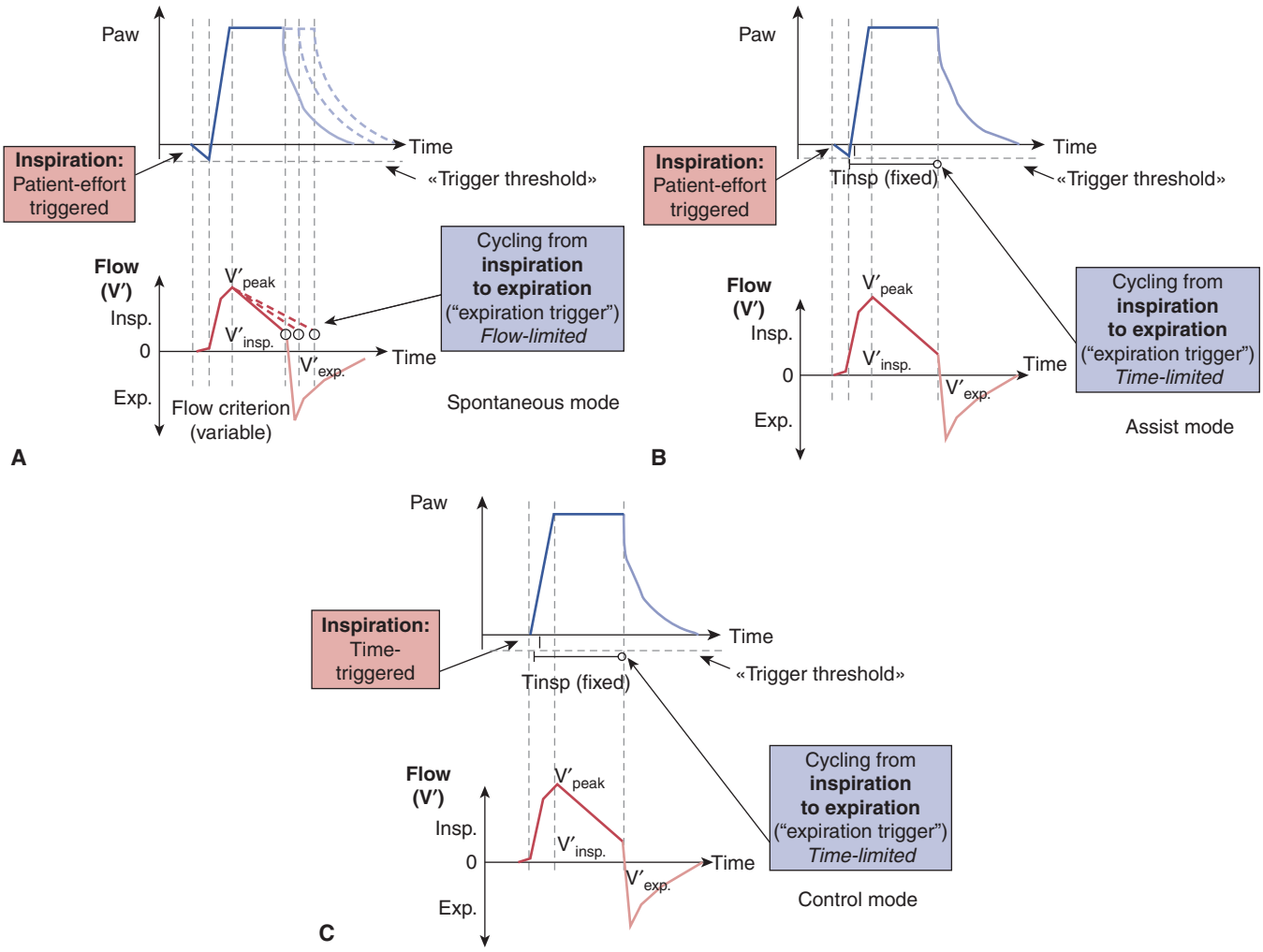

FIGURE 32-15 Impact of leaks on inspiratory-to-expiratory (I to E) cycling during pressure support ventilation (S in bilevel devices) mode (**A**) without leaks and (**B**) with leaks. Note that during leaks the flow increases to compensate for them, prolonging the inspiratory time (*dashed lines*) and switching to time-limited if maximal inspiratory time ($T_I$max) is available. Interestingly, $T_I$max is adjustable in most recent noninvasive ventilation devices. *Paw,* pressure in the airways. (Reproduced with permission from BMJ Publishing Group Ltd from Rabec C, Rodenstein D, Leger P, Rouault, Perrin C, Gonzalez-Bermejo, and on behalf of the Somno NIV group. Ventilator modes and settings during non-invasive ventilation: effects on respiratory events and implications for their identification. *Thorax.* 2011;66:170–178.)

hypercapnia and improving nocturnal saturation and symptoms.[65]

Recently, average volume-assured pressure-support ventilation (AVAPS) (Fig. 32-17) has gained use. This mode guarantees any tidal volume compatible with the physician-set upper pressure limit. It applies the benefits of pressure control while avoiding its potential complications. It is an ideal mode for individuals with low respiratory compliance, such as those with morbid obesity, scoliosis, and atelectasis. AVAPS can also reduce the leak related to the interface and reduce the rate of asynchrony related to the underlying disease process. In the only randomized, crossover trial in patients with a chest wall disorder (obesity-hypoventilation syndrome), the addition of AVAPS to bilevel pressure ventilation reduced hypercapnia as well as improved sleep quality and health-related quality of life.[66]

ROLE FOR POSITIVE END-EXPIRATORY PRESSURE

PEEP is used primarily to improve oxygenation in patients with severe and refractory hypoxemia. PEEP should recruit gas exchange units in neuromuscular weakness as most patients have reduced functional residual capacities and dependent alveolar units that fail to open during inspiration.

The most practical application of PEEP is in the form of the expiratory positive airway pressure delivered by bilevel positive airway pressure. Although pressure-cycled ventilators can compensate partially for mask leaks, excessive leaks can prolong the inspiratory phase and worsen intrinsic PEEP and patient–ventilator asynchrony. The latter problem can be corrected with the use of time-cycled expiratory triggers better than with flow-cycled expiratory triggers.[67]

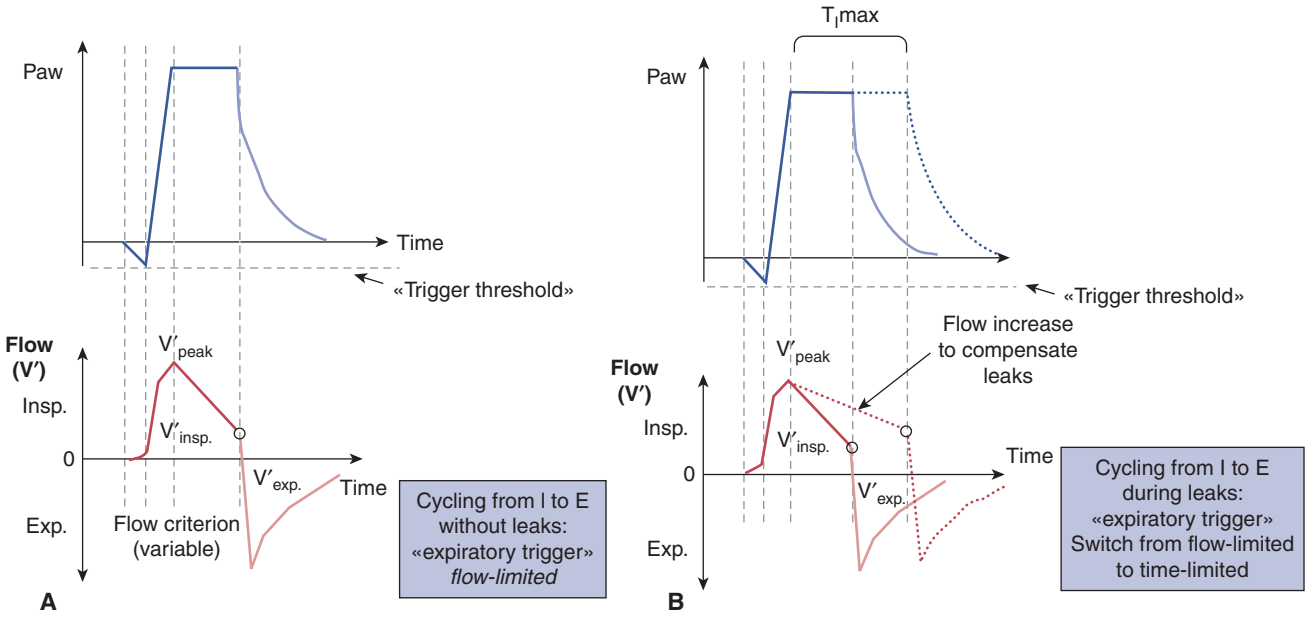

FIGURE 32-16 Different modes of inspiratory and expiratory triggering. **A.** Spontaneous mode. The patient controls the beginning and end of inspiration. Inspiration starts when the ventilator is triggered by the patient, and cycling from inspiration to expiration occurs when the inspiratory flow reaches a predetermined percentage of peak inspiratory flow. This mode is also called "pressure support" and, in some ventilators, "spontaneous (S) mode." **B.** Assisted mode. The patient controls the onset of inspiration but the end of inspiration is time triggered. When a backup respiratory rate (RR) is preset, this mode is called assist or control. In this last mode, if the patient's RR is lower than the preset ventilator backup RR, the system moves to control mode. **C.** Control mode. There is a preset automatic cycle based on time. The ventilator controls the beginning and end of inspiration and thus the RR. In some ventilators, this mode is also called "timed (T) mode." *Paw,* pressure in the airways. (Reproduced with permission from BMJ Publishing Group Ltd from Rabec C, Rodenstein D, Leger P, Rouault, Perrin C, Gonzalez-Bermejo, and on behalf of the SomnoNIV group. Ventilator modes and settings during non-invasive ventilation: effects on respiratory events and implications for their identification. *Thorax.* 2011;66:170–178.)

As in any patient with impaired left-ventricular function receiving high levels of PEEP, excess pressures can lead to a decrease in cardiac output, a potential problem in dystrophic cardiomyopathies.

SELECTING VENTILATOR SETTINGS

For most patients who present with findings of respiratory impairment, as shown in Table 32-2, ventilator assistance usually is begun nocturnally. Bach[3] recommends that most patients be started on a volume-cycled ventilator to achieve air "stacking" for maximum insufflations and for eventual daytime use. Occasional patients will benefit more from a pressure-cycled ventilator if they have glottic incompetence and cannot stack breaths.[3,60] If they do use a pressure-cycled device, the pressure spans must be high enough to generate adequate volumes. The expiratory positive airway pressure should be set as low as possible (e.g., 2 cm H_2O) unless the patient has underlying lung disease or documented sleep apnea. The spontaneous-timed mode is recommended. Patients with oral leaks can be switched to a full-face mask or, if this is uncomfortable, to chin straps, or mouth or lip seals. Because such interfaces result in an open system, and patients can take in as much volume as they want, the set volume should be able to compensate for leaks (starting at 600 to 1000 mL, with eventual increases to 800 to 1500 mL).[3]

In patients with severe respiratory muscle weakness, patient–ventilator dyssynchrony may result in hypoventilation, particularly at night, when changes in the pattern of recruitment of the respiratory muscles may occur during different sleep stages and disrupt sleep. Settings of NIPPV chosen on an empirical basis while the patient is awake may not predict ventilator asynchrony during sleep, and improper titration of inspiratory support or PEEP may impede the trigger of the mechanical breath. These abnormalities can be reduced when a physiologic setting, based on recordings of inspiratory muscle efforts, is applied.[68]

Noninvasive ventilation may be initiated in the hospital, a sleep laboratory, the outpatient office, or the patient's home, depending on the resources available. Ideally, the procedure should be initiated with the patient alert, under the guidance and supervision of experienced personnel. The goals should be to familiarize and encourage the patient with the technique and to establish initial ventilator settings (determined by optimizing both by physiology and patient comfort). Once gas-exchange and patient-comfort goals have been reached, transition to nocturnal use is initiated. Evaluations should be conducted using nocturnal oximetry and daytime arterial gases (Fig. 32-18). Polysomnography (and where available continuous percutaneous or end-tidal CO_2 monitoring) are recommended in patients in whom sleep hypoventilation is suspected.[69,70,103]

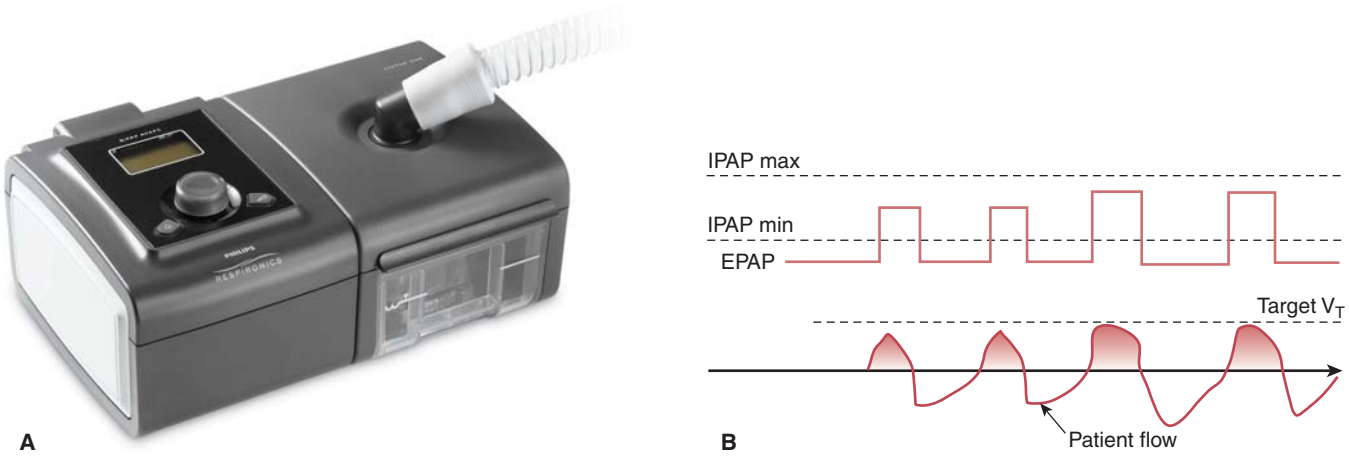

FIGURE 32-17 **A.** Average volume-assured pressure-support (AVAPS) ventilator with humidifier. **B.** Tracings taken from AVAPS mode. Based on a sensitivity algorithm performance, the device estimates the patient's tidal volume (V_T) with each breath and compares it with the target tidal flow/volume. If necessary, the algorithm slowly increases or decreases inspiratory pressure for each breath (0.5 to 1 cm H_2O/min) so as to achieve the preset V_T. (Image provided by Philips Respironics, Murrysville, PA.)

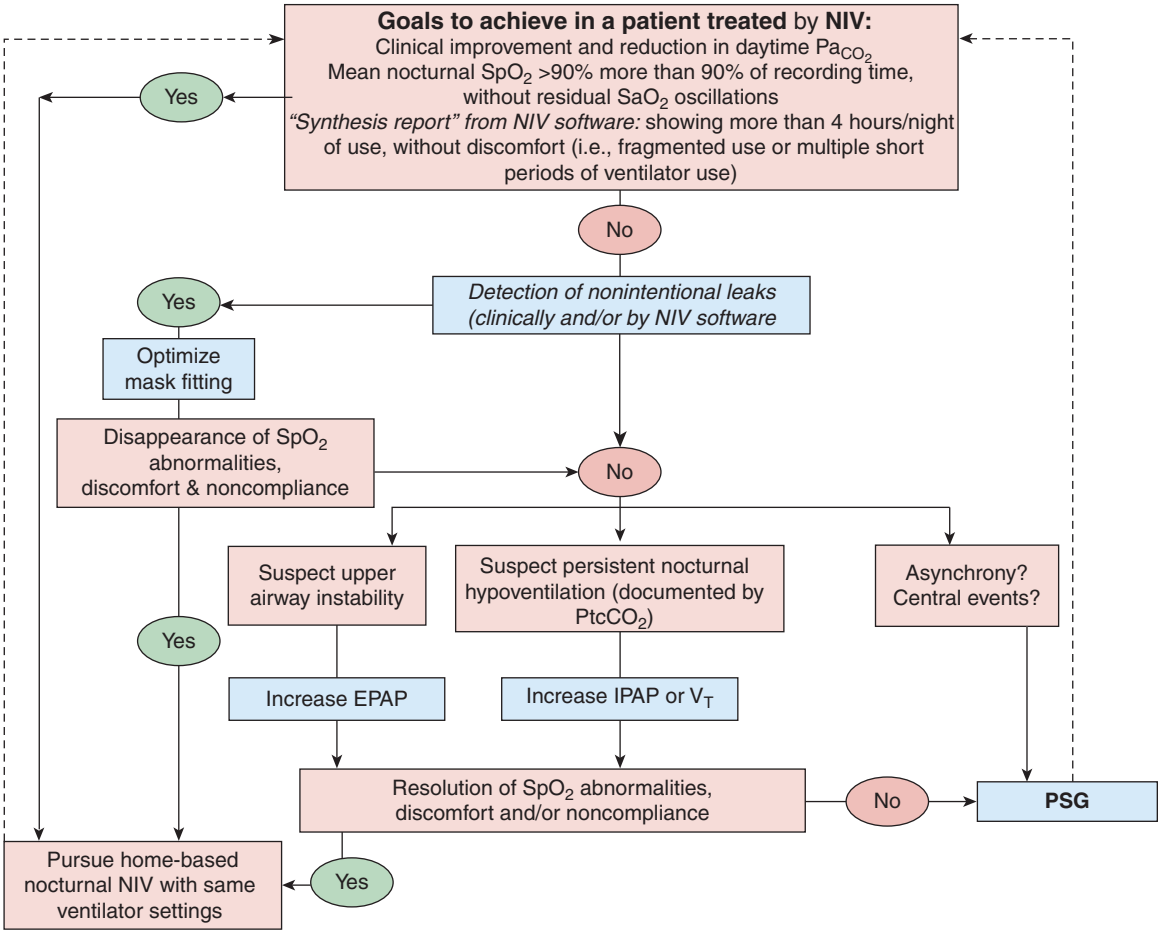

FIGURE 32-18 Suggested algorithm for monitoring noninvasive ventilation (NIV) during sleep. *IPAP,* inspiratory positive airway pressure; Pa_{CO_2}, arterial carbon dioxide tension; $PtcCO_2$, transcutaneous pressure of carbon dioxide; *PSG,* polysomnography; SaO_2, arterial oxygen saturation; SpO_2, oxygen saturation measured by pulse oximetry; V_T, tidal volume. (Used, with permission, from Janssens J-P, Borel J-C, Pépin J-L, on behalf of the SomnoNIV group. Nocturnal monitoring of home non-invasive ventilation: the contribution of simple tools such as pulse oximetry, capnography, built-in ventilator software and autonomic markers of sleep fragmentation. *Thorax.* 2011;66(5):438–445. Adapted with permission from BMJ Publishing Group Limited.)

VULNERABILITY TO VENTILATOR COMPLICATIONS

Many patients tend to have ventilation increased, especially during an acute respiratory infection, and neglect to restore their settings to their original values. Reducing the ventilation of chronically hyperventilated patients results in immediate dyspnea and demands to restore the previous ventilator settings.[71,72] In contrast to tracheostomy-assisted ventilation, NIPPV provides an open system of ventilation with maintenance of more optimal levels of partial pressure of carbon dioxide (P_{CO_2}), allowing restoration of the ventilatory drive.[3] The correction should be done with small decrements in tidal volume and/or respiratory rate over time. Periodic assessments of blood gases or end-tidal or rebreathe P_{CO_2} values[73] should be done to optimize ventilation. Progressive weight loss in patients with chronic neuromuscular disorders may also necessitate a decrease in tidal volume requirements.

Adverse effects of the interface, although not life-threatening, can lead to serious discomfort and the possibility of discontinuation. They include skin and eye irritation, drying of mucus membranes, aerophagia, leaks around the nasal and full-face interfaces, and abdominal distension with colic.[74]

Volume-cycled ventilation in control mode may result in a decrease in effective ventilation secondary to glottic closure.[3,60,75,76] Mechanical dysfunction and power outages occur occasionally, leaving the ventilator-dependent patient vulnerable to acute or progressive respiratory failure. The physician may have to exert influence as the patient's advocate to persuade third-party payors to provide reimbursement for a backup ventilator.

Other respiratory aids such as rocking beds, pneumobelts, diaphragmatic pacing, and negative pressure ventilators are discussed elsewhere in this book. In general, they are not as effective as NIPPV, particularly in patients with severe scoliosis and bulbar dysfunction. Negative pressure ventilators and diaphragmatic pacers can promote obstructive apneas, whereas the disadvantages of diaphragmatic pacers also include their high cost, lack of alarms, and potential to fail.

ADJUNCTIVE THERAPY

Glossopharyngeal Breathing

Originally taught to persons with poliomyelitis, glossopharyngeal breathing (GPB) may be useful in other neuromuscular diseases in maintaining ventilation. In individuals with weak inspiratory muscles and no tolerance off the ventilator, GPB is a nonmechanical form of breathing that can be handy in the case of sudden ventilator failure or to augment spontaneous breathing.[77] With each closure of the glottis (a "gulp"; 40 to 200 mL) can be inhaled and then exhaled to augment breathing. GPB can be used to stack breaths (up to 1.6 L) and promote cough.[3]

Assisted Coughing

Respiratory complications are the principal causes of morbidity and mortality in advanced neuromuscular diseases, in particular, inability to eliminate airway secretions because of ineffective coughing. Clearance of secretions with assisted coughing can prevent respiratory failure and delay or avoid the need for a tracheostomy. Effectiveness of secretion clearance depends on the peak expiratory flow rate. A peak cough flow of 160 to 270 L/min is an indication to provide manually or mechanically applied cough assistance.[26,78] These values should be used as guidelines and not as absolute cutoffs because some patients may develop difficulty eliminating secretions despite higher peak flows.

Manually assisted coughing requires cooperation and coordination between the patient and caregiver. The patient achieves a maximal inspiratory capacity, preferably with use of a positive-pressure device (such as with a resuscitator bag, or ventilator, or mechanical insufflation–exsufflation device) and breath "stacking," closes his or her glottis, and then "lets go" with the help of an externally applied upward and inward abdominal thrust.[79] A mouth pressure of 60 cm H_2O or more during relaxation at peak insufflation against a closed shutter usually indicates a recoil pressure adequate to generate a good cough flow.[79]

Patients with quadriplegia can contract the clavicular portion of the pectoralis major to compress the rib cage during forced expiration and cough.[80] They have decreased ability to increase intrathoracic pressure, however, because of paralysis of expiratory rib cage and abdominal muscles. Electrical or magnetic stimulation can increase intrathoracic pressure inversely and may be used to augment dynamic airway compression and clearance of airway secretions.[81]

Mechanical Insufflation–Exsufflation Devices

A mechanical insufflation–exsufflation device is a positive-pressure generator that produces a deep inspiration followed by a powerful sucking action that achieves a high expiratory flow rate (see Fig. 32-19). Minimum pressures of 35 to 40 cm H_2O are required to expel secretions but should be increased gradually over time according to the patient's comfort level.[82] Such pressures would be required to overcome small lungs and stiff chest walls, as in scoliosis. The mechanical insufflation–exsufflation device can be used with tracheostomies and full-face masks, avoiding the mucosal trauma that results from suctioning. Frequency of use can vary depending on the amount of secretions produced. Many patients note that they can breathe more easily after using the mechanical insufflation–exsufflation device. These devices are useful in patients with most neuromuscular conditions, including amyotrophic lateral sclerosis.[83,84] Children with neuromuscular disorders exhibit pressure-dependent short-term improvements in inspiratory and expiratory pressures and flows, associated with

FIGURE 32-19 (**A**) A mechanical insufflation-exsufflation device shown ready to use with a full-face mask (**B**) shown in use through a tracheostomy. (Image provided by Philips Respironics, Murrysville, PA.)

expired volume measured during the mechanical insufflation–exsufflation maneuver with good tolerance.[85] For optimal results, use of the mechanical insufflation–exsufflation device can be augmented with application of manual cough technique and proper positioning of the patient to promote drainage of airway secretions.

The mechanical insufflation–exsufflation device can also function as an alternative to intermittent positive-pressure breathing. By increasing lung volume during assisted cough, it can generate a higher peak cough flow than unassisted cough. It can improve other respiratory variables, including oxygen saturation and dyspnea, in neuromuscular diseases.[86]

Complications with mechanical insufflation–exsufflation devices are rare and include nausea, bradycardia, tachycardia, and abdominal distension. The most common reason for intolerance of the mechanical insufflation–exsufflation device is inadequate caregiver training regarding its application. As with any respiratory device used for life support, education of the patient and caregivers is important to ensure best results.

Bronchoscopy is useful only in selected cases of atelectasis caused by mucus plugging and should be tried after other methods of secretion removal have failed.

BULBAR DYSFUNCTION AND NUTRITIONAL SUPPORT

Patients with severe dysphagia require a gastrostomy for continued nutritional support. The gastrostomy is often placed in patients with an artificial airway under general anesthesia. Avoiding intubation and general anesthesia decreases the risk of respiratory complications and can prolong noninvasive ventilator management. Bach et al[87] reported placement of gastrostomies in sixty-two patients with neuromuscular disease while receiving NIPPV supplemented by mechanically assisted coughing. Normal gas exchange was able to be maintained and there were no complications.

As with any patient in a critical care setting, the patient with neuromuscular disease must be guarded against overfeeding. Because of progressive muscle wasting, caloric replacement based on ideal body weight (assuming intact muscle mass) can lead to rapid weight gain, reductions in lung volume and respiratory compliance, and an increase in work of breathing.

TIMING OF TRANSFER FROM INTENSIVE CARE UNIT TO THE COMMUNITY

Patients may be hospitalized for a number of acute consequences of respiratory muscle weakness, including pneumonia, atelectasis, hypoventilation, and sleep apnea. After the complication has resolved, the patient must be prepared for discharge into the community using a multidisciplinary approach incorporating potential caregivers in the planning. During this period, there should be clarification of the patient's advance directives, particularly with regard to interventions for long-term survival. If the patient is supported with NIPPV, attention must be given to maintenance of appropriate ventilator settings, the oral–nasal interface, seating, mobility, and nutrition (including gastrostomy or jejunostomy feeding).[3,60] Caregivers must be trained in techniques of manual and mechanical cough assistance. Only if such measures are unsuccessful in clearing secretions (as in severe bulbar involvement with amyotrophic lateral sclerosis or postpolio syndrome) should tracheostomies be resorted to. As yet, professional organizations do not provide guidelines for extubating patients with neuromuscular diseases and critical care neuropathy-myopathy. The use of assisted coughing can be used to transition from tracheostomy-assisted ventilation to noninvasive ventilation in suitable patients who meet certain criteria, the main ones including being oxygenation and absence of hypercapnia, being fully alert and cooperative, and a peak expiratory flow of at least 160 L/m.[3] Many patients have expressed a preference to NIPPV, even after many years of having lived with tracheostomies.

LONG-TERM SURVIVAL AND QUALITY OF LIFE

Home NIPPV improves survival in amyotrophic lateral sclerosis[61,88,89] and Duchenne muscular dystrophy,[90–92] as well as quality of life in most patients.[47,56,61] Yet clinical practice remains variable among physicians,[93–96] most likely because of a perception that mechanical ventilation may prolong suffering in progressive disease. In general, health care workers tend to underestimate quality-of-life scores of life satisfaction.[97]

Patients appreciate having meaningful discussions about assisted ventilation throughout the course of their illness, and they should begin before the onset of respiratory impairment. Care should be conducted in a multidisciplinary setting involving neurologists, pulmonologists, psychologists, social workers, physical and occupational therapists, speech pathologists, nutritionists, and respiratory therapists.[98–102] In some respects, working closely with the family and other caregivers is even more vital than working with the patient, but the workload associated with supporting home-ventilated patients can be considerable. Despite patients and caregivers receiving competency training before discharge, regular reeducation is required. Urgent calls to a dedicated respiratory support system may be reduced by a more flexible problem-solving approach. Reports in which no technical fault is found may indicate declining health and require clinical reevaluation.[102]

IMPORTANT UNKNOWNS AND THE FUTURE

Although it is agreed that NIPPV is the preferred means of managing ventilatory impairment and failure in neuromuscular disease, many patients have difficulty in tolerating mask ventilation. Inability or unwillingness to use the ventilator detracts from quality of life as well as survival. Glottic closure, patient–ventilator asynchrony leading to increased work of breathing in those patients with remaining respiratory muscle function, a sensation of suffocation, and facial pressure points and abrasions contribute to this lack of success. Increased use of spontaneous-timed ventilator mode ventilation and of oral or lip seals may circumvent some of these problems. Well-designed, randomized, controlled trials and cost-effectiveness studies would help to increase the acceptability of NIPPV at an earlier stage of respiratory impairment, enabling the patient to increase its use with disease progression. Ethical issues also present problems, for example, by not comparing hospitalization rates of an untreated group with the hospitalizations of patients who have avoided tracheostomy through the use of NIPPV, respiratory muscle aids, and cough-assist techniques. Such studies also would increase physician acceptance of the use of NIPPV as a routine means of improving quality of life and survival. A change in physician attitudes will lead to greater acceptance among patients who, unfortunately, still face indifferent and even negative attitudes concerning life support.

SUMMARY AND CONCLUSION

Noninvasive ventilation is now the accepted form of respiratory support for people with neuromuscular and chest wall disorders. Improvements in ventilator modes, interfaces, and adjunctive secretion-removal techniques have facilitated care and increased the quality of life in such individuals. An interdisciplinary approach aimed at not only the patient but also the family and other caregivers is essential for coping with the rigors of providing care under potentially stressful conditions. Close involvement by third-party payors and private community-based and governmental agencies is also crucial to ease the cost of home care.

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33

CHRONIC VENTILATOR FACILITIES

Stefano Nava
Michele Vitacca

Chronic ventilator facilities (CVFs) are meant to be "protected" environments for the treatment of patients who require prolonged mechanical ventilation. Numerous words are included under the umbrella of CVFs: long-term acute care facilities, respiratory special care units, chronic ventilator-dependent units, regional weaning centers, ventilator-dependent rehabilitation hospitals, prolonged respiratory care units, noninvasive respiratory care units, high-dependency units, and respiratory intensive care units. And this is without even considering nursing homes and hospice care.

A 16-year study showed that the number of acute care hospital beds in the United States has decreased over time, but the number of critical care beds has increased progressively in both absolute and proportional terms. Indeed, the total number of non–critical care beds decreased by 31%, whereas critical care beds increased by 26%[1]; nevertheless, admissions to an intensive care unit (ICU) are very strongly influenced by bed shortages. Most beds in an ICU are occupied by patients requiring mechanical ventilation. A subset of patients receiving mechanical ventilation may have weaning difficulties, so that the duration of ventilation may be abnormally prolonged (commonly defined as greater than 15 days). Several reports indicate that these ICU patients are affected by complex cardiopulmonary disease or multisystem problems and have a relatively poor outcome.[2–6]

Of 6,469,674 hospitalizations in six American states, 180,326 (2.8%) received invasive mechanical ventilation. A total of 44.6% had at least one major comorbidity condition. The most common comorbidities were diabetes (13.2%) and pulmonary disease (13.2%), and only 30.8% of patients were discharged to home from the hospital, while the others ultimately required care in a skilled care facility.[7]

Increased life expectancy has dramatically increased the age of patients requiring critical care. Medical ICU admission is associated with a high long-term mortality even in healthy elderly patients, while most of the oldest survivors undergo prolonged mechanical ventilation, which is often a marker not only of respiratory system insufficiency, but also a multisystems insufficiency caused by many factors, including a chronic underlying disease, infections, malnutrition, complications, invasive procedures, and medications.[8,9]

Prolonged mechanical ventilation is not just a "medical" problem; it also has social and economic impact. Costs for mechanical ventilation in the United States are estimated to be $27 billion, representing 12% of all hospital costs. Incidence, mortality, and cumulative population costs rise significantly with age.[7] Each year in the United States, approximately 300,000 patients receive prolonged life support in an ICU, and this number is likely to double within a decade, with associated costs of more than $50 billion.[10]

These patients, once discharged from the ICU, have a readmission rate of 67% and spend an average of 74% of all days alive in a hospital or in an acute care facility, or receiving home health care. Indeed, patients who survive for 1 year are left with a serious burden of pervasive and persistent disability despite aggressive care that cost

306,135 $ for cohort members.[11] The burden of prolonged mechanical ventilation also affects the families because of financial implications, disruption of family routine, and uncertainly of the future, as well as community financial resources. Even after these "chronically ill" patients are discharged from the ICU, which occurs once the precipitating cause of their acute episode of respiratory failure has been reversed, they still require mechanical ventilation. Thus, they either require transfer to a long-term care or rehabilitation facility.[12]

RATIONALE

At the time of ICU discharge, patients who still need dedicated care or mechanical support are usually in a phase of clinical stability, but they have several "open" problems that prevent them being transferred to a regular ward or directly to home. Several reasons justify their transfer to a dedicated CVF.

First, weaning from prolonged mechanical ventilation is a complex, time-consuming process that involves not only the selection of the best ventilation method for a particular patient, but comprehensive procedures, such as protocol-driven weaning, have the potential for improving clinical outcome through increased use of efficacious weaning methods, such as daily weaning screening, spontaneous breathing trials, and management of the ventilator and sedation.[13] Rapid turnover in a busy ICU and its clinical burden does not always allow devoting the necessary time for these procedures, and discontinuation of mechanical ventilation is not always a priority.[14]

Second, given the nature of critical illnesses and the modalities used to manage them, prolonged bed rest, with well-known adverse physiologic effects, is the rule in the ICU. Rehabilitation has the potential to restore lost function. Yet, with few exceptions,[15] it traditionally does not start until after ICU discharge. Critically ill patients are often viewed as "too sick" to tolerate physical activity in the early phase of their illness, frequently prolonging immobilization.

Third, psychiatric symptoms are quite common in chronic patients who survive an ICU stay and in their relatives at the time of ICU discharge, as well as 90 days later.[16] Open visiting hours for family members and comfort among patients and caregivers may be enhanced by return to a more physiologic circadian rhythm as opposed to that found in a typical ICU. Delirium, probably the most common psychiatric problem in critically ill patients, may still occur after discharge from an ICU, albeit with a lower incidence. The environment and the strategy of care adopted in CVFs seems to positively affect the recovery from a delirious state.[17]

Fourth, sleep disruption is a well-documented problem during ICU stay and it persists at ICU discharge.[18] Sleep deprivation can have significant consequences and has been shown to impair cognitive function, increase protein catabolism, decrease immune function, and alter respiratory mechanics that could eventually impact weaning from mechanical ventilation. A more "natural setting," like a CVF, may minimize the number and intensity of some environmental factors, involved in the genesis of poor sleep, such as noise and light intensity.[19]

Fifth, aspiration is common in patients with tracheostomies receiving prolonged ventilation and with advanced age the risk of aspiration increases. Swallowing problems are seldom assessed with the appropriate technique (i.e., videofluoroscopy) in the ICU, and the most important specific rehabilitative therapy is rarely started. Figure 33-1 illustrates the incidence and types of swallowing dysfunction in a cohort of 188 patients admitted to a CVF after ICU discharge.

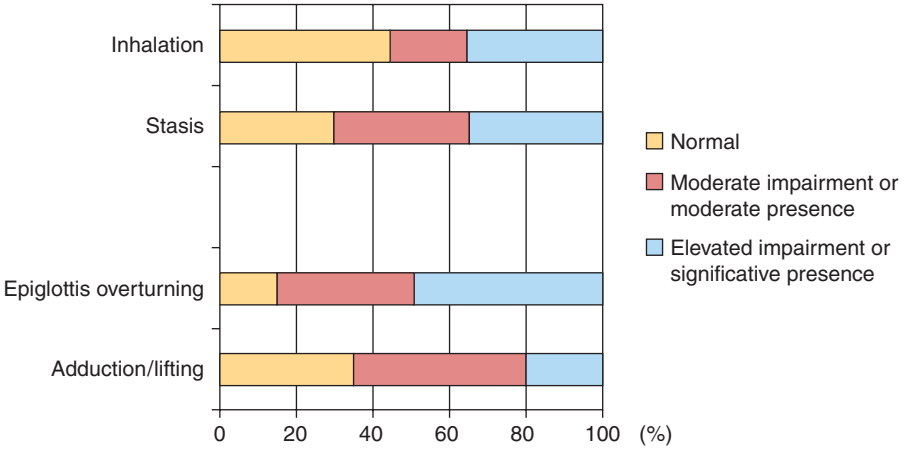

FIGURE 33-1 Incidence and types of swallowing dysfunction in a cohort of 188 patients admitted to a chronic ventilator facility after discharge from an ICU (Ceriana et al, unpublished data). Epiglottic overturning refers to the backward movement of the epiglottis during closure of the laryngeal vestibule. Adduction/lifting refers to the adduction of the vocal folds and movement of the larynx observed during inspection when the patient is requested to phonate and swallow.

Sixth, the number of tracheotomies has dramatically increased over the last few years, not only because of increasing numbers of difficult-to-wean patients, but also because of early timing of the procedure. The vast majority of these patients are discharged with a tracheal tube still in place, even when they no longer need ventilator support. A Spanish study shows that lack of tracheostomy decannulation in the ICU is associated with markedly increased ward mortality, at least in a large subset of these patients. The increased ward mortality may have resulted because the care of a tracheotomy is suboptimal outside a specialized environment.[20] Ceriana et al[21] highlighted the possibility of safely removing the tracheotomy cannula from almost 80% of patients breathing autonomously among a group of seventy-two patients recovering from weaning in a CVF, while decannulation was achieved in approximately 40% of patients transferred to a similar environment in the United States.[22]

Seventh, the interaction between ICU physicians and patients or their surrogates is far from optimal, especially when discussing the problem of prolonged ventilation including its outcome. A lack of prognostication, discordance between surrogates and physicians about potential outcomes, and unreasonably optimistic expectations of surrogates are potentially modifiable factors in surrogate–physician interactions. A less stressful environment than the ICU, combined with fewer sedative drugs and more comprehensive teamwork—nurses, respiratory therapists, psychologists, and clergy—typical of a CVF, may improve the patient–clinician relationship so that expectations and outcomes may be better defined and discussed.[23]

Overall, the disproportionate number of days of care required by chronically ventilated patients contributes to overcrowding despite the limited availability of ICU beds.[24] As Figure 33-2 shows the number of ICU beds, in several countries. The demand for ICU beds far exceeds their availability in many European and non-European countries, so that many patients are denied ICU admission because the ICU beds are already fully occupied.[25] Consequently, many critically ill patients are cared for in non-ICU beds throughout the hospital. The outcome of patients who fit ICU admission criteria but who are hospitalized in regular wards was assessed in a study performed in Israel.[26] Early survival advantage in an ICU suggests that a window of critical opportunity exists for these patients. Given economic constraints and the dearth of ICU beds, it is possible that increased turnover of patients in an ICU, thus providing an opportunity for more needy patients to avail of the early benefits of intensive management, may be advantageous. This study highlights both the risk of not admitting critically ill patients to the ICU and the advantages of early discharge from the ICU for the subset of patients not in immediate life-threatening situations, but yet not ready for discharge to a nonprotected environment.[26]

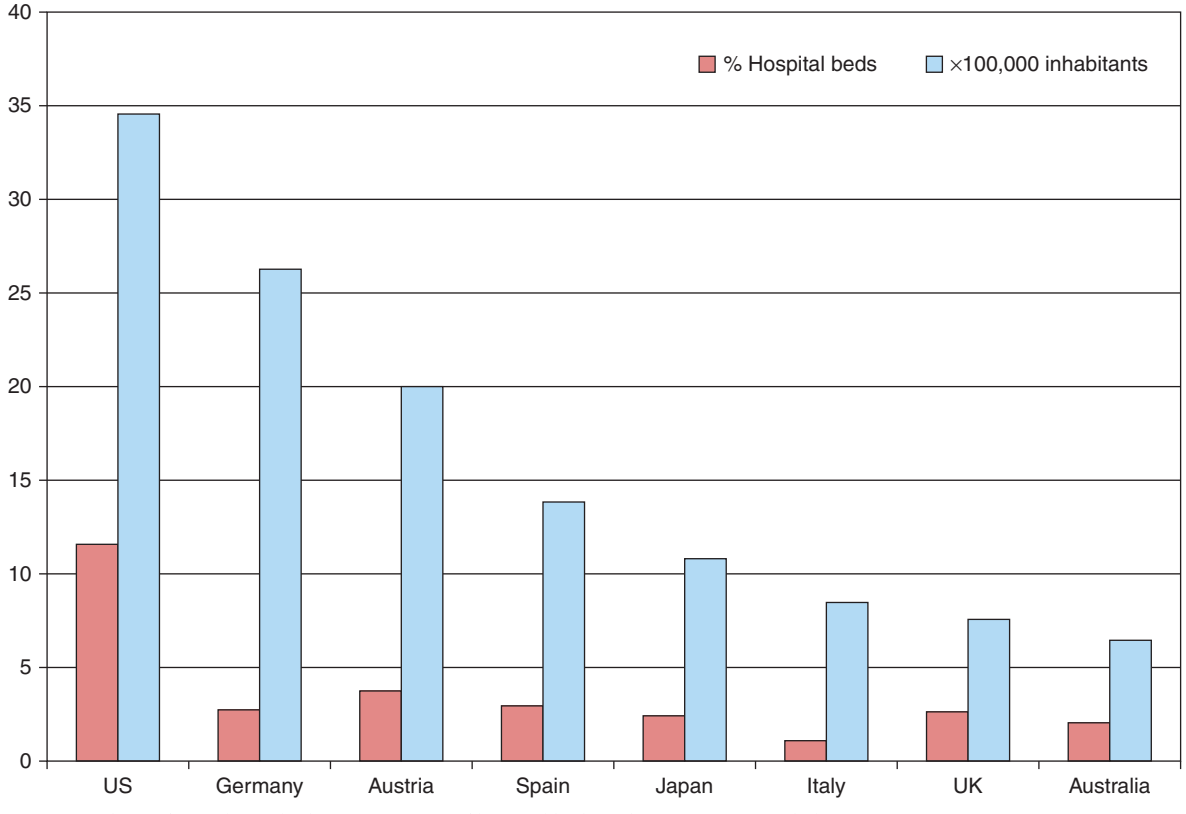

FIGURE 33-2 Numbers of actual ICU beds as percentage of hospital beds and as per 100,000 inhabitants.

The paucity of ICU beds is not as dramatic in the United States as in Europe, but discharge of chronic ventilator patients is still problematic. There has been an increase in the number of facilities specializing in the care of chronically ventilated patients. In Massachusetts, for example, the estimated prevalence of prolonged ventilation increased from 2.8 per 100,000 inhabitants in 1983 to 7.1 per 100,000 inhabitants in 2006, and most of these ventilator-dependent patients are in long-term acute care facilities, large urban teaching hospitals, and at home. The number of long-term acute care hospitals in the United States increased at a mean rate of approximately 9% per year, from 192 in 1997 to 408 in 2006, which resulted in an increased incidence of long-term acute care utilization after critical illness from 38.1 per 100,000 in 1997 to 99.7 per 100,000 in 2006.[27]

ORGANIZATION OF CHRONIC VENTILATOR FACILITIES

The term *CVF* is not necessarily synonymous with the so-called intermediate care unit or high-dependency unit, which are meant for patients who do not require full ICU care but are thought to need more care than usually can be offered in a general ward.[28–32] Not all patients in the latter units may be ventilator-dependent, but they may require either noninvasive monitoring or noninvasive mechanical ventilation. There is no agreement about the classification of facilities for patients needing prolonged mechanical ventilation because of geographic differences, lack of consensus regarding the appropriate timing of transfer from the ICU, and different criteria of admission. For example, the American College of Critical Care Medicine states in its guidelines for admission to and discharge from adult intermediate care units that "medically stable ventilator patients for weaning and chronic care" are the ideal candidates for these environments.[33] Unfortunately, these units were described only generically as "progressive-care units or single-organ subspecialty floors or chronic ventilator respiratory-care units." Details were not provided on how these units should be organized or financially reimbursed.

Timing of discharge from the ICU is also critical. Long-term ventilator patients are often old (i.e. >75 years) and have various underlying chronic comorbidities that may complicate or exacerbate their respiratory condition at any time after discharge from the ICU.[34,35] The 6-month rate of readmission to an acute care hospital is close to 40%, and readmission is often within the first 2 months after discharge from the ICU.[36] Surprisingly, this rate is not influenced by the initial discharge disposition; that is, it does not differ for patients discharged to a nursing home, a CVF, or their own home. These findings indirectly suggest that not all CVFs are presently prepared to cope with the burden of a new "acute exacerbation" in such patients. For example, Nasraway et al[37] found that despite a 31-fold increase in the number of all adults transferred from ICUs to extended care facilities in the Boston area between 1990 and 1996, the level of care of these facilities varied greatly depending mainly on the availability of skilled nurses.

There is still disagreement about the definition of a ventilator-dependent patient. The ninth revision of the *International Classification of Diseases*[38] defines long-term ventilation patients as those who have received 5 or more days of ventilation. Various authors, however, have used limits as short as 48 to 72 hours and as long as 40 days.[39–41] Realistically, approximately 20% of patients in an ICU require mechanical ventilation for more than 1 week, and about half of them are weaned successfully over the following few days.[42] Therefore, a limit of 2 weeks has been chosen by most authors to define the threshold for ventilator dependency. The Health Care Financing Administration[43] has expanded this limit to 21 days of mechanical ventilation for at least 6 hours a day. A definition based only on time, however, does not consider that for a particular patient to be regarded as ventilator-dependent (and therefore eligible for transfer to a chronic care facility), the precipitating cause of the respiratory failure must have been reversed.

CVFs have been described in the literature only in North America,[44] Europe,[45] and Asia.[46] Substantial differences exist in their organization, location, and criteria of admission. An editorial entitled, "The Challenge of Prolonged Mechanical Ventilation: A Shared Global Experience,"[47] stressed the need for common international consensus. Yet international guidelines and/or "position papers" are lacking.

Given the confusion of terminology, we submit that the most logical classification of CVFs is one based on the location of the different facilities, specifically whether the facility is inside or outside a so-called acute care hospital. Figure 33-3 illustrates the possible sites of care for patients who are chronically ventilator-dependent. It should be borne in mind that access to these different environments may differ internationally or even regionally within the same country.

Facilities within Acute Care Hospitals

Mechanical ventilation is initiated outside the hospital in a relatively small proportion of patients; ventilation is mostly started and stabilized in an ICU.[48] The timing of discharge of ventilator-dependent patients from the ICU is linked strictly to the criteria of admission of each single CVF, which are described in Chapter 34.

In the late 1980s, CVFs started to emerge in acute care hospitals as an attempt to provide an alternative therapeutic environment for ICU patients requiring prolonged mechanical ventilation. Krieger et al[49,50] probably were the first to establish a CVF within an acute care hospital (Central Respiratory Monitoring Unit at Mount Sinai Medical Center, Miami, FL). They were followed shortly after by Elpern et al[51,52] (Noninvasive Respiratory Care Unit of St. Luke's Medical Center, Chicago, IL). These units were devoted mainly to patients requiring prolonged mechanical ventilation. In 1990,

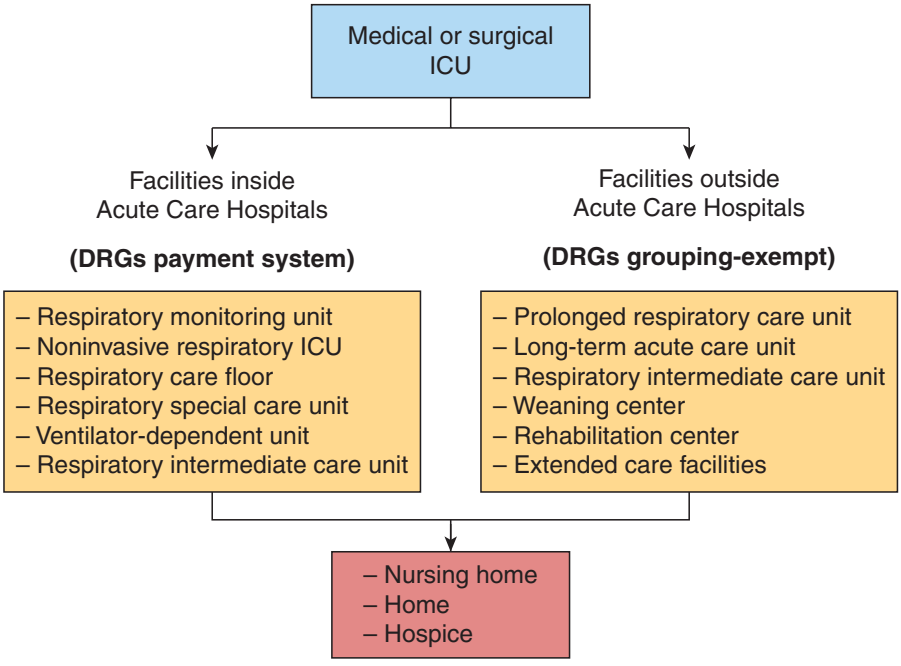

FIGURE 33-3 Potential sites of care for ventilator-dependent patients when discharged from an intensive care unit (ICU). *DRG*, diagnostic-related grouping.

the Mayo Clinic opened a ventilator-dependent unit inside Saint Mary's Hospital.[53–56] Its mission was to create an environment conducive to the rehabilitation of patients with respiratory failure and also to lower the costs of ventilator-dependent patients.[57] Shortly thereafter, new CVFs were opened. These went under different names at Saint Vincent's Hospital and Medical Center in New York, (NY)[58] (Nonmonitored Respiratory Care Floor) and at Cleveland Clinic Foundation in Cleveland, Ohio[59] (Respiratory Special Care Unit). As discussed later (see "Outcomes and Effectiveness" below), the overall rate of weaning success was high (>50%), with a mortality rate below 40%.

In Europe, the first report on this subject was published in 1995 by Smith and Shneerson[60] from England. Rather than opening a special unit for patients requiring prolonged ventilation, they described the institution of a progressive-care multidisciplinary program carried out within the ICU by a dedicated team of respiratory physicians and nurses. As soon as patients were judged ready for discharge from the ICU, they were transferred to a respiratory unit, where they continued the multidisciplinary program. The program was very successful with regard to discharge to home (80% of the patients) and 1-year survival (76%). A survey[45] of the European Respiratory Society on respiratory intermediate care units (RICUs) showed that during 1999, most (58%) of the 11,890 patients admitted to fifty-five RICUs received invasive mechanical ventilation. These units almost always (>90%) were inside an acute care hospital. Unfortunately, no data were available on how many of these patients actually were ventilator-dependent. Nevertheless, an Italian survey published in 2001[61] reported that 61% of patients receiving invasive mechanical ventilation in Italian RICUs were tracheotomized and therefore considered ventilator-dependent. The percentage is similar to that reported in Britain and Germany, where most patients survived to leave hospital, most having been weaned from the ventilator. Survivors were younger and spent less time ventilated in the referring ICU.[62,63]

Irrespective of location on either side of the Atlantic, the organization and staffing of CVFs inside acute care hospitals appear to be homogeneous and more similar to that of an ICU than to that of a CVF located outside an acute care hospital.[64,65] Most of these CVFs provide noninvasive monitoring, the nurse-to-patient ratio is usually 1:2 to 1:4,[45,51,53,58,59] and a lead respiratory therapist is assigned permanently and is present in the unit. General medical care is provided around the clock by medical house staff under the direction of an attending physician in either critical care or pulmonology. The nursing staff usually is specially trained through orientation and in-service programs to address the needs of this particular patient population. The approach to the patients is multidisciplinary, involving dieticians, psychologists, physical therapists, speech therapists, social workers, and clergy as needed. Because these CVFs are located within an acute care hospital, all the diagnostic (e.g., computed tomographic scans, nuclear magnetic resonance imaging) and therapeutic (e.g., major surgery) options are readily available. In Europe, the nurse-to-patient ratio varies slightly according to the three levels of care of RICUs.[29,45] Because of the different education and responsibilities of the respiratory therapists (rarely present around the clock), an attending physician is always present in the units.[66,67]

Facilities outside Acute Care Hospitals

This classification consists of several CVFs going under names such as regional weaning centers, prolonged respiratory care units, long-term acute care units, and RICUs inside rehabilitation hospitals. The need for these special facilities outside the acute care health system was recognized a long time ago in North America, but only recently in Europe. For example, the Comprehensive Critical Care of the British Department of Health[68] stated that "the effectiveness of specialist weaning and progressive care programs for long-term ventilation of patients has been demonstrated by research, and NHS Trusts should review the need for provision of such services."

The first experience of a CVF dedicated to the problem of ventilator-dependent patients was reported by Indihar,[69–71] who described 10 years of activity, starting in 1979, of a unit located in Bethesda Lutheran Medical Center. In the late 1980s there was substantial growth of regional weaning centers in the United States. Examples include the Barlow Respiratory Hospital in Los Angeles,[72,73] the Medical Center of Central Massachusetts,[74] and the Hospital for Special Care, New Britain, Connecticut.[75,76] Later, there was an impressive burgeoning of new long-term acute care units. By 1997, these had a capacity of about 15,000 patients per year.[77] These units were established either as free-standing hospitals, as in the case of most regional weaning center, or within an acute care hospital but operating with total independence. As such, their governance is independent of the host hospital, and reimbursement is not based on a diagnosis-related grouping (DRG) system.

CVFs within a rehabilitation hospital are also popular in the United States and Europe, especially in Germany and Italy, where approximately 15% of RICUs are located inside rehabilitation centers.[45,62,78,79]

Unlike CVFs located within acute care hospitals, CVFs located outside appear to have a rather heterogeneous organization and staffing. This heterogeneity occurs despite these facilities espousing a program based on the common ideal of providing comprehensive medical, nursing, and respiratory care to ventilator-dependent patients. For example, New England[37] has several "extended care facilities" outside acute hospitals; the skills and level of care vary dramatically among different centers. Despite the personnel being fully licensed health care practitioners, they may not all be completely familiar with the complexities of ventilator-dependent patients. Patient outcome is likely to depend on the different levels of care provided.

In most North American centers, the nurse-to-patient ratio is approximately 1:4 during the day and 1:8 at night and on weekends. A full-time respiratory therapist[72,80] usually is present. The primary physicians are either internists or specialists in pulmonary and/or critical care medicine, whereas nighttime coverage commonly is provided by junior doctors. The comprehensive care team includes physical therapists, occupational therapists, speech and swallowing therapists, and clinical psychologists. Screening for admission is performed either by an attending physician or by a nurse in consultation with an attending physician.[80] Weaning protocols and selection of ventilator settings during this process are implemented by respiratory therapists.[81] Discharges are planned by nurses or social-work care managers. With the exception of a few facilities, which may have operating rooms for minor surgery, most CVFs located outside acute care hospitals cannot offer surgery or sophisticated diagnostic procedures.

In Europe, CVFs outside acute care hospitals are run mainly by full-time attending physicians who are specialists in respiratory and/or critical care medicine.[29,45,61] These physicians are in charge of the admission and discharge of patients and the weaning protocols. They are on duty 24 hours a day. The doctor-to-patient ratio is at least 1:8. The nurse-to-patient ratio is usually similar to that of North American centers. Because of their different educational training, respiratory therapists in Europe tend to be involved mainly in rehabilitation programs, for approximately 8 hours a day (excluding Sundays and holidays), rather than in the weaning process.[21] In common with North American facilities, most European CVFs do not offer major surgery.

Irrespective of their geographic location, CVFs located outside acute care hospitals are intended to provide privacy, rest, and longer visiting hours for relatives and friends. Above all, they provide physical and pulmonary rehabilitation, which has been shown to help in freeing patients from mechanical ventilation and restoring them to an acceptable level of autonomy.[82]

Nursing Homes

A small percentage of ventilator-dependent patients are discharged from an ICU[36] directly to a nursing home. Nursing homes, however, are more likely to receive such patients once they have left a CVF. In 1991, a survey by the American Association for Respiratory Therapists[83] found that nearly 30% of ventilator-dependent patients remained in CVFs for nonmedical reasons, such as reimbursement obstacles to discharge or lack of postdischarge placement options. Indeed, approximately 20% of patients cared for in a ventilator-dependent unit are transferred to a nursing home simply because they are not ready to go home.[36]

Nursing homes have been established all over the United States,[84] either as independent units inside larger facilities or as stand-alone facilities. To the best of our knowledge, in Europe specialized units for the care of ventilator-dependent patients are very few.[85] Apparently, there is no standardization of admission criteria, staffing, or organization of these units apart from the person needing "24-hour nursing care for a cognitive or a physical impairment."[86] Nurses working in this specialized area should be trained by respiratory therapists to perform specific procedures such as suctioning, tracheotomy care, and monitoring of ventilator parameters. In some cases, for example, Lakeside Hospital in Wisconsin, Eau Claire[87] weekly care rounds led by a pulmonary physician with the participation of the care

team, including not only the certified nurses but also respiratory therapists, dieticians, social workers, and, when possible, family members, have been introduced. In the very few observational studies performed in this kind of facility, weaning outcomes are very promising.[87] Further studies are needed to define the characteristics of ventilator-dependent patients who are most likely to benefit from admission to this environment.

CRITERIA FOR ADMISSION

Table 33-1 lists criteria for defining the "ideal" candidate for a CVF. The concept of ventilator dependency is the primary criterion for selecting admissions to a CVF. Accordingly, most centers accept only tracheotomized patients because tracheotomy per se is assumed as evidence of ventilator dependency. Significant differences on the best location of care at the time of ICU discharge between patients with and without tracheostomy has been demonstrated.[88] Indeed, the dramatic increase in tracheotomies performed over the last 10 years[89] suggests that ICU physicians tend to perform an early tracheotomy before trying to complete weaning. This change may reflect attempts to decongest busy ICUs more rapidly by allowing transfer of ventilator-dependent patients to extended care facilities. To avoid this problem, some units request proof that a patient has failed at least two weaning trials before being admitted.[55] Other centers, however, accept patients based mainly on the availability of resources (bed and nursing staff) rather than on the basis of perceived ability to wean.[62]

Another criteria used for selecting patients for admission to CVFs are the clinical stability and the potential to benefit from a rehabilitation program.[53,59] The clinical stability is defined as reversal of the precipitating cause of respiratory failure, hemodynamic stability (not needing invasive measurements of blood pressure or pulmonary artery pressure, not requiring vasoactive drug infusion before transfer) and absence an arrhythmia requiring telemetry. Patients with multiorgan failure often are not admitted. Patients receiving hemodialytic support are usually accepted, particularly if the unit is inside an acute care hospital. When transferring a patient from the ICU, because errors in discharge reports are frequent, it is necessary to double check to avoid errors. It has been shown, for example, that of 123 transfer reports, seventy-six (62%) were affected by at least one error, with 28% of the errors being potentially harmful to the patients.[90]

The idea of the ability to benefit from rehabilitation or other comprehensive program is subjective and depends strongly on the judgment of the proposing or accepting physician. In some facilities, the proposing physician must make a written statement where the physician states that the patient is either capable of being weaned from the ventilator or is likely to return to the community despite receiving ventilator assistance.[54] Other facilities specifically ask that a patient be returned to the referring hospital once the patient has been weaned successfully or when it becomes obvious that weaning will not be possible. To ensure that all parties understand this policy, a letter of confirmation may be required from the referring physician, countersigned by the patient or the patient's surrogate.[91] A more liberal attitude is shown by other facilities, for example, the Worcester County Ventilator Unit, Worcester, Mass[74] where "specifically no admission decision is based on prognosis, weaning or rehabilitation potential." Also, at the Long-Term Acute Care Unit of the University of Chicago,[80] "patients are accepted regardless of the severity of their illness, provided they are stable for transfer." The latter institution theoretically accepts patients requiring positive end-expiratory pressure of more than 10 cm H_2O or a fractional inspired oxygen concentration (FI_{O_2}) of greater than 60%. Finally, methods have been proposed for identifying patients suitable for admission to CVFs based on severity-of-illness scores or activity of treatments.[92–95]

With few local differences, the classification of ventilator-dependent patients admitted to CVFs follows that illustrated[96] in Table 33-2.

TABLE 33-1: CRITERIA FOR DEFINING THE IDEAL CANDIDATE TO A CHRONIC VENTILATOR FACILITY

Patients ventilated for more than 14 days, necessitating prolonged weaning
Presence of a tracheostomy
Potential weaning possibility
Defined diagnosis
Single-organ failure
Hemodynamically stable (no pressor infusion)
No sepsis or active infections
Absence of surgical problems
No need of continuous sedation
Absence of chronic renal failure necessitating hemodialysis
$Pa_{O_2}/FI_{O_2} > 200$ and need for external PEEP <10 cm H_2O
Need for aggressive rehabilitation program
Potential to benefit from a rehabilitation program

Abbreviations: FI_{O_2}, fractional inspired oxygen concentration; Pa_{O_2}, partial pressure of arterial oxygen; *PEEP*, positive end-expiratory pressure.

OUTCOMES AND EFFECTIVENESS

Comparisons with Intensive Care Units

Commenting on the rationale for opening an intermediate care unit, Vincent and Buchardi[97] stated they "would recommend that instead of fragmenting ICU facilities by separating 'intensive' from 'intermediate,' with the potential risk of reduced staff morale and less adequate patient care, intensive and intermediate care beds should be combined in one unit." As stated earlier, intermediate care units are not necessarily equivalent to CVFs. Despite the lack of strong scientific evidence, specific facilities for ventilator-dependent patients

TABLE 33-2: CLASSIFICATION OF PATIENTS ADMITTED TO A CHRONIC VENTILATOR FACILITY

- Acute lung injury
  - Acute respiratory distress syndrome
  - Pneumonia
  - Aspiration injury
  - Burns
- Chronic lung disease
  - Chronic obstructive pulmonary disease
  - Asthma
  - Pulmonary fibrosis
  - Fibrothorax
- Postoperative
  - Lobectomy or pneumectomy
  - Cardiac surgery
  - Major abdominal surgery
- Neuromuscular diseases
  - Amyotrophic lateral sclerosis
  - Multiple sclerosis
  - Postpolio syndrome
  - Spinal cord injuries
  - Kyphoscoliosis
  - Critically ill polyneuropathy
  - Guillain-Barré syndrome
- Cardiovascular disorders
  - Chronic congestive heart failure
  - Ischemic cardiomyopathy

do have some clinical and financial advantages over ICU care (they are not, however, "in competition").[31,98–101] Table 33-3 lists the main differences between ICUs and CVFs located inside or outside acute care hospitals.

A retrospective review[101] of 429 ICU patients tracheotomized for respiratory failure and needing prolonged mechanical ventilation showed that only 57% of survivors had been free from mechanical ventilation by the time of discharge from the ICU. Patients who were finally weaned and had their tracheostomy tubes removed had better survival than patients who did not. Improved survival, however, came at higher hospital cost and a longer ICU stay. This study illustrated the need to compare the clinical outcomes and financial burdens of these "difficulties to wean" patients when treated exclusively in a traditional ICU or transferred during hospitalization to a CVF. The study also demonstrated that the emotional status of these patients at ICU discharge was generally good, whereas physical function was quite limited.[101]

The only randomized, controlled study directly comparing the outcomes of chronically ill patients, most of them ventilator-dependent, managed entirely in the ICU or transferred when clinically stable to a special care unit (SCU), managed mainly by specialized nurses, was performed by Rudy et al.[102] The SCU had a case-management approach for clinical problems, a full rehabilitation program, weaning protocols, and control of resource use. A total of 220 patients were assigned randomly to either the SCU or the ICU. Overall mortality rates were similar in the two groups, but the rate of readmission was lower and hospital stay shorter in the SCU group. The average cost of delivering care was $5000 less per patient in the SCU than in the ICU, and the cost to produce a survivor was $19,000 less. It makes sense that specialized care may achieve better outcomes. It is difficult, however, to draw up standardized recommendations based on a relatively small single-center study where the two groups were not fully comparable in either number or baseline conditions.

Using a retrospective chart review and questionnaires, Seneff et al[103] analyzed 6-month mortality and hospital costs in fifty-four acute care referral hospitals and twenty-six long-term acute care institutions. Hospital costs included the amount of uncompensated care incurred by the ICU under the Medicare prospective payment DRG system. The authors compared 432 patients ventilated for an average of 3 weeks who were referred but not transferred to

TABLE 33-3: DIFFERENCES IN SERVICES PROVIDED BY INTENSIVE CARE UNITS AND CHRONIC VENTILATOR FACILITIES

	ICU	CVFs Inside an Acute Care Hospital	CVFs Outside an Acute Care Hospital
Medical-centered care	+++	++	+
Dedicated multidisciplinary team	+	+++	++++
Nurse-to-patient ratio	+++	++	++
Invasive monitoring	+++	++	+
Diagnostic availability	+++	+++	++
Privacy	+	++	+++
Family contact	+/–	++	+++
Noise and artificial light	+++	++	++
Surgical availability	+++	+++	+
Hemodialysis	+++	+++	+
Physiotherapy and rehabilitation	+	+++	++++
Costs	+++	++	++

Abbreviations: +++, High; +++, Quite High; ++, Moderate; +, Low; +/–, Poor.

CVFs (Vencor) with 1702 patients who were referred and transferred to CVFs. Six-month mortality was not adversely affected by transfer to a CVF. Because patients had long hospital stays and consumed much resources, overall cost of care was very high. Acute care hospitals, however, theoretically can reduce the amount of uncompensated care for these patients by timely referral to an appropriate CVF. Only approximately 10% of the two groups were discharged directly home; most patients were transferred to a nursing home or another CVF.

The latter study[103] leaves three major unsolved issues. First, the "appropriate" timing of transfer has not been clearly defined because some CVFs accept sicker patients with "overt" nonpulmonary dysfunction, whereas others only accept patients with the "single-organ failure." Second, although the authors showed that transfer to a CVF is associated with a reduction of ICU uncompensated costs of care, the issue of best reimbursement system for the CVF was not assessed. Third, even after patients were transferred to a CVF, the rate of discharge home was disappointingly low; there is an urgent need to identify the best location of care for these patients once they are discharged from a CVF.

One of the most important rationales for using a CVF is the expected reduction in ICU stay. Otherwise, the marginal variable cost of the ICU is relatively small compared with the average total cost.[104] For this reason, interventions that reduce ICU length of stay and duration of mechanical ventilation may not result in significant actual cost savings.[104]

Observational Studies

The patient populations admitted to CVF, as reported by recent observational studies from the United States and Europe, span a wide range of ages and admission diagnoses, and generally have significant comorbidities. Table 33-4 summarizes outcome indices for patients admitted to an acute care setting for weaning. Although comparisons between studies is difficult, the rate of weaning success ranges from 25% to greater than 90%. Variability of hospital mortality is equally great, ranging from 10% to 50%.

A U.S. study showed that, over time, patients transferred to CVFs had a higher number of comorbidities (5 in 1997 to 2000 vs. 5.8 in 2004 to 2006) and were more likely to receive mechanical ventilation at the long-term acute care hospital (16.4% in 1997 to 2000 vs. 29.8% in 2004 to 2006). One-year mortality after long-term acute care hospital admission was high throughout the study period: 50.7% in 1997 to 2000 and 52.2% in 2004 to 2006.[27] Similar data were recently reported in Europe: Over a period of 15 years, there were increases in the number of comorbidities per patient (from 1.8 to 3) and the duration of previous ICU stay (from 25 to 32 days). Given, the greater severity of disease among patients, the overall weaning success rate decreased from 87% to 66%, and the discharge destination changed over time: Fewer patients were discharged to home (decrease from 22% to 10%) and more were discharged to chronic care facilities (increase from 3% to 6%), acute hospitals (increase from 6% to 10%) and rehabilitative units (increase from 70% to 75%). The mortality rate also increased over time (from 9% to 15%).

A total of 1419 patients were enrolled in the United States for the Ventilation Outcomes Study. Patients were old (i.e. >75 years) and averaged 6.9 procedures and treatments during hospitalization with a median length of stay of 40 days (range: 1 to 365 days). The patients had very poor functional status at admission; nearly all were totally bedridden as a result of prolonged critical illness. The prevalence of penetrating or indwelling catheters, each breaching host defenses against infection, was striking. Discharge disposition included 28.8% to home, 49.2% to rehabilitation and extended care facilities, and 19.5% to short-stay acute care hospitals.[106]

Bigatello et al[14] noted that many patients are able to be separated from the ventilator at the time of admission to a CVF, which implies that discontinuation of mechanical ventilation was not a top priority in the referring ICU. Their data show that a number of patients may wean rapidly once ventilator management becomes the focus of care in a specialized CVF, confirming a similar observation by Vitacca et al[107] in patients with chronic obstructive pulmonary disease (COPD) and a tracheostomy.

Table 33-5 summarizes the outcome indices for patients admitted to nonacute settings for weaning. There is overall agreement that a rehabilitation-based weaning unit can assist with weaning and maximal functional independence and prepare the family for the discharge of the ventilated patient to home.[74]

Clinical outcome of patients requiring prolonged ventilation depends on the underlying disease. Weaning success is highest in postoperative patients (58%) and patients with acute lung injury (57%), and lowest in patients with COPD or neuromuscular disease (22%).[74] Chronically ventilated patients with respiratory failure caused by COPD have a worse prognosis than patients with respiratory failure from other causes.[75] This observation is consistent with the findings of Schonhöfer et al[62] that long-term survival rate was worse in patients with severe COPD than in other patients. In a homogeneous group of forty-two patients with COPD, Nava et al[78] observed a successful weaning rate of 55% when a rehabilitation program was continued for a long period outside the ICU.

Physical function is limited and reduced in most patients[60,116,117] but it is sometimes good or improved after discharge.[60,80,111,117] Quality of life is defined as good, quite good, reasonable, or normal, although severe impairment is reported in a minority of studies;[60,80,111,117] often it is improved 1 year after discharge.[118] Ambrosino et al[117] conducted a prospective, controlled cohort study in a respiratory intermediate ICU in sixty-three patients with COPD requiring mechanical ventilation. Perceived health status and cognitive function were worse in patients recovering from acute-on-chronic respiratory failure (requiring mechanical ventilation) than in stable patients receiving long-term

TABLE 33-4: OUTCOMES FOR VENTILATOR-DEPENDENT PATIENTS ADMITTED TO A CHRONIC VENTILATORY FACILITY WITHIN AN ACUTE CARE HOSPITAL

Auhor (Ref)	Year	Patients (*n*)	Age (years)	Patients	Patients Weaned (%)	Patients Died in Hospital (%)	Patients Died within 1 Year (%)	Duration of MV (days)	Postdischarge Location (%)
Elpern[51]	1989	95	71.6	Mixed	31%	67%	?	8.1	?
Rudy[102]	1995	145	64 ± 12	Mixed	?	44%	?	?	?
Latriano[58]	1996	224	66 ± 17	Mixed	51% (all patients) 92% (survived)	50%	?	50 ± 66	H = 31% CVFo = 64% Other = 5%
Douglas[3]	1997	57	61 ± 20	Mixed	?	44%	50%	28	H = 33% CVFo = 42% NH = 18% Other = 7%
Gracey[55]	1997	206	65 ± 14	Mixed	74%	8%	31%	?	?
Dasgupta[59]	1999	212	68	Mixed	60%	18%	?	17	H = 34% Other = 66%
Robson[98]	2003	161	69	Mixed	89%	14%	?	8	?
Engoren[101]	2004	429	68	Mixed	57%	22%	36%	29	?
Engoren[105]	2005	113	47 ± 21	Trauma patients	75%	2%	81%	25 ± 21	H = 5% CVFo = 5%; Rehabilitation = 32% Other = 6%
Kahn[27]	2010	244,621	76.9	Mixed	?	25%	50.4%	?	H = 30.73% Acute care = 17.63% Other = 26.4%

Abbreviations: *CVFo*, chronic ventilator facility outside an acute care hospital; *H*, home; *MV*, mechanical ventilation; *NH*, nursing home hospital.

TABLE 33-5: OUTCOMES FOR VENTILATOR-DEPENDENT PATIENTS ADMITTED TO A CHRONIC VENTILATORY FACILITY OUTSIDE AN ACUTE CARE HOSPITAL

Auhor (Ref)	Year	Patients (n)	Age (years)	Patients	Patients Weaned (%)	Patients Died in Hospital (%)	Patients Died within 1 Year (%)	Duration of MV (days)	Postdischarge Location (%)
Indihar[71]	1991	171	60	Mixed	34%	60%	?	55	?
Freichels[108]	1993	442	?	Mixed	?	31.7%	?	48	H = 20%; CVFo = 35% Other = 45%
Nava[78]	1994	42	67 ± 9	COPD	55%	29%	35%	44	?
Scheinorn[72]	1994	421	68 ± 0.9	Mixed	74%	28%	72%	?	H = 50% Other = 50%
De Vivo[109]	1995	435	40	SCI	?	?	25%	?	?
Bagley[74]	1997	278	67	Mixed	38%	31%	?	(11 to 75)	H = 29% CVFo = 71%
Scheinorn[73]	1997	1123	69 ± 3	Mixed	56%	29%	62%	29 (1 to 226)	?
Escarrabil[110]	1998	10	59 ± 8	ALS	0%	10%	70%	90 (15 to 150)	H = 100%
Votto[75]	1998	293	(45 to 70)	Mixed	?	?	29% to 60%	?	?
Carson[80]	1999	133	71	Mixed	70% (discharged) 38% (total)	50%	77%	?	H = 18%; CVFo = 63%; Other = 19%
Modowal[111]	2002	145	66 ± 16	Mixed	50%	34%	?	94 ± 82	?
Schonhofer[63]	2002	403	66	Mixed	68%	24%	51%	41	H = 28% CVFo = 16% Other = 56%
Stoller[112]	2002	162	65 ± 14	Mixed	?	17%	57%	?	H = 28% CVFo = 63% CVFi = 9%
Ceriana[113]	2003	40	67 ± 12	Mixed	67%	15%	?	?	?
Lindsay[87]	2004	102	?		67%	20	?	?	H = 36% NH = 20% Other = 44%
Pilcher[62]	2005	153	62 (49 to 72)	Mixed	38% (19% NM; 56% COPD)	28% (15% NM; 50% surgical)	42%	?	?
O'Connor[22]	2009	135	74 (36 to 91)	Mixed	43%	37%	37%	<37	?
Chadwick[114]	2009	30	66 ± 8	Motoneuron disease	53.4%	10%	56.7%	34 ± 24	H = 57%
Polverino[115]	2010	3106	76 ± 4	Mixed	87 to 66%	9% to 15%	13% at 3 months	<28	H = 16% NH = 3.7% Rehabilitation = 72%

Abbreviations: *ALS*, amyotrophic lateral sclerosis; *COPD*, chronic obstructive pulmonary disease; *CVFi*, chronic ventilator facility inside an acute care hospital; *CVFo*, chronic ventilator facility outside an acute care hospital; *H*, home; *MV*, mechanical ventilation; *NH*, nursing home; *NM*, neuromuscular; *SCI*, spinal cord injuries; (), Range.

oxygen therapy who never required ICU admission. After discharge, cognition and mobility improved to levels found in stable COPD patients on oxygen therapy.

PROBLEMS UNIQUE TO CHRONIC FACILITIES

Finances

Comparison between studies of different centers and different periods may be inappropriate because weaning success seems strongly related to patient complexity and comorbidities, hospital organization and personnel expertise, availability of early physiotherapy, use of weaning management techniques, patient autonomy, and family preparation for home discharge with a ventilator. Published data based on small samples, different clinical histories, costs based on patients in a single hospital, different reimbursements, variations in care habits among different countries, and differences in interventions, equipment, and staff involvement reduce the generalizability of cost assessment. In all studies, lower costs principally arise from a lower staffing ratio; other reductions are related to decreased room charges, lower overheads, simpler (usually noninvasive) monitoring, and changes in the pattern of diagnostics and therapeutics.

Costs are likely to change across years, particularly for admissions and related provisions because reimbursement based on DRG does not necessarily reflect real costs of individual treatment. In this respect, CVFs have a peculiar system of reimbursement that deserves special attention.[119] As shown in Table 33-6, most observational studies estimate that the daily cost of care for ventilator-dependent patients is lower in a CVF than in an ICU. Indeed, the difference in health care systems between the United States and most other industrialized countries (i.e., near universal health insurance coverage)[122] makes any comparison between different countries futile.

Proposed modalities of reimbursements in the United States include: (a) single payment for all patients within a DRG with specific weight severity; (b) payment according to variability of units dedicated to prolonged mechanical ventilation; (c) reduced payment for short length of stay; (d) ability to balance with very long stay costs; and (e) bonuses for unweanable patients.

Familiarity with correct reimbursement codes for documentation of time spent caring for patients and appropriate documentation has been advocated for physicians involved in CVFs[123] because of the complexity of the encounter with subsequent different payments. To address the problem of underreimbursement, some CVFs are now licensed as DRG-grouping-exempt,[56] and are required by the Health Care Financial Administration to maintain a mean length of stay more than 25 days and usually fewer than 90 days. In the United States, long-term acute care facilities are reimbursed under regulations of the Tax Equity and Fiscal Responsibility Act (TEFRA)[124] for care provided to Medicare patients. Charges are reimbursed up to the annual maximum cap for the facility, calculated during a 12-month period designated as the base year. Hospitals incur penalties when charges for Medicare exceed the discharge target amount and receive incentives if charges are reduced in the subsequent years. This policy, unfortunately, has led, as it did for rehabilitation hospitals, to substantial extra costs, including increases in payments to hospitals and doctors and numbers of hospital days for the average patient.[124] In most European countries, the health care system is funded primarily by government. Therefore, the vast majority of public hospitals and some private hospitals receive most of their funds through a national health service. Most beds are devoted to the treatment of acutely ill patients, independent of the baseline disease (i.e., medical or surgical), and are reimbursed through

TABLE 33-6: COSTS PER DAY FOR A VENTILATOR-DEPENDENT PATIENT ADMITTED TO AN INTENSIVE CARE UNIT OR TO A CHRONIC VENTILATOR FACILITY

Authors (Ref)	Year of Publication	Year of Analysis	Type of Unit	Daily Costs
Sheinhorn[72]	1994	?	WC (outside acute care H)	$980
Latriano[58]	1996	?	Nonmonitored care floor (inside acute care H)	$453
Bagley[74]	1997	1995	WC (outside acute care H)	$630
Nava[120]	1997	1995	RICU (outside acute care H)	$865
Gracey[56]	2000	1998	CVDU (inside acute care H)	$1084
Engoren[116]	2000	?	Cardiac stepdown unit (inside acute care H)	$439
Seneff[103]	2000	?	ICU	$4174
Linsday[87]	2004	?	Nursing home	$303
Halpern[1]	2004	2000	Daily cost per patient admitted to a critical care bed	$2647
Pilcher[62]	2005	1997 to 2000	Cost per day	€1350
O'Connor[21]	2009	2002 to 2003	Cost per day	$1054
Carpene[121]	2010	2008 to 2009	Mean cost saving per patient	€39.8452
Kahn[27]	2010	1997 to 2006	Mean cost per patient	$21.766

Note: Reference 1 is the actual daily cost of a critical care bed in year 2000 in the United States.

Abbreviations: CVDU, chronic ventilator-dependent unit; *H*, hospital; *RICU*, respiratory intensive-care unit; *WC*, weaning center.

a DRG-based system. A minor share is devoted to the care of chronically ill patients. The latter beds are located inside rehabilitation wards of acute care hospitals or within independently structured rehabilitation hospitals. For acute care, the DRG-based reimbursement *per case* is applied. For chronic care, reimbursement is on a *per diem* basis, allowing for some increase according to DRG classification. This *per diem* fee applies for only a limited number of days (40 to 60), after which the fee is curtailed drastically.

Mean duration of stay in CVFs differs considerably between patients with an impressively high standard deviation. Nasraway et al[37] reported the duration of hospital stay to range from 1 to 2125 days. Because the time spent in CVFs differs so greatly, it is clear that exemption from the DRG-based payment system is granted to avoid massive losses. The *per diem* reimbursement up to relatively small ceiling of days, however, may not achieve reasonable reimbursement.

Staffing

CVFs, especially those outside acute care hospitals, are still characterized by heterogeneous staffing. Most of the centers share common views about the equipment to be used (i.e., ventilators and monitoring systems) and the overall multidisciplinary organization, aimed at improving the autonomy of patients, privacy, and environment. There is, however, considerable discrepancy concerning the training of personnel, especially of nurses. The availability of skilled nurses in extended care facilities in the Boston area, as determined by an informal survey.[37] Marked differences exist in the care that each center provides to long-term ventilated patients. The authors[37] state that "some facilities may accept ventilator-dependent patients but may not be able to provide for all their needs, especially when serious infections or other setbacks ensue." Nurses working in a CVF should be specifically trained not only in acute lifesaving procedures, such as resuscitation, but also in specific "chronic" procedures, such as bronchial toilet, prevention of sores at the tracheotomy site, and positioning of the tracheal cannula.

Vitacca et al[125] studied the allocation of nursing time in a respiratory unit belonging to a rehabilitation center. In the first 2 days after admission, time devoted to care of a ventilator-dependent patient consumed approximately 45% of a nursing shift.

Respiratory therapists should be skilled in weaning protocols that shorten the duration of mechanical ventilation. The hospital team should be trained in clinical tests (i.e., bronchoscopy, fluoroscopy, assessment of respiratory muscle function) that may help the clinicians decide whether or not a patient can have the tracheotomy removed.[21] Special attention should be paid to the diagnosis of ICU-acquired neuromuscular abnormalities, which increase the time to weaning. Diagnosis may require electrophysiologic studies and needle electromyography of the limb and respiratory muscles.[126,127]

The global economic crisis in recent years may induce administrators to reduce the number of hospital employees, especially outside critical care settings. In the past, however, a reduction of hospital staff caused a worsening in clinical performance. For example, studies show a lower mortality and length of stay with high-intensity physician staffing.[128] Dara and Afessa observed a longer stay during the periods with less intensivists in a medical ICU.[129] Differences in the intensivist-to-ICU-bed ratio, ranging from 1:7.5 to 1:15, were not associated with differences in ICU or hospital mortality, although a ratio of 1:15 was associated with an increased ICU length of stay.[129] An Italian multicenter study revealed a progressive decrease in the doctor-to-patient ratio secondary to a reduction of medical personnel consequent to the recent restriction in the reimbursement policy of the National Health Care System.[115] The negative influence of reduced medical staff availability on weaning success rate, home discharge, and length of stay has been previously demonstrated,[115] providing empirical evidence for a link between organization and outcome in dedicated weaning facilities.

CONCLUSION

Over the past 15 years, the availability of ICU beds, new technology, and improved levels of care have produced a new population of patients termed *survivors of catastrophic illness.* These patients commonly require prolonged weaning.

The rate of achieving complete ventilator independence in specific and dedicated weaning units is generally high. It has been demonstrated that these units are cost-saving alternatives to an ICU for carefully selected patients. Survivors have an acceptable long-term quality of life. Weaning success, however, does not in itself solve other severe problems, such as the heavy financial and human burdens that the high level of dependency imposes on families, caregivers, and health service organizations once these patients are discharged from a protected environment.

Long-term acute care hospitals play an increasingly important role in patients with chronic critical illness. Yet few data exist to guide decision making about transfer or to inform policy decisions about whether to support or restrict this rapidly growing cost center.[27] The different international medical systems need to adopt new organizational innovations and highlight the need for a diverse program of comparative effectiveness research to determine the optimal organization of care for patients recovering from critical illness, including the best way to maximize survival and control costs for this high-risk patient group.[27] For these reasons, rigorous studies on structural factors relating to the outcome of patients with mechanical ventilation are mandatory. With increased efforts to reduce health care costs, patients will be shifted away from ICUs toward other clinical settings, such as dedicated weaning facilities, to care for more, and increasingly complex, patients.[130] It is imperative that we critically evaluate these changes as they occur. More research is needed on the impact of weaning facilities on costs and outcomes. In particular, the following questions should be assessed: (a) whether weaning facilities best operate as units within hospitals or as

stand-alone hospitals; (b) the optimum nurse, physician, and ancillary staffing of weaning facilities; and (c) the spillover effects of weaning facilities on critical care.[130]

In conclusion, the main benefits of chronic ventilator facilities are (a) the possibility of relieving congestion of ICU beds, (b) maintaining a high level of nursing assistance, (c) responding to sudden changes in a patient's clinical condition, (d) allowing enough time for a multidisciplinary rehabilitation approach, and (e) acting as a bridge to home-care programs or other forms of continuous chronic assistance (e.g., telemedicine or dedicated long-term units).

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34

NONINVASIVE VENTILATION ON A GENERAL WARD

Mark W. Elliott

In any discussion about location of a noninvasive ventilation (NIV) service, it is important to note that the model of hospital care differs between countries and that there may be significant differences even between hospitals within the same country. There will be variations in staffing levels; the skills of doctors, nurses, and paramedical staff; and the sophistication of monitoring. The terms *intensive care unit* (ICU), *high-dependency unit* (HDU), and *general ward* have a different meaning to different people. Care therefore must be taken when extrapolating experience and results obtained in one environment to other hospitals and countries.

The United Kingdom's King's Fund panel[1] defines intensive care as "a service for patients with potentially recoverable diseases who can benefit from more detailed observation and treatment than is generally available in the standard wards and departments." The definition of HDU is less clear, with some HDUs allowing invasive monitoring, whereas in others only noninvasive monitoring is performed. In some countries, specific respiratory ICUs and intermediate ICUs have been developed.[2,3] Specifically, within the King's Fund definition is the consideration of intensive care as a service rather than a place; critical care is provided within a continuum of primary, secondary, and tertiary care, and patients are categorized on the basis of their needs[4] (Table 34-1). Movement through the different levels usually means transfer from one location to another. Critical care outreach teams can advise on care as patients cross organizational boundaries and also facilitate transfer when this is needed.[5,6] Although most acute NIV services are situated in a specific clinical area, a peripatetic model has been described and has some advantages.[7,8]

For the purposes of this chapter, the following definitions are used:

- *Intensive care.* High ratio of staff to patients, facility for invasive ventilation and sophisticated monitoring.
- *Intermediate respiratory ICU or HDU.* Continuous monitoring of vital signs, with a staffing ratio intermediate between an ICU and a general ward, in a specified clinical area. Intubated patients (unless with tracheostomy) usually are not cared for in this environment.
- *General ward.* Takes unselected emergency admission, and although most wards will have a particular speciality interest, it is likely that because of the unpredictability of demand, patients with a variety of conditions and degrees of severity will be cared for in the same clinical area. Nurse staffing levels vary, but the intensity of nursing input available in HDUs and ICUs is not possible. Only basic monitoring is available.

Another important issue when considering NIV in different locations is the severity and acuteness of the insult leading to ventilatory failure. Ventilatory failure can be considered *acute* when it occurs on a background of normal function, *acute-on-chronic* when there is a sudden deterioration on a background of impaired function, or *chronic* when there is ventilatory failure but with no precipitating acute event. Assisted ventilation can be considered *necessary* when

TABLE 34-1: CLASSIFICATION OF INDIVIDUAL PATIENT DEPENDENCY

Level 0: Patients whose needs can be met through normal ward care in an acute hospital

Level 1: Patients at risk of their condition deteriorating or patients recently relocated from higher levels of care whose needs can be met in an acute ward with additional advice and support from the critical care team

Level 2: Patients requiring more detailed observation or intervention, including support for a single failing organ system or postoperative care, and those stepping down from higher levels of care

Level 3: Patients requiring advanced respiratory support alone or basic respiratory support, together with the support of at least two organ systems. This level includes all complex patients requiring support for multiorgan failure

without it death will ensue over a few hours or *desirable* when the primary aim is to improve quality of life and also to improve survival over the longer term.

EVIDENCE AND RATIONALE FOR NONINVASIVE VENTILATION ON A GENERAL WARD

For additional information about noninvasive ventilation, see Chapter 18.

Acute Noninvasive Ventilation

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

NIV first became established as a viable technique for patients with acute respiratory failure secondary to an exacerbation of chronic obstructive pulmonary disease (COPD) in the ICU. The most striking finding from the early randomized, controlled trials (RCTs) comparing NIV with conventional therapy was a reduction in the need for intubation,[9,10] which in the largest study translated into improved survival and reduced length of both ICU and hospital stays.[9] Complications, particularly pneumonia and other infectious complications, were reduced markedly.[9,11–15] It is striking that NIV was administered for only a relatively small proportion (mean: 6 hours) of each day[9] or at modest levels for a longer period.[10] With NIV, paralysis and sedation are not needed, and ventilation outside the ICU is an option. Given the considerable pressure on ICU beds in some countries, the high costs, and that for some patients admission to ICU is a distressing experience,[16] this is an attractive option.

There have been seven prospective, randomized, controlled studies of NIV outside the ICU either on general wards, in an intermediate unit, or in the emergency department.[17–23] A more rapid improvement in abnormal physiology is a consistent finding, but it was only in the largest,[22] adequately powered, study that a benefit in terms of outcome was seen. Plant et al[22] recruited 236 patients with an acute exacerbation of COPD, who were still hypercapnic, with a pH less than 7.35, and respiratory rate greater than 23 breaths/min on arrival on the ward. A proportion of patients will improve just with medical therapy. In a 1-year-period prevalence study[24] of patients with acute exacerbations of COPD, 20% of 954 patients were acidotic on arrival in the emergency department; of these, 25% had completely corrected their pH by the time of arrival on the ward. There was a weak relationship between partial pressure of arterial oxygen (Pa_{O_2}) on arrival at hospital and the presence of acidosis, suggesting that, in at least some patients, respiratory acidosis had been precipitated by high-flow oxygen therapy administered on the way to hospital.

The study was performed on general respiratory wards in thirteen centers. NIV was applied, by the usual ward staff, using a bilevel device in spontaneous mode according to a simple protocol. "Treatment failure," a surrogate for the need for intubation, defined by a priori criteria, was reduced from 27% to 15% by NIV. In-hospital mortality was reduced from 20% to 10%. This study suggests that with adequate staff training, NIV can be applied with benefit outside the ICU by the usual ward staff and that early introduction of NIV in a general ward results in better outcomes than providing no ventilator support for acidotic patients outside the ICU. A recent national audit in the United Kingdom,[25] however, raised significant concerns about the provision of NIV in the "real" world. Although it was not recorded in the audit, it is likely that the majority of patients received NIV outside of ICUs, mostly on general wards. Two hundred and thirty-two hospital units collected data on 9716 patients of whom 1077 received NIV. Of concern 30% of patients with persisting respiratory acidosis did not receive NIV. The mortality was higher in all acidotic groups receiving NIV than in those treated without. Patients who had late-onset acidosis had a particularly poor prognosis confirming the results of an earlier case series.[26] Interestingly, 11% of acidotic admissions had a pure metabolic acidosis. There is a challenge in translating the results of RCTs into everyday clinical practice, especially when the particular technique involves significant technical expertise. It reinforces the need for ongoing audit to ensure that standards are maintained.

CONDITIONS OTHER THAN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Trials in acute exacerbations of COPD provide the biggest body of evidence on NIV. NIV, however, is also used in other conditions, often on the basis of what has been learned in COPD.

Hypoxemic and Hypercapnic Respiratory Failure.

Obesity. Obese patients may present with acute or acute-on-chronic respiratory failure. In numerical terms this patient group is increasing; the number of patients requiring home ventilation because of obesity-hypoventilation syndrome

is increasing year on year, and in one study, patients with obesity now comprise the largest single group.[27] For obese patients requiring ventilator support acutely, the outcome from invasive ventilation is generally poor.[28] There are major practical problems associated with nursing critically ill obese patients, often requiring many pairs of hands and specialized lifting equipment for basic tasks. There are no RCTs of the use of NIV in patients with ventilatory failure secondary to obesity. A case series in which patients who received NIV were compared with those who refused it showed a survival advantage for those receiving NIV (97% vs. 42%)[29]; this was not controlled and there may have been other reasons for the difference. Very obese patients may have upper airway obstruction during sleep and because the impedance to inflation may be very high may require different ventilator modes.[30]

Neuromuscular Disease and Chest Wall Deformity. Patients with acute respiratory failure secondary to neuromuscular disease and chest wall deformity are not widely studied because they are small in number. Because of markedly reduced respiratory reserve, however, these patients are often challenging to wean from invasive ventilation and endotracheal intubation is best avoided if possible. Ideally, at-risk patients should already be under follow-up in a specialist unit and have been warned of the symptoms of evolving respiratory failure and of the necessity to present to hospital early in case of changes in their condition. Some patients will already have experienced a trial of domiciliary NIV. As such they represent good candidates for NIV outside the ICU. In addition to staff skilled in the delivery of NIV, therapists with expertise in secretion clearance techniques, including the use of mechanical insufflators or exsufflators,[31,32] are vital in the management of these patients.

Cardiogenic Pulmonary Edema. Cardiogenic pulmonary edema (CPE) represents a special case because the onset and recovery are usually both rapid. Most patients present to the emergency room, but some develop CPE in the ward. There have been seven systematic reviews (meta-analyses) on noninvasive ventilator assistance in CPE published since 2005.[33–40] Overall, there was a significant reduction in mortality for those patients treated with continuous positive airway pressure (CPAP) and a trend toward improved survival with NIV.[34] Both CPAP and NIV showed benefit when intubation was an outcome. There was no difference in any outcome when CPAP and NIV were compared. There was a trend toward an increase in myocardial infarction rate with NIV, but this was largely caused by the weighting of one study.[41] Two recent trials may result in the reappraisal of the role of NIV in acute CPE.[42,43]

In the 3CPO trial,[42] a multicenter, open, prospective RCT, patients were randomized to standard oxygen therapy, CPAP, or bilevel ventilation. There was no difference between 7-day mortality for standard oxygen therapy (9.8%) and NIV (CPAP and bilevel ventilation, 9.5%; $P = 0.87$). The combined end point of 7-day death or intubation rate was similar irrespective of NIV modality (11.7% vs. 11.1%, CPAP vs. bilevel ventilation respectively; $P = 0.81$). In comparison to standard oxygen therapy, NIV was associated with greater reductions in breathlessness scores, heart rate, acidosis, and hypercapnia at 1 hour. There were no treatment-related adverse events. There were no differences in other secondary outcomes, such as myocardial infarction rate, intubation, length of hospital stay, or ICU admission rate.

In another trial,[43] 120 patients were enrolled in three French emergency departments to either CPAP or NIV. There was no difference between interventions for any outcome. Respiratory distress and physiology improved in both arms. Only 3% of patients required intubation and one died within the first 24 hours.

These outcomes are different from the outcomes in the above meta-analyses, despite similar improvements in physiologic and gas exchange variables. The 3CPO trial was adequately powered and recruited more patients than the total of all the studies included in the meta-analyses. The discrepancy between results from one large, multicenter RCT and previous pooled data are not unique and the limitations of meta-analysis are well known.[44] Individual trials were composed of small treatment group sizes that varied between nine and sixty-five patients with recruitment rates of only 10% to 30% (compared to 62% randomized in the 3CPO trial). In the meta-analyses, the small total number of outcome events was well below the recommended threshold of 200,[45] limiting the generalizability of the findings.

The 3CPO trial may have failed to reveal a difference because the intervention was ineffectively delivered. Mean pressures for both CPAP (10 cm H_2O) and noninvasive positive pressure ventilation (IPAP 14/EPAP 7 cm H_2O) are comparable with previous studies, and improvements in physiologic variables are similar. There was crossover between interventions in all three arms of the 3CPO trial and these were analyzed on an intention-to-treat basis. There were differing reasons with respiratory distress and hypoxia being more likely in the control arm and lack of patient tolerance in the two intervention arms. After these patients were removed from primary outcome analysis, there remained no significant difference between groups, although mortality rates were lower.

Previous trials have indicated that the physiologic improvement seen with NIV is translated into a reduction in tracheal intubation rates.[33,34] In contrast, the 3CPO trial found no benefit in reducing intubation rates by NIV. Reasons for this are unclear but may reflect the differing patient populations, concomitant therapies, and thresholds for intubation and mechanical ventilation. Intubations rates in the standard therapy arms vary from 35% to 65% in early trials to 5% to 7% for recent trials in emergency department settings, despite similar severity of illness. Intubation rate in the intervention arms have fallen considerably over time, with some initial trials reporting intubation rates of up to 35% whereas recent reports have consistently suggested rates of around 5%. The recent trial[43] from France reported a 3% intubation rate, almost identical to that in the 3CPO trial. It is difficult

to make direct comparisons because studies differ in the time at which mortality is recorded, but, if anything, survival has probably improved as intubation rates have fallen, suggesting better overall management.

One danger of NIV is that other aspects of medical therapy may be forgotten because the focus is on the application of NIV. Nitrates are key and the total dose delivered has been shown to be an important predictor of outcome.[46,47] Positive pressure is beneficial to the failing heart and has some similarities to the effects of nitrates (preload and afterload reduction); if medical management is suboptimal, ventilation will have a beneficial effect on the failing heart, which may be lost if these effects have already been achieved with medication.

Finally, the patients recruited may have been less unwell than those in other studies. There was no difference in survival between recruited and nonrecruited patients, and no interaction with disease severity making this unlikely. The physiologic disturbance in these patients put them at the sickest end of the spectrum of patients studied, and, indeed, in contrast to other studies, acidosis (mean pH: 7.22) and hypercapnia (mean partial pressure of arterial carbon dioxide [Pa_{CO_2}]: 7.6 kPa) were invariable.

Despite these negative findings, a reduction in dyspnea, which was very intense, was a striking feature in patients receiving ventilator support, and this alone is sufficient reason to utilize ventilation in CPE. There is a trade-off between the beneficial effects of this reduction in dyspnea against discomfort from the mask and other factors.

Hypoxemic Respiratory Failure. There are no RCTs of NIV outside the ICU in hypoxemic respiratory failure. An RCT in the ICU[12] showed that patients receiving NIV had significantly lower rates of serious complications, and those treated successfully with NIV had shorter ICU stays. Post hoc analysis of patients grouped according to the Simplified Acute Physiology Score (SAPS) showed that NIV was superior to conventional mechanical ventilation in patients with a SAPS less than 16. In patients with a SAPS equal to or greater than 16, outcome was similar irrespective of the type of ventilation. Another study,[48] in immunocompromised patients, introduced NIV at a much lower level of physiologic compromise than would be required for invasive ventilation, and the sequential strategy (predefined periods on and off NIV) suggests that these patients could manage periods of spontaneous breathing safely. Further data are needed but it is reasonable for selected patients to have a trial of NIV in an experienced noninvasive unit outside the ICU; rapid access to intubation and mechanical ventilation must be available.

Elective Ventilation for Chronic Ventilatory Failure

This subject is dealt with in more detail in Chapters 28 and 33. In summary, there is no prospective RCT evidence to support the chronic use of NIV in any patient group. Most practitioners, however, would consider it unethical not to offer NIV to patients with chest wall deformity and neuromuscular disease, and it is unlikely that there will ever be any RCTs of NIV in these conditions. Chronic NIV is not appropriate for most patients with COPD; RCTs are ongoing.

WHERE SHOULD NONINVASIVE VENTILATION BE PERFORMED?

Acute Noninvasive Ventilation: ICU or General Ward?

There have been no direct comparisons of outcome with NIV delivered in the ICU, in intermediate units, and in a general ward. It should be appreciated that while there is some overlap, the skills needed for NIV are different from those required for invasive ventilation. Familiarity with and confidence in NIV by all members of the multidisciplinary team is the most important factor. Nurses, physiotherapists, or respiratory therapists may be the primary caregiver; this will depend on local availability, enthusiasm, and expertise. The outcome from NIV is likely to be better on a general ward where the staff has a lot of experience of NIV than in an ICU with high nurse-to-patient, therapist-to-patient, and doctor-to-patient ratios, and a high level of monitoring, but little experience of NIV. The less intensive atmosphere of a noninvasive unit may not be as distressing for patients and their relatives. NIV may be quite time-consuming in the early stages, and patients may benefit from extra attention, more likely in an ICU compared with less-well-staffed areas. Staffing is usually less at night, but a study in an ICU revealed no difference between patients failing NIV during the day and the night[49]; because of the greater number of patients under the care of an individual nurse, this may not be true on a general ward and should be evaluated further.

Assuming that the skills to deliver NIV are equal in the various possible locations, there are a number of other factors to be considered. These include whether or not intubation is considered appropriate should NIV fail, the presence of other system failure, comorbidity, severity of the respiratory failure, and likelihood of success with NIV (Fig. 34-1). Patients who cannot sustain ventilation for more than a few minutes when acutely unwell require continuous observation. This level of support is more likely to be available in the ICU than in other ward environments.

Although there are no published data, anecdotally there may be a tendency to abandon NIV more readily in an ICU because intubation is easily available, and in some ways it is easier for staff to manage a paralyzed, sedated patient than one who is struggling with NIV. When intubation is not immediately an option, there is a need to keep going a little longer, and a number of patients who at first sight appear to be failing can be managed successfully with persistence. It certainly has been the experience of the author that problems have been solved between the time that the ICU staff has been contacted and its arrival in the ward to intubate and/or transfer the patient (10 to 15 minutes).

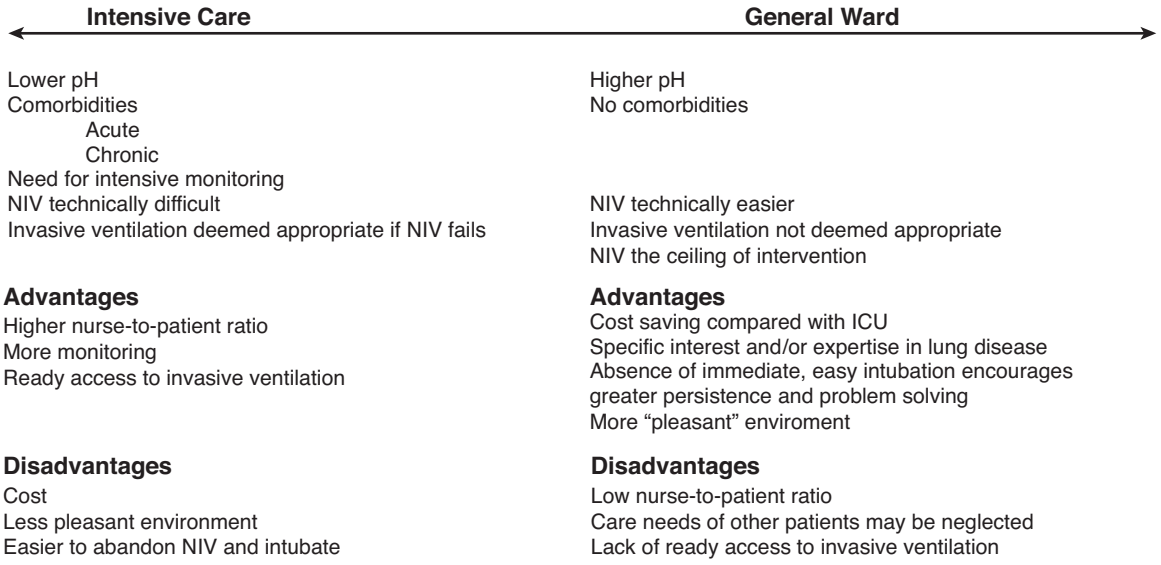

FIGURE 34-1 The spectrum of provision for an acute NIV service.

Another important difference between the ICU and the general ward is the complexity of monitoring and the types of ventilators available. Monitoring serves two roles: (a) safety and (b) optimization of ventilator settings. ICU ventilators differ from the portable devices designed primarily for home use but frequently used in general wards. The principal limitation to the use of home ventilators during acute respiratory failure is the lack of direct online monitoring of pressure, volume, and flow provided by these devices. The evaluation of patient–ventilator asynchrony is easier with visualization of flow and pressure waveforms.[50] This may be important, particularly during the initiation of ventilation, when it is important to assess patient–ventilator interaction, respiratory mechanics, and the expired tidal volume.[51] Further work is needed to establish which variables should be monitored to optimize NIV. It should be appreciated that high-technology monitoring is never a substitute for good clinical observation.[52] For safety, it is recommended that all patients receiving NIV for acute ventilatory failure should have continuous monitoring of oxygen saturation (SO_2) by pulse oximetry, regular assessments of arterial blood-gas tensions (because there is no accurate and reliable noninvasive measure of P_{CO_2} or, more importantly, of pH), and respiratory rate.[53,54] The SO_2 should be maintained at around 88% to 92%[55,56] to avoid the twin dangers of dangerous hypoxia and the risk of worsening hypercapnia secondary to altering the dead-space-to-tidal-volume ratio.[57] There is no reason why this level of monitoring cannot be provided in a general ward (Table 34-2).

If NIV is only to be provided in the ICU, the number of patients needing ICU care will increase, and this may not be necessary or appropriate. The study of Plant et al[22] showed that NIV is an option outside the ICU, but the outcome for patients with a pH of less than 7.30 was not as good as that seen for comparable patients in the studies performed in a higher-dependency setting. Also, for reasons of training, throughput, quality of service, and skill retention, NIV is best performed in a single location.[24] An intermediate unit with ready access to an ICU is probably the best compromise.[58] A study[3] of 756 consecutive patients admitted to twenty-six respiratory intermediate care units in Italy showed a better outcome than that expected on the basis of Acute Physiology and Chronic Health Evaluation (APACHE) II scores. The predicted inpatient mortality was 22.1%, whereas the actual mortality was 16%. All but forty-eight patients had chronic respiratory disease, mainly COPD ($n = 451$).

Patients with acute CPE should usually receive ventilator support where they are, because by the time arrangements have been made and transfer effected, most patients will have either improved or deteriorated to the point at which intubation is needed. Sufficient patients will attend the emergency room with CPE or develop it in the coronary care unit to make staff training in NIV in these areas worthwhile and to

TABLE 34-2: MONITORING DURING NONINVASIVE VENTILATION

Essential

- Regular clinical observation
- Continuous pulse oximetry
- Arterial blood gases after 1 to 4 hours of NIV and after 1 hour of any change in ventilator settings or fractional inspired oxygen concentration (FI_{O_2})
- Respiratory rate—continuous or intermittent

Desirable

- Electrocardiogram
- More detailed physiologic information such as leak, expired tidal volume, and measure of ventilator–patient asynchrony

ensure enough throughput to maintain skills. When patients develop CPE outside these areas (e.g., in a surgical ward), it is likely to be sufficiently infrequent that it is not worth training the staff, or if trained, staff will not have had sufficient opportunity to use and develop their skills. This is a situation in which the peripatetic NIV team or critical care outreach service may have a role. There may also be a role for CPAP delivered by helmet as it is easier to train staff in its use; it has been used successfully in the prehospital setting.[59] It is important that personnel are able to recognize and treat arrhythmias and myocardial ischemia.[60]

Elective Noninvasive Ventilation: General Ward or Chronic Care Facility?

The onset of established chronic ventilatory failure is usually insidious. Patients at risk are best seen and regularly reviewed in specialist centers so that the onset of significant nocturnal hypoventilation and the development of diurnal ventilatory failure can be anticipated. As a result, NIV usually should be instituted before the patient becomes critically ill. It is advisable to acclimatize patients to NIV at an early stage once the development of significant ventilatory failure becomes likely. In one study, 90% of patients without daytime hypercapnia but with a rise in transcutaneous CO_2 during sleep required NIV within 1 year.[61] Decompensation may occur with an intercurrent event, most commonly respiratory tract infection. NIV is much easier in the acute situation if the patient has experienced it previously when reasonably well. In such patients, if they are clinically stable, there is no need for assisted ventilation to "work" immediately; indeed, it does not matter if the patient is hardly able to use the ventilator at all initially.

There is little reason to admit these patients to the ICU, and it is questionable whether, with appropriate teams in place, the patient even needs admission to hospital. Similar outcomes were seen in an RCT of inpatient versus outpatient initiation of home ventilation in patients with neuromuscular disease and chest wall deformity. The mean (SD) inpatient stay was 3.8 (1.0) days, and the outpatient attendance sessions 1.2 (0.4). Health care professional contact time, including telephone calls, was: inpatient 177[99] minutes versus outpatient 188[60] minutes (p = NS). Two-month ventilator compliance was: inpatient 4.32 hours per night[7] versus outpatient 3.92[8] (p = NS) hours per night.[62]

Some patients, particularly those with severe neuromuscular disease, have complex nursing needs, and their home environment may be better adapted to their needs than a hospital ward. It is more pleasant for relatives and caregivers to stay in their own home. Particular issues for that patient concerning positioning of equipment, ensuring adequate access to electrical power, and so on can be addressed.[63]

If the patient is to be admitted to hospital, the choice may be between a chronic care facility and a general ward. As for acute NIV, staff expertise is the most important factor determining the best location (Table 34-3). Staffing and expertise being equal, advantages of the general ward include access to the ICU if things go wrong, and more ready access to other specialist teams because some of these patients have other complex needs, which the need to start NIV brings into focus. These advantages, however, are generalizations; depending on the nature of the chronic care facility, it may be better suited than a general ward for providing the care and support for the other needs of patients. Regardless of location, adequate control of nocturnal hypoventilation needs to be confirmed. For some patients, overnight oximetry may suffice; for others, particularly those receiving supplemental oxygen, monitoring of P_{CO_2} is necessary. Patients also will need intermittent arterial blood-gas analyses. Increasingly, it is possible to interrogate, including remotely, the home NIV ventilator, which can give important insights into why ventilation is poorly tolerated or supoptimal? Many days' data are recorded, important in a technique with which problems may be intermittent and subject to night-to-night variation. More detailed respiratory variable monitoring, including chest wall and abdominal motion, may provide important insights,[64] but is not of itself a reason for admission to hospital.

The Advantage of the General Ward

An acute and a chronic NIV service depends critically on local factors, particularly the skill levels of doctors, nurses, and therapists. The major advantage of the general ward is that it sits in the middle of the spectrum of locations for NIV provision and is likely to treat the greatest number of patients. Use of skills is a key factor in developing and retaining them. The skills learned looking after patients needing NIV acutely are equally relevant for patients being started electively on NIV. Familiarity with the nonrespiratory needs of patients with complex neuromuscular or musculoskeletal disorders, learned when patients are admitted electively to start NIV, are transferable to the care of such patients needing NIV acutely or for weaning. Continuity of care is also important. Some patients start home ventilation after an acute event, and the option of dealing with both aspects in the same place and with the same care team probably is advantageous to the patient and caregivers. If NIV is the ceiling of

TABLE 34-3: ELECTIVE VENTILATION FOR CHRONIC VENTILATORY FAILURE

There is likely to be great local variation. Factors that determine the best location

- Enthusiastic and trained staff
- Possibility of colocating with acute NIV unit
- Access to expertise in the management of nonrespiratory aspects of care
- Diagnostics, e.g., sleep laboratory
- Access to ICU

treatment, admission to an ICU is not necessary; if NIV is failing, the patient may be allowed to die in a less high-tech environment than that afforded by most ICUs.

There is an emerging role for NIV in the management of patients with end-stage COPD. It is well recognized that these patients receive suboptimal palliative care toward the end of life[65]; in part, this relates to the great difficulty in recognizing when the end is near. The boundary between life-sustaining therapy and palliation can move on a daily basis during an exacerbation as a patient's condition improves and then deteriorates again.[66] One of the biggest challenges facing doctors now and in the future is knowing when "enough is enough."[67] NIV provides a useful alternative to life-sustaining therapy, with limited palliative care, that is, invasive ventilation, or to treatment that may not be sufficient to sustain life, but does allow effective palliative care, that is, medical therapy alone. With NIV, patients retain a real say in their care, and, because assisted ventilation is not all or nothing, it is possible to move relatively easily between life sustaining and palliative care as the patient's situation changes.

SELECTION OF PATIENTS FOR NONINVASIVE VENTILATION IN A GENERAL WARD

Acute Respiratory Failure

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

The pH at the time NIV is initiated is the best single predictor of severity and the likelihood of success with the noninvasive approach.[68] Moreover, changes in pH and respiratory rate are easily measurable and useful in predicting the likelihood of a successful outcome from NIV.[9,17,69–73] Arterial blood gases should be checked at baseline and after 1 to 4 hours. Data from the largest study[74] showed that hydrogen ion concentration at enrollment (odds ratio 1.22 per nmol/L) and Pa_{CO_2} (odds ratio 1.14 per kPa) were associated with treatment failure. After 4 hours of therapy, improvement in acidosis (odds ratio 0.89 per nmol/L) and/or fall in respiratory rate (odds ratio 0.92 per breath per minute) were associated with success. If at least one of these two variables was improving, successful NIV was likely. pH, therefore, is useful in determining, first, who should receive NIV, second, in what location, and, finally, when the patient can move to a more or less intensive location. Generally speaking, the lower the pH, the greater is the risk to the patient of needing invasive ventilation if NIV is not offered or, if it is attempted, of failure. The more acidotic the patient, the greater is the need for that patient to be managed in an ICU because the risk of failure of NIV and the potential need for endotracheal intubation is higher.[75]

The same criteria can be extended to other patients with acute-on-chronic hypercapnic respiratory failure, for instance those with obesity. The pH criterion is less important as some of these patients will require chronic ventilator support, with either CPAP or NIV, if they already have symptoms of excessive daytime sleepiness or peripheral edema before admission. The patient should be reassessed post discharge because a significant proportion will be able to change their mode of ventilation or even need no ongoing ventilator support.[29] NIV certainly should not be delayed until acidosis occurs in patients with neuromuscular disease; by the time these patients become hypercapnic, respiratory reserve is very reduced and they are at high risk. NIV should be considered even if the patient is normocapnic if he or she is also tachypneic; these patients will tire out and the Pa_{CO_2} will start to rise. NIV will prevent this and also offload the respiratory muscles providing relief from dyspnea. Although it is less clear cut, the same principles apply to patients with chest wall deformity; chronic hypercapnia is an indication to start domiciliary NIV,[76] and there is therefore no reason not to start NIV if the patient is admitted to hospital with respiratory disease, even if not accompanied by acidosis. These patients do not require admission to an ICU.

HYPOXEMIC RESPIRATORY FAILURE

These patients are best managed in an ICU because the risks of failure are higher and because the major problem is inadequate oxygenation. Patients are more likely to need prompt invasive ventilation if they are deteriorating or have other organ failure; moreover, ventilators usually used on general wards are those designed primarily for home use, and a high FI_{O_2} cannot be delivered. One further consideration was highlighted by Delclaux et al[77] in a study on the use of noninvasive CPAP in patients with hypoxemic respiratory failure; there was a trend toward more cardiorespiratory arrests in the CPAP group. The increase was attributed to the improvement in oxygenation and other physiologic parameters while the patients were using CPAP, which led to a false sense of security; when patients take the mask off, even for a short period, SO_2 may fall rapidly, putting them at high risk. Any patient who desaturates within seconds of removing a mask should be monitored very carefully, usually in an ICU, and probably this should be considered an indication for intubation.

IMPLICATIONS FOR STAFFING AND TRAINING

Table 34-4 lists key training requirements.

NIV has been reported to be a time-consuming procedure.[78] As with any new technique, there is a learning curve, and the same authors subsequently published more encouraging results.[79] A number of ICU studies have shown that a significant amount of time is required to establish the patient on NIV, but this drops off substantially in subsequent days.[10,80,81] It is possible, therefore, that NIV may have a much greater impact on nursing workload outside the ICU, where nurses have responsibility for a larger number of patients. In the study of Plant et al,[22] NIV resulted in a modest increase

TABLE 34-4: KEY TRAINING REQUIREMENTS

Understanding the rationale for assisted ventilation
Mask and headgear selection and fitting
Ventilator circuit assembly
Theory of operation and adjusting ventilation to achieve desired outcome
Principles and practice of humidification
Inhaled therapy for the patient receiving NIV
Cleaning and general maintenance
Understanding how to monitor progress
Ethical issues relevant to the care of patients with incurable disease
Problem solving—the ability to recognize serious situations and act accordingly

in nursing workload, assessed using an end-of-bed log, in the first 8 hours of the admission, equivalent to 26 minutes, but no difference was identified thereafter. No data exist, however, on the effect NIV on the care of other patients on the ward, nor whether outcome would have been better had nurses spent more time with patients receiving NIV. Most of the centers that participated in the study had little or no previous experience of NIV and therefore required training in mask fitting and application of NIV. Formal training in the first 3 months of opening a ward by a research doctor and nurse was 7.6 hours (SD 3.6). Thereafter, each center received 0.9 hour per month (SD 0.82) to maintain skills. It should be appreciated that there was no need to make subtle adjustments to ventilator settings, which all was done according to protocol. Much more training would be needed if sophisticated ventilators are used. This underlines the fact, however, that NIV, in whatever location, is not just a question of purchasing the necessary equipment but also of staff training.

Although considerable input is likely when a unit commences to provide an NIV service, thereafter, as long as a critical mass remain, new staff will gain the necessary skills from their colleagues. Given that NIV in the more severely ill patient may require as much input as an invasively ventilated patient,[81] there usually should be one nurse responsible for no more than three or four patients, although this will depend on the other care needs of the patients. In the less severely affected patient, NIV can be successful with a lower level of staffing.[22]

ECONOMIC CONSIDERATIONS

Although the findings are not consistent, some of the larger studies show that NIV can shorten length of an ICU and/or hospital stay compared, for example, with medical therapy or invasive ventilation.[9,10,12,13,48,82] In no study has NIV been shown to lengthen hospital stay. Although not the primary aim of the studies, the finding of reduced length of stay creates or saves resources and thereby indicates a cost benefit from NIV.

In a North American cost-effectiveness analysis[83] in which NIV was delivered in the ICU, the authors concluded that NIV was more effective than standard treatment in reducing hospital mortality and also less expensive, with a cost saving of about $2500 per patient admission. Intensive care is also expensive care. Intermediate units provide an alternative to the classic ICU at reduced cost.[58] The daily costs of a ventilated patient may be reduced by two-thirds when NIV is performed in a specialized respiratory unit rather than in an ICU.[84] These costs can be reduced still further when NIV is performed on a general ward,[85] although effectiveness may not be as good as in higher-dependency settings. Carlucci et al[86] showed that over time practice changes. They found that after a few years, patients with more severe acidosis were ventilated successfully with NIV; more patients received NIV on general wards, with significant cost savings, compared with when they first started providing an acute NIV service.

THE FUTURE AND IMPORTANT UNKNOWNS

As the population ages, the pressure on ICU beds will increase and alternatives to intensive care will need to be developed further, even in health care systems that currently enjoy high levels of ICU provision. It is likely that, as has been seen in COPD, the management of more patients with NIV will take place outside of the ICU. The challenge will be to ensure that standards are maintained and that the real-world experience in the United Kingdom is avoided.[25] Technology will play a part, but staff training will remain key. The effect of provision of NIV upon the care of other patients on the general ward is an important consideration.

CONCLUSION

Staff training and experience are more important than location. Adequate numbers of staff, skilled in NIV, must be available throughout 24 hours. Because of the demands of looking after acutely ill patients, and to aid training and skill retention, acute NIV usually is best carried out in one single-sex location with one nurse responsible for three to four patients. Basic monitoring, at least pulse oximetry and facilities for arterial blood-gas analysis, should be available. Because the skills, both for NIV and for the other care needs of the patient population likely to need NIV, are transferable, there are significant advantages to locating both the acute and elective NIV service in the same place, but there must be ready access to invasive ventilation. The best location for both an acute and chronic NIV service will vary from institution to institution, and local expertise, enthusiasm, and hospital geography will be the major determinants of where the service should be located and how it is delivered.

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IX

PHYSIOLOGIC EFFECT OF MECHANICAL VENTILATION

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EFFECTS OF MECHANICAL VENTILATION ON CONTROL OF BREATHING

Dimitris Georgopoulos

The main reasons for instituting mechanical ventilation are to decrease the work of breathing, support gas exchange, and buy time for other interventions to reverse the cause of respiratory failure.[1] Mechanical ventilation can be applied in patients who are making or not making respiratory efforts, whereby assisted or controlled modes of support are used, respectively.[1] In patients without respiratory efforts, the respiratory system represents a passive structure, and thus the ventilator is the only system that controls breathing. During assisted modes of ventilator support, the patient's system of control of breathing is under the influence of the ventilator pump.[2–4] In the latter instance, ventilatory output is the final expression of the interaction between the ventilator and the patient's system of control of breathing. Thus, physicians who deal with ventilated patients should know the effects of mechanical ventilation on control of breathing, as well as their interaction. Ignorance of these issues may prevent the ventilator from achieving its goals and also lead to significant patient harm.

PHYSIOLOGY

The respiratory control system consists of a motor arm, which executes the act of breathing, a control center located in the medulla, and a number of mechanisms that convey information to the control center.[5,6] Based on information, the control center activates spinal motor neurons that subserve the respiratory muscles (inspiratory and expiratory); the intensity and rate of activity vary substantially between breaths and between individuals. The activity of spinal motor neurons is conveyed, via peripheral nerves, to respiratory muscles, which contract and generate pressure (Pmus). According to equation of motion, *Pmus* at time *t* during a breath is dissipated in overcoming the resistance (*Rrs*) and elastance (*Ers*) of the respiratory system (inertia is assumed to be negligible) as follows:

$$\text{Pmus}(t) = Rrs \times \dot{V}(t) + Ers \times \Delta V(t) \quad (1)$$

where $\Delta V(t)$ is instantaneous volume relative to passive functional residual capacity and $\dot{V}(t)$ is instantaneous flow. Equation (1) determines the volume–time profile and, depending on the frequency of respiratory muscle activation, ventilation. Volume–time profile affects Pmus via neuromechanical feedback; inputs generated from other sources (cortical inputs) may modify the function of control center. Ventilation, gas-exchange properties of the lung, and cardiac function determine arterial blood gases, termed *arterial oxygen tension* (Pa_{O_2}) and *arterial carbon dioxide tension* (Pa_{CO_2}), which, in turn, affect the activity of control center via peripheral and central chemoreceptors (chemical feedback). This system can be influenced at any level by diseases or therapeutic interventions.

During mechanical ventilation, the pressure provided by the ventilator (Paw) is incorporated into the system.[3] Thus, the total pressure applied to respiratory system at

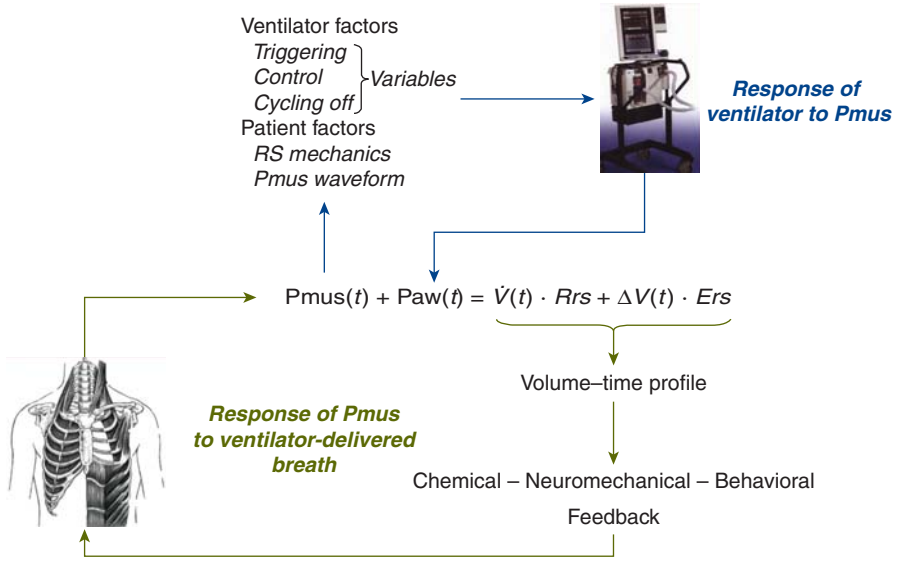

FIGURE 35-1 Schematic of variables that determine the volume–time profile during mechanical ventilation. Neuromechanical, chemical, and behavioral feedback systems are the main determinants of Pmus. The functional operation of the ventilator mode (triggering, control, and cycling-off variables) and patient-related factors (namely, respiratory system mechanics and the Pmus waveform) determine the response of the ventilator to Pmus. $\Delta V(t)$, instantaneous volume relative to passive functional residual capacity of respiratory system; *Ers,* elastance of the respiratory system; *Paw*(*t*), airway (ventilator) pressure; *Pmus*(*t*), instantaneous respiratory muscle pressure; *Rrs,* resistance of the respiratory system; *RS,* respiratory system; $\dot{V}(t)$, instantaneous flow.

time t [$P_{TOT}(t)$] is the sum of Pmus(t) and Paw(t). As a result, the equation of motion is modified as follows:

$$P_{TOT}(t) = \text{Pmus}(t) + \text{Paw}(t) = \dot{V}(t) \times Rrs + \Delta V(t) \times Ers \quad (2)$$

The relationships of Equation (2) determine the volume–time profile during mechanical ventilation, which via neuromechanical, chemical, and behavioral feedback systems affects the Pmus waveform (Fig. 35-1). The ventilator pressure, by changing flow and volume, may influence these feedback systems and thus alter either the patient's control of breathing itself or its expression. In addition, Pmus, depending on several factors, alters the Paw waveform (Fig. 35-1). Thus, during assisted mechanical ventilation (i.e., Pmus $\neq 0$), ventilatory output is not under the exclusive influence of patient's control of breathing; instead, it represents the final expression of an interaction between ventilator-delivered pressure and patient respiratory effort.

EFFECTS OF MECHANICAL VENTILATION ON FEEDBACK SYSTEMS

Chemical Feedback

Chemical feedback refers to the response of Pmus to Pa_{O_2}, Pa_{CO_2}, and pH.[5–7] In spontaneously breathing and mechanically ventilated patients, this system is an important determinant of respiratory motor output both during wakefulness and sleep.[7–11]

Mechanical ventilation can influence chemical feedback simply by altering the three variables Pa_{O_2}, Pa_{CO_2}, and pH. Hypoxemia, hypercapnia, or acidemia may be corrected by mechanical ventilation and thus modify activity of the medullary respiratory controller via peripheral and central chemoreceptors.[5,12] The effects of mechanical ventilation on gas-exchange properties of the lung are beyond the scope of this chapter and are discussed in Chapter 37. In this chapter, the fundamental elements of the response of respiratory motor output to chemical stimuli, their relationship to unstable breathing, and the operation of chemical feedback during mechanical ventilation are reviewed.

Response of Respiratory Motor Output to Chemical Stimuli

CARBON DIOXIDE STIMULUS

Carbon dioxide (CO_2) is a powerful stimulus of breathing.[5,12] This stimulus, expressed by Pa_{CO_2}, largely depends on the product of tidal volume (V_T) and breathing frequency (f) (i.e., minute ventilation) according to Equation (3):

$$Pa_{CO_2} = 0.863\ \dot{V}_{CO_2}/[V_T \times f(1 - V_D/V_T)] \quad (3)$$

where $\dot{V}_{CO_2}$ is CO_2 production, and V_D/V_T is the dead-space-to-tidal-volume ratio. Because minute ventilation is an adjustable variable in ventilated patients, understanding the relationship between respiratory motor output and CO_2 stimuli is of fundamental importance.

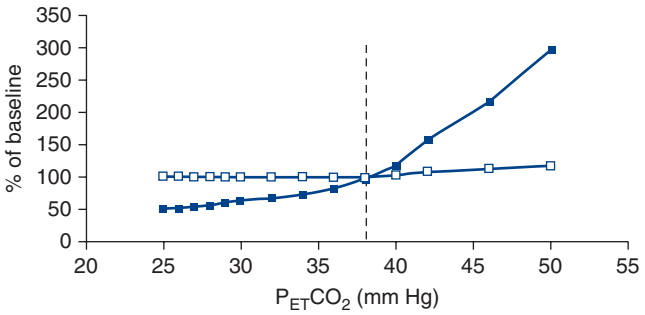

FIGURE 35-2 Schematic of the response of respiratory frequency (*open squares*) and pressure-time product of the inspiratory muscles per breath (an index of the intensity of patient effort, *closed squares*), both expressed as a percentage of values during spontaneous eupnea (baseline), to CO_2 challenge in conscious healthy subjects ventilated with a high level of ventilator assistance. $P_{ET}CO_2$ is end-tidal P_{CO_2}, and the *dotted vertical line* is $P_{ET}CO_2$ during spontaneous breathing (eupnea). Contrast the vigorous response of intensity of inspiratory effort to CO_2, even in the hypocapnic range, with the response of respiratory frequency, which remains at eucapnic level over a broad range of CO_2 stimuli. The response is based on data from references 7 and 13 to 16.

Several studies have examined the respiratory motor output to CO_2 in ventilated, conscious, healthy subjects.[7,13–16] Major findings include

1. Manipulation of Pa_{CO_2} over a wide range has no appreciable effect on respiratory rate. Despite hypocapnia, subjects continue to trigger the ventilator with a rate similar to that of eucapnia. Respiratory rate increases slightly when Pa_{CO_2} approaches values well above eucapnia (Fig. 35-2).
2. The intensity of respiratory effort (respiratory drive) increases progressively as a function of P_{CO_2}. This response is evident even in hypocapnic range. The response slope increases progressively with increasing CO_2 stimuli, reaching its maximum in the vicinity of eucapnic values (see Fig. 35-2).
3. There is no fundamental difference in the response to CO_2 between various ventilator modes.
4. Above eupnea, the slope of the response does not differ significantly with that observed during spontaneous breathing, suggesting that mechanical ventilation per se does not considerably modify the sensitivity of respiratory system to CO_2.

During sleep (or sedation), the response of respiratory motor output to CO_2 differs substantially from that during wakefulness, secondary to loss of the suprapontine neural input to the medullary respiratory controller.[10,17] In ventilated sleeping subjects, a decrease in Pa_{CO_2} by a few millimeters of mercury causes apnea.[10] Respiratory rhythm is not restored until Pa_{CO_2} has increased significantly above eupneic levels. The difference between eupneic Pa_{CO_2} and Pa_{CO_2} at apneic threshold, referred to as *CO_2 reserve*,[18] depends on several factors (see Response of Respiratory Motor Output to Chemical Stimuli—Chemical stimuli and unstable breathing). This reserve determines the propensity of an individual to develop breathing instability during sleep; propensity increases as CO_2 reserve decreases. Similar to wakefulness, the response of respiratory motor output to CO_2 is mediated mainly by the intensity of respiratory effort, whereas respiratory rate decreases abruptly to zero (apnea) when the CO_2 apneic threshold is reached.[19]

OTHER CHEMICAL STIMULI

The effects of mechanical ventilation on the response of respiratory motor output to stimuli other than CO_2 have not been studied adequately. In a steady state during wakefulness, the effects of oxygen (O_2) and pH on breathing pattern are similar qualitatively to that observed with CO_2: Changes in O_2 and pH mainly alter the intensity of patient effort, whereas respiratory rate is affected considerably less.[5,12] There is no reason to expect a different response pattern during mechanical ventilation. Indeed, this is the case regarding the hypoxic response in normal conscious subjects ventilated in assist-control mode during eucapnia.[20] Indirect data also revealed that during eucapnia, the sensitivity of respiratory motor output to hypoxia was not modified by mechanical ventilation.[20] During mild hypocapnia, however, the response was attenuated, whereas at moderate hypocapnia (end-tidal P_{CO_2} approximately 31 mm Hg) the response was negligible. The latter observations may be relevant clinically because ventilated patients do not always keep Pa_{CO_2} at eucapnic levels and can become hypocapnic.[16]

CHEMICAL STIMULI AND UNSTABLE BREATHING

The response pattern of respiratory motor output to CO_2 during sleep is relevant to the occurrence of periodic breathing in mechanically ventilated patients. Studies indicate that this breathing pattern might increase the morbidity and mortality of critically ill patients because it can cause sleep fragmentation and patient–ventilator dyssynchrony.[21–23] Sleep deprivation may cause serious cardiorespiratory,[24,25] neurologic,[26,27] immunologic, and metabolic consequences.[28–31]

The following is a brief review of the factors that can lead to unstable breathing. In a closed system governed mainly by chemical control (such as occurs during sleep or sedation), a transient change in ventilation at a given metabolic rate ($\Delta\dot{V}_{initial}$) will result in a transient change in alveolar gas tensions. This change is sensed by peripheral and central chemoreceptors, which, after a variable delay, exert a corrective ventilatory response ($\Delta\dot{V}_{corrective}$) that is in the opposite direction to the initial perturbation[32,33] (Fig. 35-3). The ratio of $\Delta\dot{V}_{corrective}$ to $\Delta\dot{V}_{initial}$ defines the loop gain of the system.[32] Loop gain is a dimensionless index that is the mathematical product of three types of gains: plant gain (the relationship between the change in gas tensions in mixed pulmonary capillary blood and $\Delta\dot{V}_{initial}$), feedback gain (the relationship between gas tensions at the chemoreceptor level and those at the mixed pulmonary capillary level), and controller gain (the relationship between $\Delta\dot{V}_{corrective}$ and the change in gas tensions at the chemoreceptor level) (Fig. 35-3). Loop gain has both a magnitude and a dynamic component.[32,33] In this

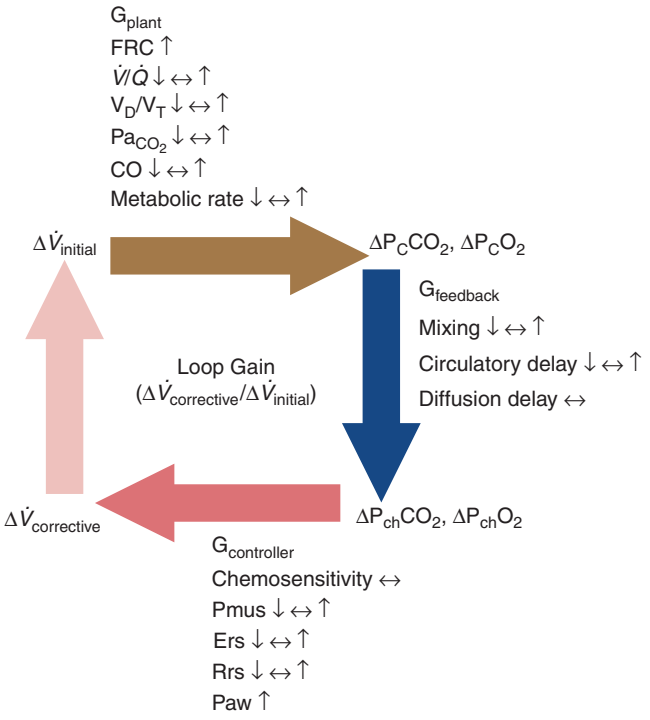

FIGURE 35-3 Schematic of the variables that determine the propensity of an individual to develop periodic breathing in a closed system dominated by chemical feedback. Loop gain is the product of three gains: plant, feedback, and controller. Instability occurs when $\Delta\dot{V}_{corrective}$ (the final response) is 180 degrees out of phase with $\Delta\dot{V}_{initial}$ (the transient initial perturbation) and $\Delta\dot{V}_{corrective}/\Delta\dot{V}_{initial}$ is greater than 1. Mechanical ventilation, by affecting almost all variables of the system (↑, increase; ↔, no change; ↓, decrease), may change both the magnitude and the dynamic component of loop gain and thus the propensity of an individual to develop periodic breathing. CO, cardiac output; ΔP_CCO_2 and ΔP_CO_2, the difference in partial pressures of CO_2 and O_2 in mixed pulmonary capillary blood, respectively; $\Delta P_{ch}CO_2$ and $\Delta P_{ch}O_2$, the difference in partial pressure of CO_2 and O_2 at chemoreceptors (peripheral and central), respectively; Ers and Rrs, elastance and resistance of respiratory system, respectively; FRC, functional residual capacity; *LG*, G_{plant}, $G_{feedback}$, and $G_{controller}$, loop, plant, feedback, and controller gains, respectively; Pa_{CO_2} alveolar partial pressure of CO_2; Paw, airway (ventilator) pressure; Pmus, pressure developed by respiratory muscles; $\dot{V}/\dot{Q}$, ventilation–perfusion ratio; V_D/V_T, dead-space fraction.

system, instability occurs when the corrective response is 180 degrees out of phase with initial disturbance (dynamic component) and loop gain is greater than 1 (magnitude component). This instability leads to fluctuation in chemical stimuli, namely, P_{CO_2}. If P_{CO_2} reaches the apneic threshold, apnea occurs.

Positive-pressure breathing exerts multiple effects on loop gain by influencing almost all the factors that determine plant, feedback, and controller gains. The effects are complex and at times opposing and variable (Table 35-1; see also Fig. 35-3). Nevertheless, the effect of mechanical ventilation on controller gain exerts the most powerful influence on the propensity to develop breathing instability.[8,19,21,23] The magnitude and direction of the change in controller gain depends on the ventilator mode, the level of assistance, the mechanics

TABLE 35-1: EFFECTS OF MECHANICAL VENTILATION ON GAIN FACTORS AND GAIN CHANGES

Gain Factors (Influence)	Ventilator Effect*	Gain Change
Lung volume (stabilizing)	↑	$\downarrow G_{plant}$
Cardiac output (destabilizing)	↓	$\uparrow G_{plant}$, $\uparrow G_{feedback}$
Thoracic blood volume (destabilizing)	↓	$\uparrow G_{feedback}$
Paw response to Pmus (destabilizing)	↑	$\uparrow G_{controller}$
Alveolar P_{CO_2} (stabilizing)	↓	$\downarrow G_{plant}$
Alveolar P_{O_2} (stabilizing)	↑	$\downarrow G_{plant}$, $\downarrow G_{controller}$
Respiratory elastance (destabilizing)	↓	$\uparrow G_{controller}$

Abbreviations: ↓, decrease; ↑, increase; Paw, airway pressure; Pmus, respiratory muscle pressure.

*Mechanical ventilation may also exert opposite effects on the various gain factors.

of the respiratory system, and the Pmus waveform (see the section Interactive Effects of Patient-Related Factors and Ventilator on Control of Breathing).[8,16,19,21] Disease states as well as medications (e.g., sedatives) also may interfere with the effects of mechanical ventilation on loop gain. For example, positive-pressure ventilation may increase or decrease cardiac output, causing corresponding changes in circulatory delay depending on cardiac function and intravascular volume (see Chapter 36).[34–37] It has been shown that nocturnal mechanical ventilation in patients with congestive heart failure decreases the frequency of Cheyne-Stokes breathing, presumably by causing an increase in cardiac output secondary to afterload reduction.[38–40] Sedatives at moderate doses, commonly used in ventilated patients, decrease considerably the loop gain, partly mitigating the effect of mechanical ventilation on controller gain and thus promote ventilatory stability.[41]

In addition to CO_2, O_2 and pH can play a key role in producing unstable breathing in ventilated patients during sleep (or sedation). It is well known that hypoxia, acting via peripheral chemoreceptor stimulation, decreases Pa_{CO_2}. The result reduces the plant gain (stabilizing influence); for a given change in alveolar ventilation, Pa_{CO_2} will change less when baseline Pa_{CO_2} is low than when it is high.[18] Hypoxia, however, increases the controller gain to a much greater extent[42] because the slope of ventilatory response to CO_2 below eupnea increases,[12] a highly destabilizing influence.[32,33] Similar principles apply if pH is considered as a chemical stimulus; acidemia decreases the plant gain (lowers Pa_{CO_2}) and increases, to a much lesser extent, the controller gain.[18,42] During mechanical ventilation, the propensity to unstable breathing in the face of changing O_2 and pH stimuli depends on a complex interaction between the effects of these stimuli and mechanical ventilation on plant, feedback, and controller gains (Fig. 35-4; see also Table 35-1).

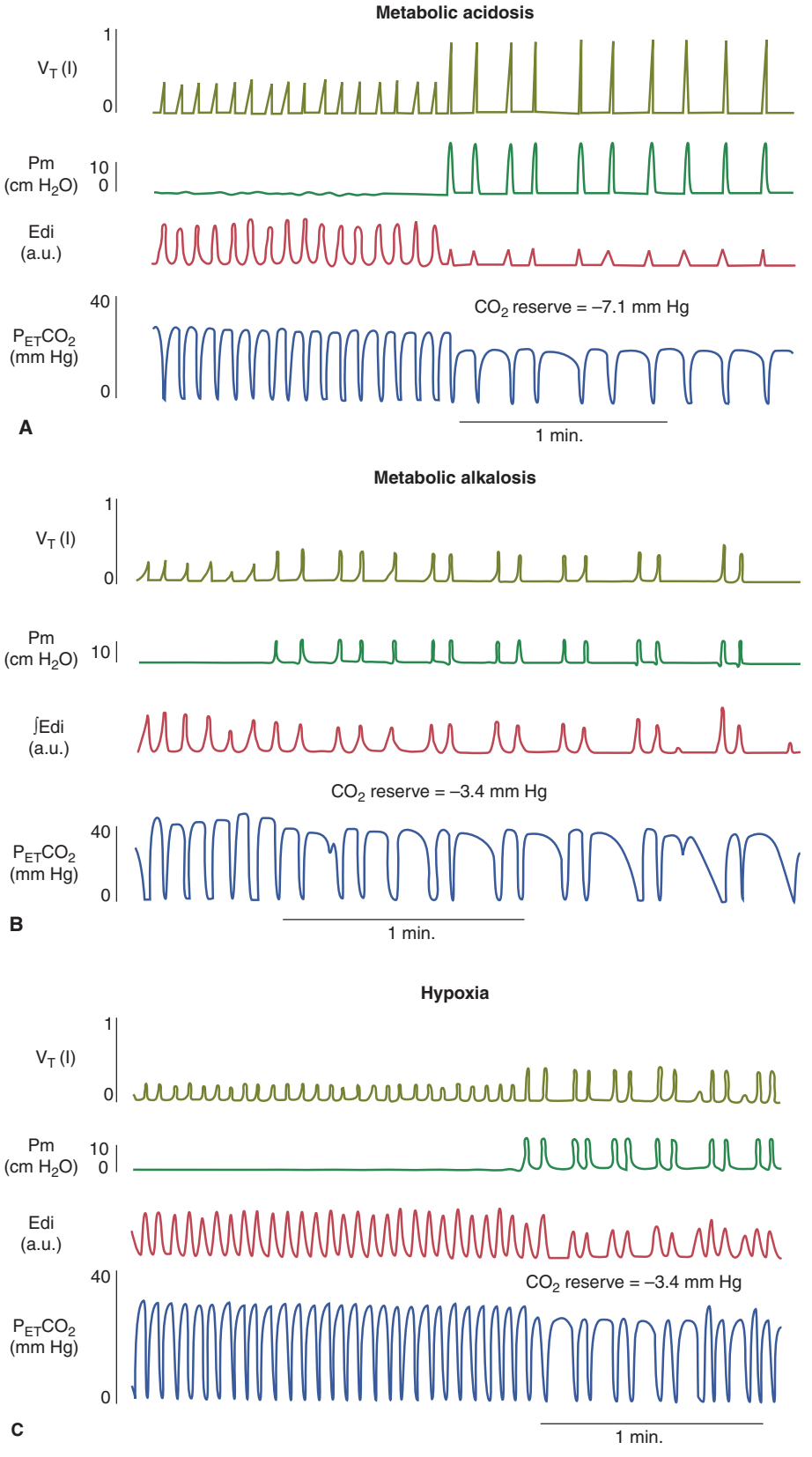

FIGURE 35-4 Tidal volume (V_T), airway pressure (*Pm*), integrated diaphragmatic electrical activity (*Edi*, arbitrary units), and partial pressure of end-tidal CO_2 ($P_{ET}CO_2$) in a tracheostomized dog during non–rapid eye movement sleep without and with pressure-support ventilation at a pressure level that caused periodic breathing. (**A**) At a background of 5 hours of metabolic acidosis (pH 7.34, HCO_3^- 16 mEq/L, Pa_{CO_2} 30 mm Hg). (**B**) At a background of 1 hour of metabolic alkalosis (pH 7.51, HCO_3^- 35 mEq/L, Pa_{CO_2} 44 mm Hg). (**C**) During hypoxia (Pa_{O_2} 47 mm Hg, Pa_{CO_2} 31 mm Hg). At a background of metabolic acidosis, CO_2 reserve was quite high; consequently, the pressure level that caused periodic breathing (20 cm H_2O) was significantly higher than the corresponding values (approximately 10 cm H_2O) during metabolic alkalosis or hypoxia. Hyperventilation during spontaneous breathing was similar during metabolic acidosis and hypoxia (similar stabilization influence via a decrease in plant gain secondary to low Pa_{CO_2}), indicating that the destabilizing influence of hypoxia was caused by an increase in controller gain (hypoxic increase in the slope of CO_2 below eupnoea). (Used, with permission, from Dempsey et al. *J Physiol.* 2004;560:1–11, based on data from Nakayama H, Smith CA, Rodman JR, et al. Effect of ventilatory drive on carbon dioxide sensitivity below eupnea during sleep. *Am J Respir Crit Care Med.* 2002;165:1251–1260.)

Operation of Chemical Feedback

The ventilator mode is a major determinant of driving pressure for flow and thus arterial blood gases. Before discussing the operation of chemical feedback, it is useful to review briefly the functional features of three main modes of assisted ventilation, namely, assist-control ventilation (ACV), pressure-support ventilation (PSV), and proportional-assist ventilation (PAV) (for detailed descriptions, see Chapters 6, 8, and 12). Figure 35-5 shows the response of the ventilator to respiratory effort in a representative subject ventilated with each mode in the presence and absence of CO_2 challenge.[16] With CO_2 challenge, Paw decreases with ACV, it remains constant with PSV, and it increases with PAV. Pressure-time product of inspiratory muscle pressure (PTP-$Pmus_I$) is an accurate index of the intensity of inspiratory effort.[43] With ACV, the ratio of V_T to PTP-$Pmus_I$ per breath (neuroventilatory coupling) decreases with increasing Pmus; the ratio is largely independent of inspiratory effort with PAV. With PSV, V_T/PTP-$Pmus_I$ per breath may change in either direction with increasing Pmus, depending on factors such as the level of pressure assist and cycling-off criterion, change in Pmus, and mechanics of the respiratory system. With PSV, in the absence of active termination of pressure delivery (with expiratory muscle contraction), the ventilator delivers a minimum V_T, which may be quite high, depending on the pressure level, mechanics of the respiratory system, and cycling-off criterion.[19]

Assume that in a ventilated patient Pa_{CO_2} drops because of an increase in the set level of assistance or decrease in metabolic rate and/or V_D/V_T ratio.[44] During wakefulness, patients will react to this drop by decreasing the intensity of their inspiratory effort, whereas the breathing frequency will remain relatively constant (see "Response of Respiratory Motor Output to Chemical Stimuli," above). The extent to which a patient is able to prevent respiratory alkalosis via operation of chemical feedback depends almost exclusively on the relationship between the intensity of patient inspiratory effort and the volume delivered by the ventilator (i.e., V_T/PTP-$Pmus_I$). Similarly, if Pa_{CO_2} increases (decrease in assistance level, increase in metabolic rate and/or V_D/V_T ratio), the patient will increase the intensity of inspiratory effort and, to much lesser extent, respiratory frequency. Thus, V_T/PTP-$Pmus_I$ per breath is critical for the effectiveness of chemical feedback to compensate for changes in chemical stimuli (Pa_{CO_2}). For given respiratory system mechanics, V_T/PTP-$Pmus_I$ is heavily dependent on the mode of support. Thus, the effectiveness of chemical feedback in compensating for changes in chemical stimuli should be mode-dependent. Modes of support that permit the intensity of patient inspiratory effort to be expressed on ventilator-delivered volume improve the effectiveness of chemical feedback in regulating Pa_{CO_2} and particularly in

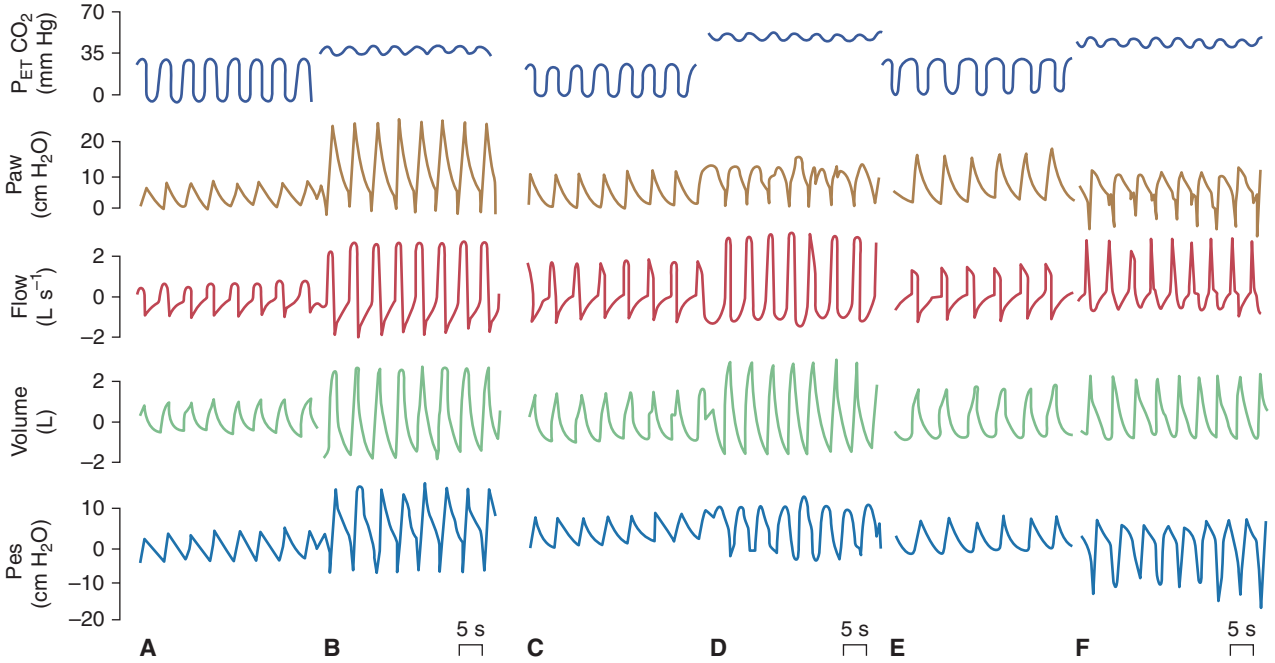

FIGURE 35-5 End-tidal carbon dioxide tension ($P_{ET}CO_2$), airway pressure (*Paw*), flow (inspiration up), volume (inspiration up), and esophageal (*Pes*) pressure in a representative subject during proportional-assist ventilation (**A**, **B**), pressure-support ventilation (**C**, **D**), and volume-control ventilation (**E**, **F**) in the absence (**A**, **C**, **E**) and presence (**B**, **D**, **F**) of CO_2 challenge. With CO_2 challenge, Paw decreases with assist-control ventilation (the ventilator antagonizes patient's effort); it remains constant with pressure-support ventilation (no relationship between patient effort and level of assist); and it increases with proportional-assist ventilation (positive relationship between effort and pressure assist). (Used, with permission from Mitrouska J, Xirouchaki N, Patakas D, et al. Effects of chemical feedback on respiratory motor and ventilatory output during different modes of assisted mechanical ventilation. *Eur Respir J.* 1999;13:873–882.)

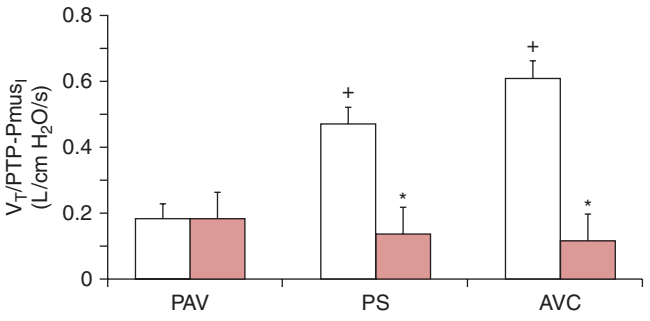

FIGURE 35-6 Ratio (mean ± SD) of tidal volume to pressure–time product of inspiratory muscles ($V_T/PTP\text{-}Pmus_I$) in normal, conscious subjects ventilated with three modes of assisted ventilation in the absence and presence of CO_2 challenge (inspired CO_2 concentration increased in small steps until intolerance developed). *Open* and *closed bars* represent zero and final (highest) concentration of inspired CO_2, respectively. *AVC,* assist-volume control; *PAV,* proportional-assist ventilation; *PS,* pressure-support ventilation. *Asterisk* indicates significant difference from the value without CO_2 challenge. *Plus* sign indicates significant difference from the corresponding value with PAV. With each mode, subjects were ventilated at the highest comfortable level of assistance (corresponding to 80% reduction of patient resistance and elastance with PAV, 10 cm H_2O of pressure support, and 1.2-L tidal volume with AVC). With CO_2 challenge, V_T/PTP-Pmus$_I$, decreased significantly when the subjects were ventilated with PS and AVC, but it remained relatively constant with PAV. Without CO_2 challenge, V_T/PTP-Pmus$_I$ was significantly higher with PS and AVC than with PAV. This response pattern caused severe respiratory alkalosis with PS and AVC ($P_{ET}CO_2$ decreased to approximately 22 mm Hg with both modes) but not with PAV ($P_{ET}CO_2$ approximately 30 mm Hg). Unlike with PS and PAV, subjects ventilated with AVC could not tolerate high values of $P_{ET}CO_2$ (final $P_{ET}CO_2$ was approximately 7, 11, and 13 mm Hg higher than baseline eupnea, respectively, with AVC, PS, and PAV). (Based on data from Mitrouska et al.[16])

preventing respiratory alkalosis. In normal conscious subjects receiving maximum assistance on the three main ventilator modes,[16] the ability of the subject to regulate Pa_{CO_2} depends on the operational principles of each mode, specifically in terms of V_T/PTP-Pmus$_I$ (Fig. 35-6). At all levels of CO_2 stimulation, preservation of neuroventilatory coupling increased progressively from ACV to PSV to PAV; the ability of subjects to regulate Pa_{CO_2} followed the same pattern.[16]

Neurally adjusted ventilatory assist (NAVA) is a new mode of support that, similar to PAV, uses patient effort to drive the ventilator.[45–47] The electrical activity of the diaphragm is obtained with a special designed esophageal catheter and serves as a signal to link inspiratory effort to ventilator pressure (see Chapter 13). Because neuroventilatory coupling is preserved, the principles described above also apply to NAVA.[46,47]

During sleep or sedation, the tendency to develop hypocapnia with ACV and PSV (see Chapter 57 for the effects of mechanical ventilation on sleep) may have serious consequences because a drop of a few millimeters of mercury in Pa_{CO_2} leads to apnea and periodic breathing.[8,19] Thus, excessive assistance with ACV and PSV promotes unstable breathing secondary to impaired neuroventilatory coupling; controller gain remains high in the face of low inspiratory effort (Fig. 35-7). Unstable breathing, however, during sleep secondary to mechanical ventilation may be prevented or attenuated with PAV and NAVA that does not guarantee a minimum V_T.[8,19,46,47] Modes that decrease the volume delivered by a ventilator in response to any reduction in the intensity of patient effort enhance breathing stability and may be associated with better sleep quality.[48] Nevertheless, if the assist setting during PAV or NAVA is such that controller gain increases considerably, and the inherent loop gain of the patient is relatively high, the patient will be at risk of developing unstable breathing.[23,33,41,49,50]

These principles may be altered by disease states and therapeutic interventions. Although little is known about the interaction between disease states and mechanical ventilation on control of breathing, two examples help in illustrating the point. First, in conscious patients with sleep apnea syndrome, a drop in Pa_{CO_2} because of brief (40 seconds) hypoxic hyperventilation resulted, contrary to healthy subjects, in significant hypoventilation and triggering of periodic breathing in some patients.[51] This hypoventilation was interpreted as evidence of a defect (or reduced effectiveness) of short-term poststimulus potentiation, a brainstem mechanism that promotes ventilatory stability.[51] In this situation, a level of assistance that causes a significant decrease in Pa_{CO_2} may promote unstable breathing in awake patients with sleep apnea syndrome, a situation closely resembling that observed during sleep. Second, studies in ventilated critically ill patients have shown that when awake patients are unable to increase V_T appropriately as a result of the mode used (i.e., PSV), they increase respiratory rate in response to a chemical challenge.[52] Behavioral feedback, however, may underlie this response pattern. In sedated patients with acute respiratory distress syndrome (in whom behavioral feedback is not an issue) receiving PSV, considerable variation in Pa_{CO_2} elicited a steady-state response limited to the intensity of breathing effort, a response pattern similar to that observed in normal subjects.[9,16]

Neuromechanical Feedback

INTRINSIC PROPERTIES OF RESPIRATORY MUSCLES

For a given neural output, Pmus decreases with increasing lung volume and flow, as dictated by the force-length and force-velocity relationships of inspiratory muscles, respectively.[53] Therefore, for a given level of muscle activation, Pmus should be smaller during mechanical ventilation than during spontaneous breathing if pressure provided by the ventilator results in greater flow and volume. It has been shown in healthy subjects ventilated with PSV that, compared with spontaneous breathing, the relationship between electrical activity (Edi) and pressure-time product of diaphragm (PTPdi) is shifted to the left; thus, at any given level of Edi, PTPdi is reduced.[54]

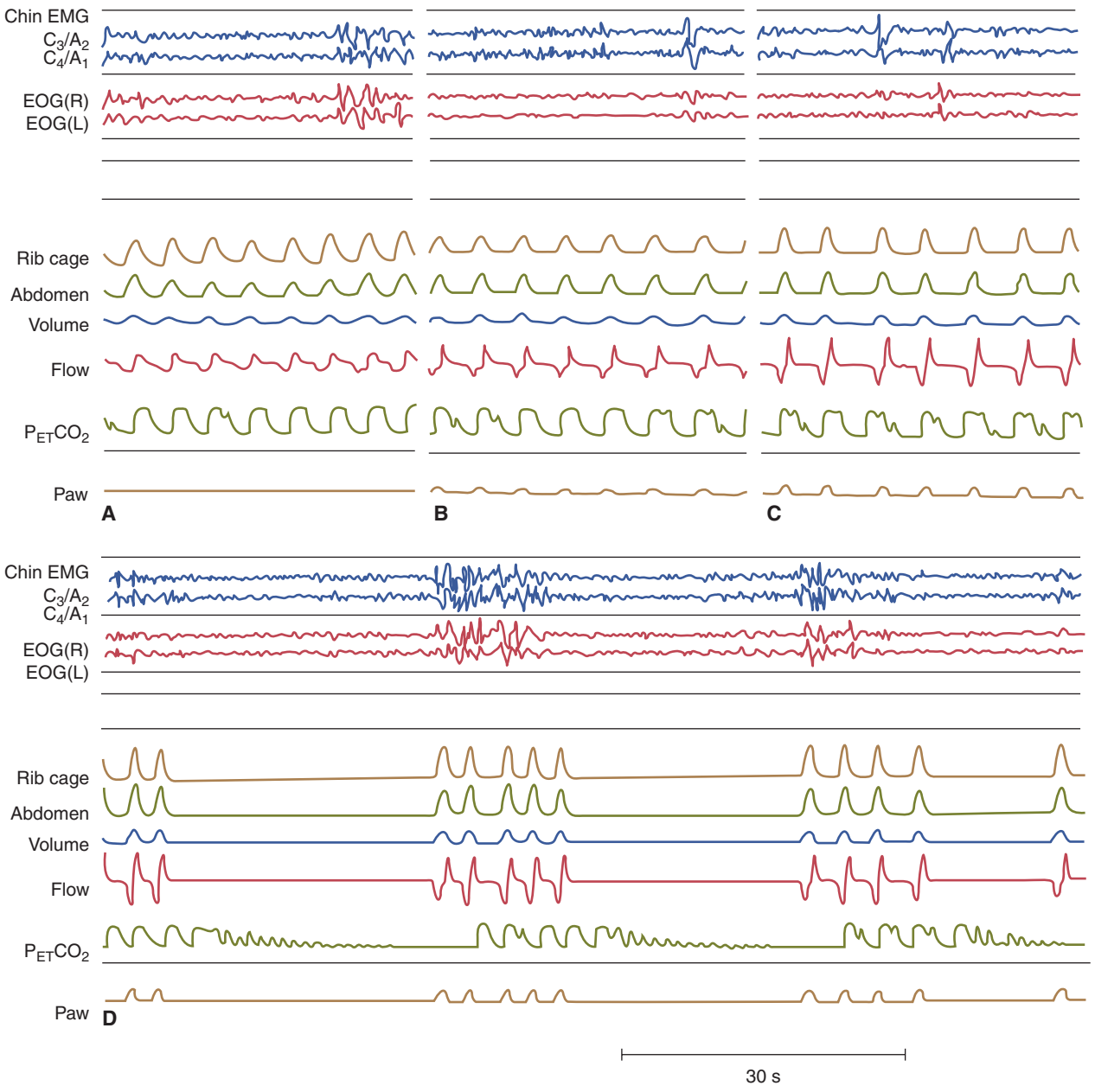

FIGURE 35-7 Polygraph tracings in a healthy subject during non-rapid eye movement sleep with and without pressure-support ventilation. (**A**) Spontaneous breathing with continuous positive airway pressure (CPAP). (**B**) to (**D**) Pressure support of 3, 6, and 8 cm H_2O, respectively. Periodic breathing with central apneas developed with pressure support of 8 cm H_2O. *C3/A2* and *C4/A1,* electroencephalogram channels; *EMG,* electromyogram; *EOG,* electrooculogram (right [*R*] and left [*L*]); *Paw,* airway pressure; $P_{ET}CO_2$, end-tidal P_{CO_2}. (Used, with permission, from Meza, et al. Susceptibility to periodic breathing with assisted ventilation during sleep in normal subjects. *J Appl Physiol.* 2003;167:1193–1199.)

The influence and consequences of mechanical feedback during mechanical ventilation have not been studied satisfactorily. It is possible that this type of feedback is of clinical significance in patients with dynamic hyperinflation (high end-expiratory lung volume), high ventilatory requirements (requirements for high flow and volume), and/or impaired neuromuscular capacity.

REFLEX FEEDBACK

The characteristics of each breath are influenced by various reflexes that are related to lung volume or flow and mediated, after a latency of a few milliseconds, by receptors located in the respiratory tract, lung, and chest wall.[5,6] Mechanical ventilation may stimulate these receptors by changing flow and volume. In addition, changes in

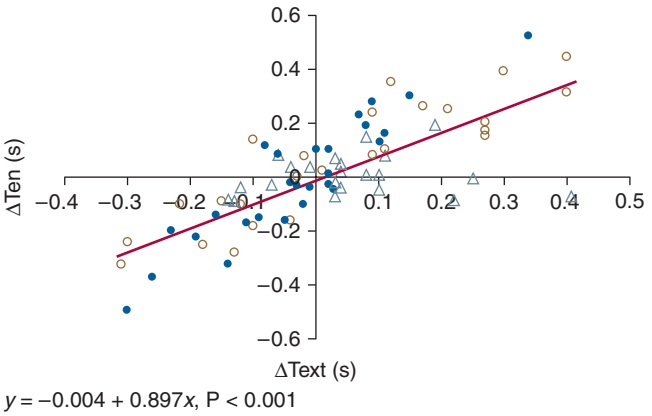

FIGURE 35-8 Relationship between the changes in the time that mechanical inspiration extended into neural expiration (Δ*Text,* expiratory asynchrony) and neural expiratory time (Δ*Ten*) in mechanically ventilated patients with acute respiratory distress syndrome. Closed circles, open circles, and open triangles represent ΔText induced by changes in volume (at constant flow), flow (at constant volume), and pressure support, respectively. Solid line, regression line. (Based on data from Kondili E, Prinianakis G, Anastasaki M, Georgopoulos D. Acute effects of ventilator settings on respiratory motor output in patients with acute lung injury. *Intensive Care Med.* 2001;27:1147–1157.)

ventilator settings, inevitably associated with changes in volume and flow, also may elicit acute Pmus responses mediated by reflex feedback. In sedated patients with acute respiratory distress syndrome, manipulation of ventilator settings altered immediately (within one breath) the neural respiratory timing, whereas respiratory drive remained constant.[9,55] Specifically, decreases in V_T and pressure support and increases in inspiratory flow caused an increase in respiratory frequency. Depending on the type of alteration, changes in respiratory frequency were mediated via alteration in neural inspiratory and expiratory time; increases in inspiratory flow caused increases in respiratory frequency mainly by decreasing neural inspiratory time; decreases in V_T and pressure support caused increases in respiratory frequency by decreasing neural expiratory time. This reflex response was similar, at least qualitatively, to that observed in healthy subjects during wakefulness and sleep.[56–60] There was a strong dependency of neural expiratory time on the time that mechanical inflation extended into neural expiration; neural expiratory time increased proportionally to the increase in the delay between the ventilator cycling off and the end of neural inspiratory time (Fig. 35-8).[9,55] This finding indicates that expiratory asynchrony may elicit a reflex timing response. A subsequent study in a general intensive care unit population confirmed the dependency of neural expiratory time on expiratory asynchrony.[61] The most likely explanation for the timing response is the Herring-Breuer reflex.

The final response may be unpredictable depending on the magnitude and type of lung volume change, the level of consciousness, and the relative strength of the reflexes involved. Nevertheless, reflex feedback should be taken into account when ventilator strategies are planned. A few examples may help in illustrating the importance of reflex feedback in patient–ventilator interaction. Assume that the patient is receiving pressure support that is being decreased during weaning. This results in lower V_T, which through reflex feedback decreases neural expiratory time, causing an increase in respiratory frequency.[9,55] This increase should not be interpreted as patient intolerance to the decrease in pressure support. Consider another patient with obstructive lung disease receiving ACV. V_T is decreased at a constant inspiratory flow so as to reduce the magnitude of dynamic hyperinflation (less volume is exhaled over a longer period). The lower V_T usually results in less delay in breath termination as compared with the end of neural inspiration, which through vagal feedback will decrease neural expiratory time, limiting the effectiveness of this strategy for reducing dynamic hyperinflation.[55] Assume in another patient receiving ACV that inspiratory flow is increased at a constant V_T, with the intent of reducing inflation time and providing more time for expiration so as to reduce dynamic hyperinflation. This step causes a reflex decrease in neural inspiratory time and an increase in respiratory frequency. Mechanical expiratory time may change in either direction depending mainly on the relation between neural and mechanical inspiratory time. In patients receiving ACV, expiratory time showed a variable response to changes in flow rate; some patients actually demonstrate a reduced expiratory time with a higher flow,[62] which cancels the desired reduction in dynamic hyperinflation.

There are neural reflexes that inhibit inspiratory muscle activity if lung distension exceeds a certain threshold, which is well below total lung capacity (Hering-Breuer reflex).[6,63,64] These reflexes protect the lung from overdistension, which is associated with lung injury.[65,66] Pressure-control or volume-control modes of assisted ventilation considerable interfere with the ability of these reflexes to regulate tidal volume.[16,67] With these modes, as a result of neuroventilatory uncoupling (high V_T/PTP-$Pmus_I$), overassistance may result in high tidal volume leading to regional or global lung overdistension. Conversely, recent evidence indicates that ventilator modes that permit reflex feedback to regulate the tidal volume and respiratory rate (viz., NAVA, PAV) may protect against or lessen ventilator-induced lung injury.

Brander et al[68] randomized anesthetized rabbits with early experimental acute lung injury into three ventilator strategies: NAVA (nonparalyzed), volume control with tidal volume of 6 mL/kg (paralyzed, protective strategy), and volume control with tidal volume of 5 mL/kg (paralyzed, injurious strategy). Animals randomized to NAVA selected an average tidal volume of 2.7 ± 0.9 mL/kg and respiratory rate up to three times higher than that in both controlled ventilation groups—a breathing-pattern response that can be explained by vagally controlled reflexes.[6,63,64] Compared to the 15 mL/kg group, animals ventilated with either NAVA or volume control at 6 mL/kg exhibited less ventilator-induced lung injury, as indicated by lung injury scores, lung wet-to-dry ratio, and lung and systemic biomarkers (Fig. 35-9). These

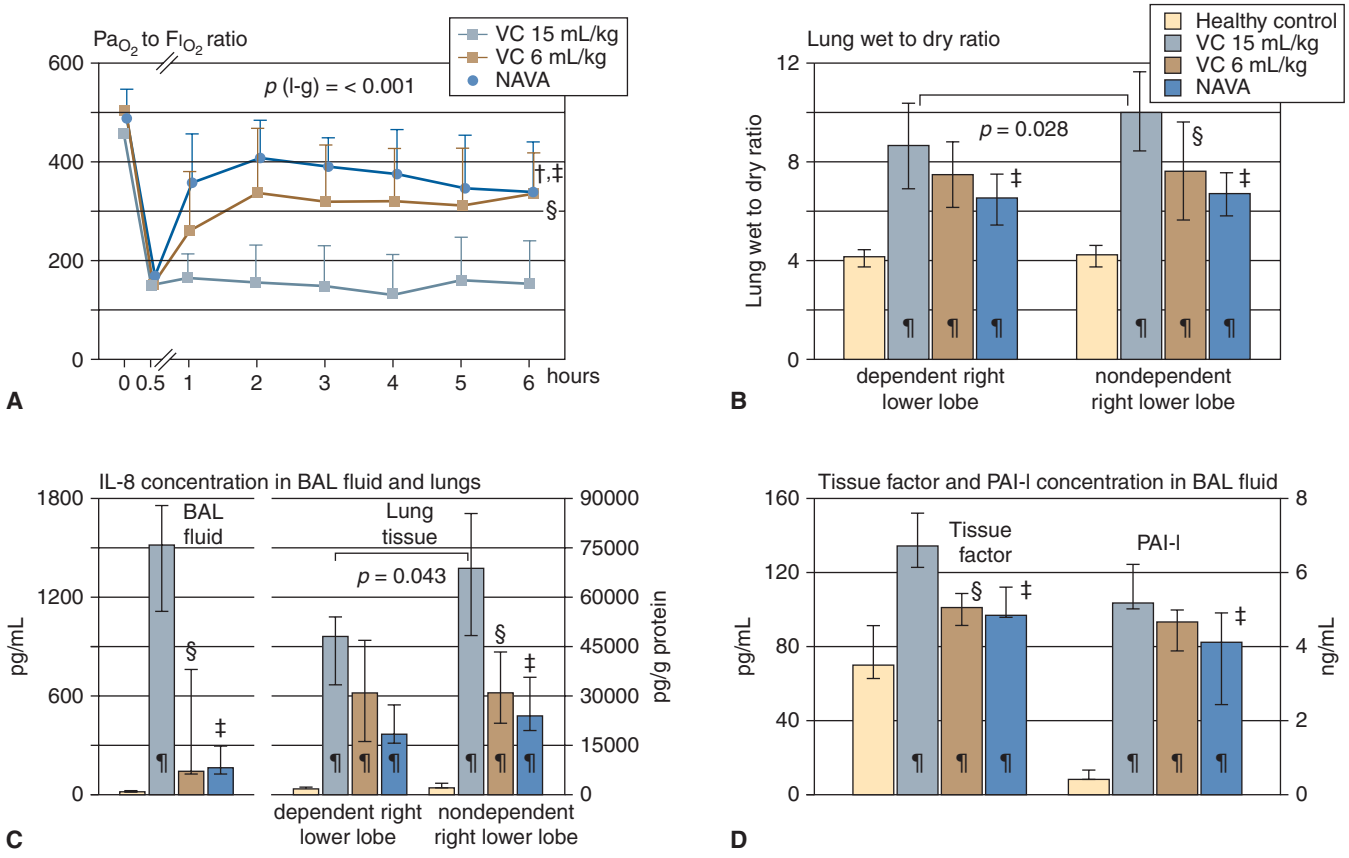

FIGURE 35-9 Parameters indicative of ventilator-induced lung injury (VILI) in rabbits with induced acute lung injury (ALI) and ventilated with three strategies: NAVA, volume control with tidal volume (V_T) of 6 mL/kg, and volume control with V_T of 15 mL/kg. (**A**) There were no differences in partial pressure of arterial oxygen to fractional inspired oxygen concentration ratio (Pa_{O_2}/FI_{O_2}) among groups before and 30 minutes after induction of ALI. The increase in Pa_{O_2}/FI_{O_2} shortly after switching to the assigned ventilation mode (i.e., after randomization into the treatment groups) was more pronounced with NAVA than with volume control (VC) 6-mL/kg ($p < 0.05$ post hoc analysis), although Pa_{O_2}/FI_{O_2} was not different between NAVA and VC 6-mL/kg at the end of the protocol. With VC 15-mL/kg, Pa_{O_2}/FI_{O_2} remained below 200. (**B**) The lung wet-to-dry ratio with NAVA and with VC 6-mL/kg was lower than with VC 15-mL/kg (albeit not significantly for the dependent lung in VC 6-mL/kg animals). (**C**) and (**D**) Interleukin 8 (IL-8), tissue factor, and plasminogen activator inhibitor type 1 (PAI-1) concentration in bronchoalveolar (BAL) fluid was higher in all study groups compared to healthy controls and was higher with VC 15-mL/kg than with the other two groups (except for PAI-1 in VC 6-mL/kg). Lung tissue IL-8 concentration was increased in all groups as compared to nonventilated controls and was highest in the nondependent lung regions with VC 15-mL/kg. In the VC 6-mL/kg and NAVA groups, lung tissue IL-8 concentration was lower compared to VC 15-mL/kg (albeit not significant for the dependent lung region). Groups are shown as mean ± standard deviation (SD) for *A* and *B*, or as median (quartiles) for *C* and *D*. *Symbols* represent group mean; *bars* indicate standard deviation. *e–g,* time–group interaction (two-way analysis of variance). Post hoc pairwise comparison procedure between groups: $^{\dagger}p$ <0.05 NAVA versus VC 6-mL/kg; $^{\ddagger}p$ <0.05 NAVA versus VC 15-mL/kg; $^{\S}p < 0.05$ VC 6-mL/kg versus VC 15-mL/kg. (Used, with permission, from Brander L, Sinderby C, Lecomte F, et al. Neurally adjusted ventilatory assist decreases ventilator-induced lung injury and non-pulmonary organ dysfunction in rabbits with acute lung injury. *Intensive Care Med.* 2009;35:1979–1989.)

results indicate that the use of NAVA, which allowed the animals to choose their own respiratory pattern, was at least as effective in preventing various manifestations of ventilator-induced lung injury as conventional, volume-controlled ventilation using a tidal volume of 6 mL/kg.

In a human study employing randomized design, Xirouchaki et al[69] ventilated 108 critically ill patients, most of whom had acute lung injury or acute respiratory distress syndrome, with PAV+ (PAV with automatic estimation of elastance and resistance of the respiratory system; see Chapter 12) Even with high assistance, tidal volume and end-inspiratory plateau pressure were comparable to these observed during protective controlled mechanical ventilation. Examination of individual end-inspiratory plateau pressures during PAV+ showed that out of a total of 744 measurements only on nine occasions (1.2%) and in five patients (4.6%) were plateau pressures above 30 cm H_2O (Fig. 35-10). Ninety-four percent of the end-inspiratory plateau pressures were below 26 cm H_2O, a value associated with lung protection.[70] Similar to the findings of Brander et al, these results can be explained by the operation of reflex feedback (vagally controlled reflexes).[6,63,64]

Is it possible to use this reflex feedback into a clinical scenario? Recent studies suggest that in patients with acute respiratory distress syndrome titration of tidal volume based on individual lung mechanics may be a better

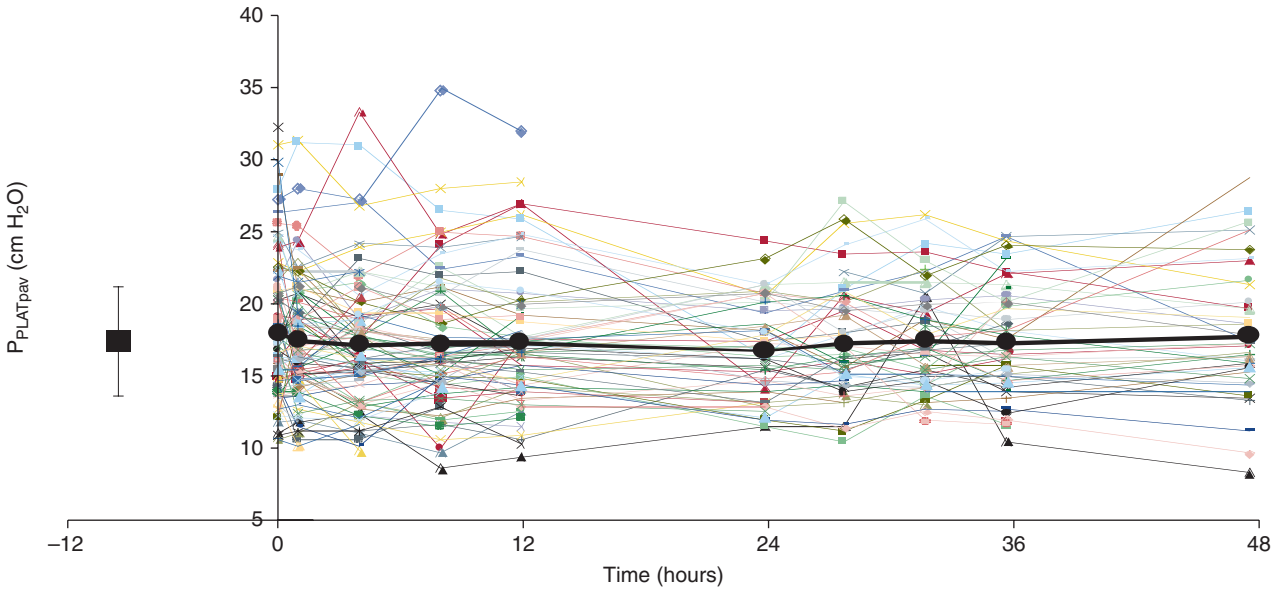

FIGURE 35-10 Individual values of quasi-static airway pressure obtained by 300 msec pause maneuver at the end of selected inspirations ($P_{PLATpav}$) as a function of time in 108 critically ill patients randomized (zero time) to proportional assist ventilation with load-adjustable gain factors (PAV+). PAV+ was continued for 48 hours unless the patients met predefined criteria, either for switching to controlled modes or for breathing without ventilator assistance. *Closed black circles* connected by solid thick line represent mean values. Each patient is denoted by a single color. For comparison the mean ± standard deviation (SD) values of static end-inspiratory airway pressure, obtained within 8 hours before randomization during controlled mechanical ventilation (CMV), is shown (*closed black square*). Notice that in the majority of the patients $P_{PLATpav}$ was below 26 cm H_2O. (Used, with permission, from Kondili et al. Patient–ventilator interaction. *Br J Anaesth.* 2003;91:106–119.)

strategy than using a fixed tidal volume (i.e., 6 mL/kg).[65,66,70–72] Obtaining lung mechanics, however, necessitates the use of cumbersome techniques not easily available at bedside. Theoretically, tidal volume selected by the patient should be based on individual lung mechanics, which serve as a guide for setting the ventilator.[73,74] Although studies support this hypothesis,[68,69] caution should be exercised in patients with strong signals of nonrespiratory origin (acidosis, brain dysfunction) that drive ventilation. Notwithstanding the limitations and feasibility of this approach, this hypothesis deserves further studies.

Neuromechanical Inhibition

Mechanical ventilation at relatively high tidal volume and ventilator frequency results in a non–chemically mediated decrease in respiratory motor output.[75–77] This decrease, referred to as *neuromechanical inhibition,* is manifested both in respiratory frequency and in amplitude of respiratory motor output. Neuromechanical inhibition lasts for several breaths after termination of mechanical ventilation, thus constituting a type of control system inertia and resetting of the spontaneous respiratory rhythm.[78] Although the mechanism underlying neuromechanical inhibition is not entirely clear, the Hering-Breuer reflex is the most plausible explanation. In addition, Sharshar et al[79] showed that mechanical ventilation reduces the excitability of cortical motor areas representing respiratory muscles. It is possible that mechanoreceptor feedback accounts for the depression of the motor-evoked potential of the diaphragm via vagal and other proprioceptive afferents to the respiratory center. The clinical relevance of neuromechanical inhibition is currently unknown. Available evidence suggests that its contribution to respiratory motor output in ventilated critically ill patients is rather minimal.[9,11,55]

ENTRAINMENT OF RESPIRATORY RHYTHM TO VENTILATOR RATE

Entrainment of respiratory rhythm to the ventilator rate implies a fixed, repetitive, temporal relationship between the onset of respiratory muscle contraction and the onset of a mechanical breath.[80–82] Human subjects exhibit one-to-one entrainment over a considerable range above and below the spontaneous breathing frequency.[83,84] Cortical influences (learning or adaptation response) and the Hering-Breuer reflex are postulated as the predominant mechanisms of entrainment. Theoretically, one-to-one entrainment should facilitate patient–ventilator synchrony, but studies of the entrainment response in critically ill patients are lacking.

Behavioral Feedback

The effects of behavioral feedback on control of breathing in ventilated patients are unpredictable, depending on several factors related to the individual patient and

surroundings. Alteration in ventilator settings, planned to achieve a particular goal, might be ineffective in awake patients because of behavioral feedback.[85,86] Inappropriate ventilator settings may cause breathing discomfort in awake patients. Consequent panic reactions further aggravate the unpleasant breathing sensation and create a vicious cycle. Behavioral feedback also may be altered considerably from time to time secondary to changes in the level of sedation, sleep–awake state, patient status, and environmental stimuli. The many factors involved in behavioral feedback complicate its study and the interpretation of its effects on the system that controls breathing in mechanically ventilated patients.

INTERACTIVE EFFECTS OF PATIENT-RELATED FACTORS AND VENTILATOR ON CONTROL OF BREATHING

Mechanics of Respiratory System

The mechanical properties of the respiratory system may influence the pressure delivered by the ventilator independent of patient effort and thus may modify the effects of mechanical ventilation on the various feedback loops. Excessive triggering delay and ineffective triggering are common in patients with obstructive lung disease and dynamic hyperinflation (Fig. 35-11). In the setting of airflow obstruction, mathematical models predict that PSV can be accompanied by marked variation in V_T and intrinsic positive end-expiratory pressure even when patient effort is constant.[87] This dynamic instability increases as the time constant of the respiratory system increases and produces patient–ventilator asynchrony of variable magnitude and type. The demonstration of increased arousals during PSV, but not during volume-cycled ventilation, may be caused in part by dynamic patient–ventilator asynchrony.[21]

Ineffective triggering has been observed with all modes of assisted ventilation. It is particularly common with tachypnea and when the level of assistance is relatively high and mechanical inflation extends well into neural expiration.[11,67,88,89] With PAV and NAVA, the likelihood of ineffective efforts is reduced significantly because mechanical inflation time is terminated close to the end of neural inspiration, and tidal volume in most cases remains relatively small.[46,47,67,69]

The phenomenon of ineffective efforts considerably influences the interpretation of ventilatory output in relation to the control of breathing during mechanical ventilation.[3,4] In the presence of ineffective efforts, ventilator frequency does not reflect the patient's spontaneous respiratory rate

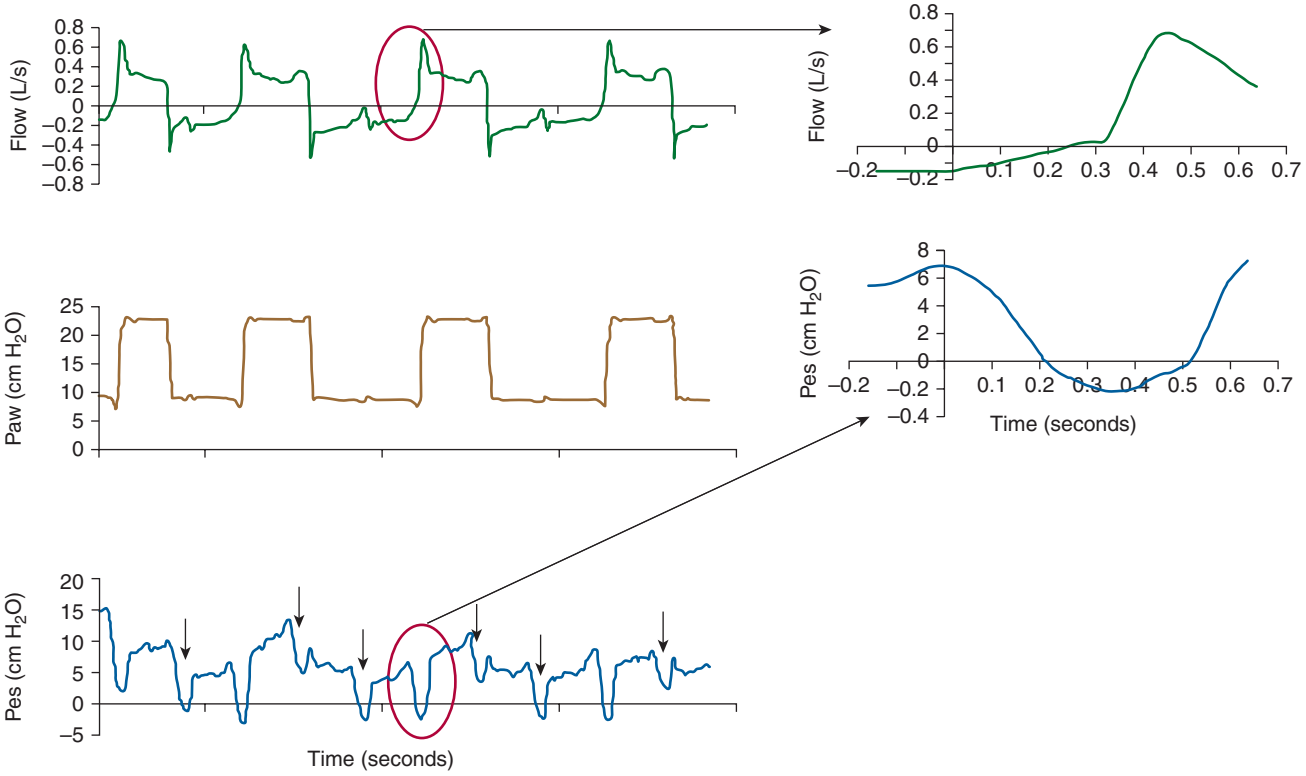

FIGURE 35-11 Airflow (inspiration up), airway pressure (*Paw*), and esophageal pressure (*Pes*) in a patient with obstructive lung disease ventilated with pressure support. Note the triggering delay with every mechanical breath (see the magnified tracing of flow and Pes) and the ineffective efforts (*arrows*). The ventilator rate was 12 breaths/min, whereas the patient's respiratory frequency was 35 breaths/min. Extrapolation from ventilator rate to the patient's system of control of breathing is misleading (Used, with permission, from Springer Science and Business Media: Brander, et al. *Intensive Care Med.* 2009;35:1979–1989.)

(see Fig. 35-11). Moreover, with ineffective efforts, significant alteration in a patient's respiratory effort occurs secondary to changes in feedback loop.

Characteristics of the Muscle Pressure Waveform

The characteristics of the Pmus waveform influence the ventilator-delivered volume in a complex manner, depending on several patient and ventilator factors. Extensive review of these factors is beyond the scope of this chapter, but some examples are provided.

The initial rate of increase in Pmus interacts with triggering of the ventilator.[11] A low rate of initial increase in Pmus occurs with a concave upward shape of Pmus or a low respiratory drive (such as with low Pa_{CO_2}, sedation, sleep, or a high level of assistance); this increases the time delay between the onset of patient inspiratory effort and ventilator triggering and promotes asynchrony. In the presence of dynamic hyperinflation, a prolonged triggering time, particularly when associated with a relatively short neural inspiratory time and low peak Pmus, may result in ineffective efforts. Alternatively, an increase in the intensity of inspiratory effort, such as occurs with an increase in metabolic rate, high Pa_{CO_2}, or decrease in the level of sedation or assistance, is manifested both in the rate of rise and in the peak of Pmus. The change may cause a decrease in the time delay, thus promoting patient–ventilator synchrony.[11] If, however, patient inspiratory effort is vigorous and longer than mechanical inflation time, the ventilator may be triggered more than once during the same inspiratory effort (Fig. 35-12).[3,90] It follows that changes in the characteristics of the Pmus waveform may influence the ventilator rate and ventilatory output despite no change in a patient's breathing frequency. Alterations in ventilatory output may secondarily modify patient effort through changes in feedback loops (see Fig. 35-1).

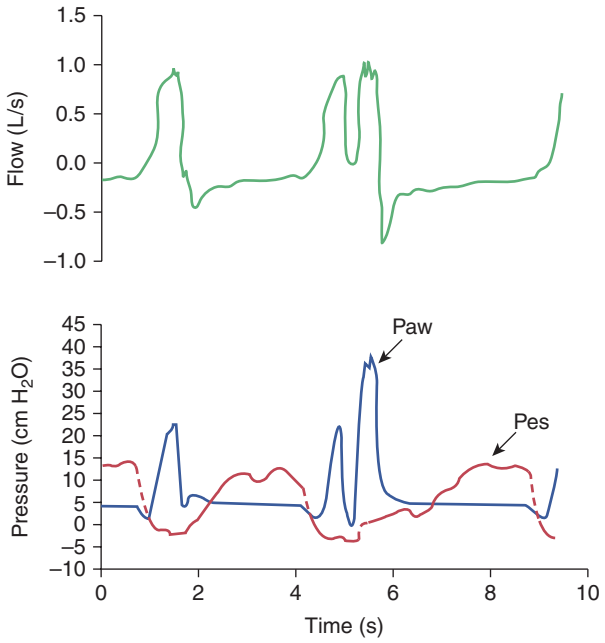

FIGURE 35-12 Flow, airway pressure (Paw), and esophageal pressure (Pes) in a patient recovering from acute lung injury and ventilated on assist volume control at constant inspiratory flow. In the second breath, tidal volume (volume was not shown) was decreased at constant inspiratory flow. As a result, there was premature termination of mechanical inspiration. Because the inspiratory muscles continued to contract, they developed sufficient pressure to overcome elastic recoil at end inspiration. As a result, Paw decreased below the triggering threshold, and the ventilator delivered a new mechanical breath. The ventilator was triggered three times by the two inspiratory efforts. Note the high Paw of the third mechanical breath secondary to high lung volume (the volume of the third breath was added to that of the second). Total breath duration of the second respiratory effort was considerably longer than that of the first effort owing to activation of Hering-Breuer reflex by the high volume. (Used, with permission, from Springer Science and Business Media: Xirouchaki, et al. Intensive Care Med. 2008;34:2026–2034.)

THE FUTURE

Over the past two decades, many studies have been performed in animals and human subjects with an aim of improving a patient's ability to control the ventilator. Various ventilator modes target either an improvement in the response of the ventilator to patient effort or tight coupling between the ventilator-delivered pressure and patient instantaneous ventilatory demands. Studies of these modes have yielded promising results. New methods of triggering have been shown to improve the response of the ventilator to patient effort.[45,91–93] Algorithms that automatically adjust the criterion for cycling off have been designed with a goal of reducing expiratory asynchrony.[94] Estimates of the inspiratory muscle pressure waveform may also be used to terminate pressure delivery, and these, theoretically, should improve patient–ventilator synchrony.[93] Mechanical[92] and electrical[46,95] activity of the diaphragm has been used to control the level and duration of inspiratory assistance. With PAV, methods of noninvasive automatic estimation of elastance and resistance of the respiratory system are now available (PAV+),[96,97] which enable controller gain to be maintained constant in the face of changes in the mechanical load of respiratory system[98] and result in fewer intervention in terms of ventilator settings compared to other modes.[99] Algorithms that use a signal generated from flow, volume, and airway pressure may be used to provide breath-by-breath quantitative information of inspiratory muscle pressure,[100] and this approach also may be used in the future to facilitate patient–ventilator synchrony. By achieving tight coupling between neural output and ventilator-delivered pressure, the ventilator is able to serve as a respiratory muscle with high capabilities and operate in harmony with the system that controls breathing. Nowadays, it seems feasible to shift from the physician who dictates the pattern of ventilation to the patient who chooses to breathe with a pattern that incorporates all the aspects of control of breathing. Because the control of ventilation is much more complex

than simply regulating blood gases, it is likely that the patient can do a better job than physicians can.

Negative-feedback methods, such as adaptive pressure-support servoventilation, have been designed recently with a goal of reducing periodic breathing through appropriate changes in the level of assistance and maintaining a target minute ventilation in the face of waxing and waning respiratory efforts.[82,101] Incorporation of this approach in assisted modes may decrease the propensity of high-risk individuals to develop periodic breathing. It is not known whether this mode could decrease morbidity in critically ill patients, although it should enhance sleep efficiency.[22,23]

CONCLUSION

Incorporating an auxiliary pressure into the system that controls breathing changes the volume–time profile of a breath. It also alters, via chemical, neuromechanical, and behavioral feedback, the pressure developed by the respiratory muscles. The latter, depending on ventilator and patient factors, may or may not modify the auxiliary pressure. The response of patient effort to a ventilator-delivered breath and the response of a ventilator to patient effort are the two essential components of control of breathing during mechanical ventilation. The physician dealing with a ventilated patient should be aware that both the basic features of control of breathing and its expression can be altered considerably by the process of mechanical ventilation.

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36

EFFECT OF MECHANICAL VENTILATION ON HEART–LUNG INTERACTIONS

Hernando Gomez
Michael R. Pinsky

The heart and lungs are intimately coupled by their anatomical proximity within the thorax and, more importantly, by their responsibility to deliver the O_2 requirements of individual cells and organs while excreting the CO_2 by-product of metabolism. During critical illness, if these two organ systems fail, either alone or in combination, the end result is an inadequate O_2 delivery to the body with inevitable tissue ischemia, progressive organ dysfunction, and if untreated, death. Thus, restoration and maintenance of normalized cardiopulmonary function is an essential and primary goal in the management of critically ill patients. Heart failure can impair gas exchange by inducing pulmonary edema and limiting blood flow to the respiratory muscles. Ventilation can alter cardiovascular function by altering lung volume, and intrathoracic pressure (ITP), and by increasing metabolic demands. These processes are discussed from the perspective of the impact that ventilation has on the cardiovascular system.

CLINICAL RELEVANCE

The ventilatory apparatus and the cardiovascular system have profound effects on each other.[1,2] Acute hypoxia impairs cardiac contractility and vascular smooth muscle tone, promoting cardiovascular collapse. Hypercarbia causes vasodilation and increases pulmonary vascular resistance. Hyperinflation increases pulmonary vascular resistance, which impedes right-ventricular (RV) ejection and also compresses the heart inside the cardiac fossa in a fashion analogous to tamponade. Lung collapse also increases pulmonary vascular resistance, impeding RV ejection.[3] Acute RV failure, or *cor pulmonale,* is not only difficult to treat, but it can induce immediate cardiovascular collapse and death.

Ventilator technologies and numerous vasoactive drugs have been developed as means to improve oxygenation of arterial blood. These advances are the subjects of other chapters in this volume. The complex interactions, however,

between the heart, circulation, and lungs often leads to a paradoxical worsening of one organ system function while the function of the other is either maintained or even improved by the use of these technologies and drugs. To minimize these deleterious events, and in the hope of more efficiently and effectively treating critical ill patients with cardiorespiratory failure, a better knowledge and understanding of the integrated behavior of the cardiopulmonary system, during both health and critical illness is essential. Based on this perspective, the health care provider can more appropriately manage this complex and challenging group of patients.

Respiratory function alters cardiovascular function and cardiovascular function alters respiratory function. A useful way to consider the cardiovascular effects of ventilation is to group them by their impact on the determinants of cardiac performance. The determinants of cardiac function can be grouped into four interrelated processes: *heart rate, preload, contractility,* and *afterload.* Phasic changes in lung volume and ITP can simultaneously change all four of these hemodynamic determinants for both ventricles. Our current understanding of cardiovascular function also emphasizes both the independence and interdependence of RV and left-ventricular (LV) performance on each other and to external stresses. Complicating these matters further, the direction of interdependence, from right to left or left to right, can be similar or opposite in direction, depending on the baseline cardiovascular state. It is clear, therefore, that a comprehensive understanding of the specific cardiopulmonary interactions and their relative importance in defining a specific cardiovascular state is a nearly impossible goal to achieve in most patients. By understanding the components of this process, however, one can come to a better realization of its determinants, and, to a greater or lesser degree for any individual patient, predict the limits of these interactions and how the patient may respond to stresses imposed by either adding or removing artificial ventilatory support.

PHYSIOLOGY OF HEART–LUNG INTERACTIONS

Both spontaneous and positive-pressure ventilation increase lung volume above an end-expiratory baseline. Many of the hemodynamic effects of all forms of ventilation are similar despite differences in the mode of ventilation. ITP, however, decreases during spontaneous inspiration and increases during positive-pressure ventilation. Thus, the primary reasons for different hemodynamic responses seen during spontaneous and positive-pressure breathing are related to the changes in ITP and the energy necessary to produce those changes.

Effect of Lung Volume

Changing lung volume phasically alters autonomic tone and pulmonary vascular resistance. At very high lung volumes, the expanding lungs compress the heart in the cardiac fossa, limiting absolute cardiac volumes analogous to cardiac tamponade, except that with hyperinflation both pericardial pressure and ITP increase by a similar amount.

AUTONOMIC TONE

Although neurohumoral processes define a few immediate effects of ventilation on the heart, these neurohumoral processes probably play a primary role in all the long-term effects of ventilation on the cardiovascular system. Most of the immediate effects of ventilation of the heart are secondary to changes in autonomic tone. The lungs are richly enervated with somatic and autonomic fibers that originate, traverse through, and end in the thorax. These networks mediate multiple homeostatic processes through the autonomic nervous system altering instantaneous cardiovascular function. The most commonly known of these are the vagally mediated heart rate changes during ventilation.[4,5] Inflation of the lung to normal tidal volumes (<10 mL/kg) induces vagal-tone withdrawal, accelerating heart rate. This phenomenon is known as respiratory sinus arrhythmia[6] and can be used to document normal autonomic control,[7] especially in patients with diabetes who are at risk for peripheral neuropathy.[8] Inflation to larger tidal volumes (>15 mL/kg), however, decreases heart rate by a combination of both increased vagal tone[9] and sympathetic withdrawal. Sympathetic withdrawal also creates arterial vasodilation.[4,10–14] This inflation–vasodilation response can reduce LV contractility in healthy volunteers[15] and in ventilator-dependent patients with the initiation of high-frequency ventilation[4] or hyperinflation.[12] This inflation–vasodilation response is presumed to be the cause of the initial hypotension seen when infants are placed on mechanical ventilation. It appears to be mediated at least partially by afferent vagal fibers, because it is abolished by selective vagotomy. Hexamethonium, guanethidine, and bretylium, however, also block this reflex.[16,17] These data suggest that lung inflation mediates its reflex cardiovascular effects by modulating central autonomic tone. Interestingly, the almost total lack of measurable hemodynamic effects of unilateral hyperinflation in subjects with normal lungs receiving split-lung ventilation[18] suggests that these autonomic cardiovascular effects require a general increase in lung volume to be realized. This is not a minor point because selective hyperinflation within lung units commonly occurs in patients with acute lung injury (ALI) and chronic obstructive pulmonary disease (COPD). If localized hyperinflation were able to induce cardiovascular impairment, these subjects would be profoundly compromised.

Humoral factors, including compounds blocked by cyclooxygenase inhibition,[19] released from pulmonary endothelial cells during lung inflation may also induce this depressor response[20–22] within a short (15 seconds) time frame. These interactions, however, do not appear to grossly alter cardiovascular status.[23] Ventilation also alters the more chronic control of intravascular fluid balance via hormonal release. The right atrium functions as the body's effective circulating blood-volume

sensor. Circulating levels of a family of natriuretic peptides increase in heart failure states secondary to right-atrial stretch.[24] These hormones promote sodium and water diuresis. The levels of these hormones vary directly with the degree of heart failure. Both positive-pressure ventilation and sustained hyperinflation decrease right-atrial stretch mimicking hypovolemia. During positive-pressure ventilation, plasma norepinephrine and renin increase,[25,26] whereas atrial natriuretic peptide decreases.[27] This humoral response is the primary reason why ventilator-dependent patients gain weight early in the course of respiratory failure, because protein catabolism is also usually seen. Interestingly, when patients with congestive heart failure (CHF) are given nasal continuous positive airway pressure (CPAP), plasma atrial natriuretic peptide activity decreases in parallel with improvements in blood flow.[28,29] This finding suggests that some of the observed benefit of CPAP therapy in heart failure is mediated in part through humoral mechanisms, owing to the mechanical effects of CPAP on cardiac function.

PULMONARY VASCULAR RESISTANCE

Changing lung volume alters pulmonary vascular resistance.[3] Marked increases in pulmonary vascular resistance, as may occur with hyperinflation, can induce acute cor pulmonale and cardiovascular collapse. The reasons for these changes are multifactorial. They can reflect conflicting cardiovascular processes and almost always reflect both humoral and mechanical interactions.

Lung volume can only increase if its distending pressure increases. Lung-distending pressure, called the *transpulmonary pressure*, equals the pressure difference between alveolar pressure (Palv) and ITP. If lung volume does not change, then transpulmonary pressure does not change. Thus, occluded inspiratory efforts (Mueller maneuver) and expiratory efforts (Valsalva maneuver) cause ITP to vary by an amount equal to Palv, but do not change pulmonary vascular resistance. Although obstructive inspiratory efforts, as occur during obstructive sleep apnea, are usually associated with increased RV afterload, the increased afterload is caused primarily by either increased vasomotor tone (hypoxic pulmonary vasoconstriction) or backward LV failure.[30,31]

RV afterload is maximal RV systolic wall stress.[32,33] By law of Laplace, wall stress equals the product of the radius of curvature of a structure and its transmural pressure. Systolic RV pressure equals transmural pulmonary artery pressure. Increases in transmural pulmonary artery pressure increases RV afterload, impeding RV ejection,[34] decreasing RV stroke volume,[35] inducing RV dilation, and passively causing venous return to decrease.[19,21] If such acute increases in transmural pulmonary artery pressure are not reduced, or if RV contractility is not increased by artificial means, then acute cor pulmonale rapidly develops.[36] If RV dilation and RV pressure overload persist, RV free-wall ischemia and infarction can develop.[37] These concepts are of profound clinical relevance because rapid fluid challenges in the setting of acute cor pulmonale can precipitate profound cardiovascular collapse secondary to excessive RV dilation, RV ischemia, and compromised LV filling. Ventilation can alter pulmonary vascular resistance by either altering pulmonary vasomotor tone, via a process known as *hypoxic pulmonary vasoconstriction*, or mechanically altering vessel cross-sectional area, by changing transpulmonary pressure.

Hypoxic Pulmonary Vasoconstriction. Unlike systemic vessels that dilate under hypoxic conditions, the pulmonary vasculature constricts. Once alveolar partial pressure of oxygen decreases below 60 mm Hg, or acidemia develops, pulmonary vasomotor tone increases.[38] Hypoxic pulmonary vasoconstriction is mediated, in part, by variations in the synthesis and release of nitric oxide by endothelial nitric oxide synthase localized on pulmonary vascular endothelial cells, and in part by changes in intracellular calcium fluxes in the pulmonary vascular smooth muscle cells. The pulmonary endothelium normally synthesizes a low basal amount of nitric oxide, keeping the pulmonary vasculature actively vasodilated. Loss of nitric oxide allows the smooth muscle to return to its normal resting vasomotor tone. Nitric oxide synthesis is dependent on adequate amounts of O_2 and is inhibited by both hypoxia and acidosis. Presumably, hypoxic pulmonary vasoconstriction developed to minimize ventilation–perfusion mismatches caused by local alveolar hypoventilation. Generalized alveolar hypoxia, however, increases global pulmonary vasomotor tone, impeding RV ejection.[32] At low lung volumes, terminal bronchioles collapse, trapping gas in the terminal alveoli. With continued blood flow, these alveoli lose their O_2 and also may collapse. Patients with acute hypoxemic respiratory failure have small lung volumes and are prone to both alveolar hypoxia and spontaneous alveolar collapse.[39,40] This is one of the main reasons why pulmonary vascular resistance is increased in patients with acute hypoxemic respiratory failure.

Based on the above considerations, mechanical ventilation may reduce pulmonary vasomotor tone by a variety of mechanisms. First, hypoxic pulmonary vasoconstriction can be inhibited if the patient is ventilated with gas enriched with O_2 increasing alveolar partial pressure of oxygen.[41–44] Second, mechanical breaths and positive end-expiratory pressure (PEEP) can refresh hypoventilated lung units and recruit collapsed alveolar units, causing local increases in alveolar partial pressure of oxygen,[3,45–47] especially if small lung volumes are returned to resting functional residual capacity (FRC) from an initial smaller lung volume.[48] Third, mechanical ventilation often reverses respiratory acidosis by increasing alveolar ventilation.[44] Fourth, decreasing central sympathetic output, by sedation or decreased stress of breathing against high-input impedance during mechanical ventilation, also reduces vasomotor tone.[49,50] Importantly, these effects do not require endotracheal intubation to occur; they occur with mere reexpansion of collapsed alveoli.[51,52] Thus, PEEP, CPAP, recruitment maneuvers, and noninvasive ventilation may all reverse hypoxic pulmonary vasoconstriction and may all improve cardiovascular function.

Volume-Dependent Changes in Pulmonary Vascular Resistance. Changes in lung volume directly alter pulmonary vasomotor tone by compressing the alveolar vessels.[39,46,47] The actual mechanisms by which this occurs have not been completely resolved, but appear to reflect vascular compression induced by a differential extraluminal pressure gradient. The pulmonary circulation lives in two environments, separated from each other by the pressure that surrounds them.[46] The small pulmonary arterioles, venules, and alveolar capillaries sense Palv as their surrounding pressure, and are called *alveolar vessels*. The large pulmonary arteries and veins, as well as the heart and intrathoracic great vessels of the systemic circulation, sense interstitial pressure or ITP as their surrounding pressure, and are called *extraalveolar vessels*. Because the pressure difference between Palv and ITP is transpulmonary pressure, increasing lung volume increases this extraluminal pressure gradient. Increases in lung volume progressively increase alveolar vessel resistance by increasing this pressure difference once lung volumes increase much above FRC (Fig. 36-1).[42,53] Similarly, increasing lung volume, by stretching and distending the alveolar septa, may also compress alveolar capillaries, although this mechanism is less well substantiated. Hyperinflation can create significant pulmonary hypertension and may precipitate acute RV failure (acute cor pulmonale)[54] and RV ischemia.[37] Thus, PEEP may increase pulmonary vascular resistance if it induces overdistension of the lung above its normal FRC.[55]

Extraalveolar vessels are also influenced by changes in transpulmonary pressure. Normally, radial interstitial forces of the lung, which keep the airways patent, only make the large vessels more distended as lung volume increases,[45,56,57] just as increasing lung volume increases airway diameter. These radial forces also act upon the extraalveolar vessels, causing them to remain dilated, increasing their capacitance.[58] This tethering is reversed with lung deflation, thereby increasing extraalveolar vascular resistance.[42,45] Thus, pulmonary vascular resistance is increased at small lung volumes owing to the combined effect of hypoxic pulmonary vasoconstriction and extraalveolar vessel collapse, and at high lung volumes by alveolar compression.

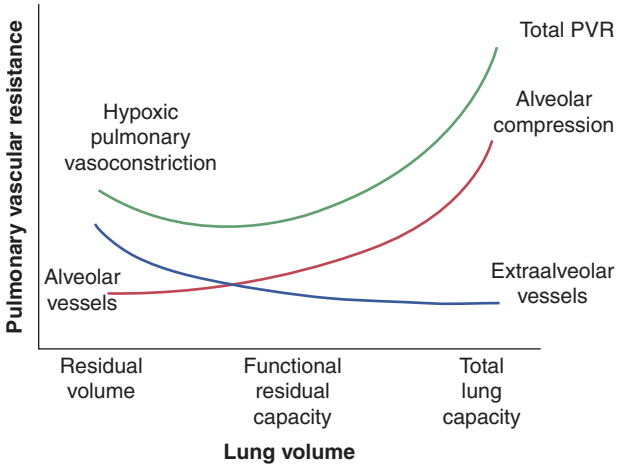

FIGURE 36-1 Schematic of the relationship between changes in lung volume and pulmonary vascular resistance (*PVR*), where the extraalveolar and alveolar vascular components are separated. Pulmonary vascular resistance is minimal at resting lung volume or functional residual capacity. As lung volume increases toward total lung capacity or decreases toward residual volume, pulmonary vascular resistance also increases. The increase in resistance with hyperinflation is caused by increased alveolar vascular resistance, whereas the increase in resistance with lung collapse is caused by increased extraalveolar vessel tone.

Right-Ventricular Afterload. The right ventricle, as opposed to the left ventricle, ejects blood into a low-pressure, high-compliance system: the pulmonary circulation. The pulmonary circulation is capable of accommodating high volumes of blood without generating high pressure, which is beneficial for the right ventricle. Despite being compliant, this circuit does pose resistance to the ejecting right ventricle as quantified by pulmonary artery pressure, which is the pressure limit the right ventricle has to overcome to open the pulmonary valve. RV afterload is conceptually similar to LV afterload and is determined by the wall tension of the right ventricle. RV afterload is highly dependent on the distribution of blood flow in the lung, namely, the proportion of West zones 1 and 2, as compared to zone 3, as originally described by Permutt et al.[59] Zones 1 and 2 exist whenever the intraluminal pressure of juxtaalveolar capillaries is lower than the Palv during the respiratory cycle, thus collapsing vessels and increasing pulmonary vascular resistance. In contrast, zone 3 occurs when intraluminal capillary pressure is higher than Palv, decreasing pulmonary resistance. Importantly, intraluminal pressure of alveolar capillaries tracks changes in ITP,[60] and thus decreases less than Palv during spontaneous inspiration, and increases less than Palv during positive-pressure inspiration. Consequently, both spontaneous and positive-pressure inspiration above FRC increase the afterload to the right ventricle as opposed to the LV afterload, which is reduced by increased ITP.

VENTRICULAR INTERDEPENDENCE

Because right ventricle output is linked to left ventricle output serially, if right ventricle output decreases, left ventricle output must eventually decrease. The two ventricles, however, are also linked in parallel through their common septum, circumferential fibers, and pericardium, which limits total cardiac volume. For this reason, the diastolic filling of the RV has a direct influence on the shape and compliance of the LV, and vice versa. This phenomenon is known as *ventricular diastolic interdependence*.[61] The most common manifestation of ventricular interdependence is *pulsus paradoxus*. Changes in RV end-diastolic volume inversely alter LV diastolic compliance.[62] Because venous return can and often does vary by as much as 200% between inspiration and expiration, owing to associated changes in the pressure gradient for venous return (infra vide, see the section "Systemic Venous Return"), right ventricle filling also changes in

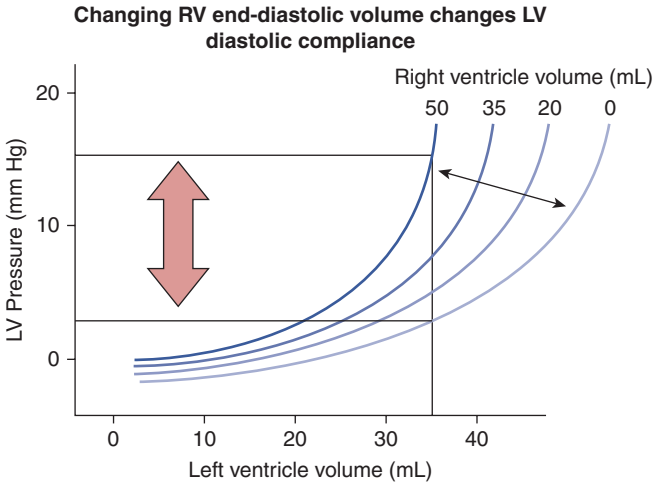

FIGURE 36-2 Schematic of the effect of increasing right-ventricular (RV) volumes on the relationship between left-ventricular (LV) diastolic pressure and left ventricle volume (filling). Increases in right ventricle volumes decrease LV diastolic compliance, such that a higher filling pressure is required to generate a constant end-diastolic volume. (Adapted, with permission, from Taylor RR, Covell JW, Sonnenblick EH, Ross J Jr. Dependence of ventricular distensibility on filling the opposite ventricle. *Am J Physiol*. 1967;213:711–718.)

parallel. Increasing RV end-diastolic volume, as occurs during spontaneous inspiration and spontaneous inspiratory efforts, will reduce LV diastolic compliance, immediately decreasing LV end-diastolic volume. Positive-pressure ventilation may decrease venous return causing RV volumes to decrease, increasing LV diastolic compliance. Except in acute cor pulmonale or biventricular overloaded states, however, the impact of positive-pressure ventilation on LV end-diastolic volume is minimal.

Ventricular interdependence functions through two separate processes. First, increasing RV end-diastolic volume induces an intraventricular septal shift into the LV, thereby decreasing LV diastolic compliance (Fig. 36-2).[63] Because left ventricle wall stress is unaltered, any change in LV output does not reflect a change in LV preload. Because spontaneous inspiration increases venous return, causing right ventricle dilation, LV end-diastolic compliance decreases during spontaneous inspiration. Whereas right ventricle volumes usually do not increase during positive-pressure inspiration, ventricular interdependence usually has less impact over the patient's hemodynamic status. Second, if pericardial restraint or absolute cardiac fossal volume restraint limits absolute biventricular filling, then right ventricle dilation will increase pericardial pressure, with minimal to no septal shift because the pressure outside of both ventricles will increase similarly.[64,65]

Positive-pressure ventilation, however, can still display right ventricle dilation-associated ventricular interdependence. If positive-pressure inspiration overdistends alveoli, as for example during lung recruitment maneuvers, pulmonary vascular resistance will increase. Despite the fact that hemodynamic changes elicited by recruitment maneuvers do not cause persistent cardiovascular insufficiency, transient right ventricle dilation and left ventricle collapse can occur during recruitment maneuvers.[66] This is an important concept when treating patients with borderline RV failure. Thus, recruitment maneuvers should be used with caution and be restricted to 10 seconds or less of an end-inspiratory hold to avoid significant hemodynamic derangements.

The presence of ventricular interdependence can be assessed in mechanically ventilated patients based on heart–lung interactions. Using echocardiographic techniques, Mitchell et al[67] and Jardin et al[68] showed that positive-pressure breaths decrease RV dimensions, whereas both LV dimensions and LV flows increase. Still, the changes in RV output generated by positive-pressure inspiration are much less than the changes in LV output.[69] If ventricular interdependence was the primary process driving hemodynamic interactions during a positive-pressure breath, then a phasic increase in LV stroke volume would occur during inspiration. If the primary process was a phasic decrease in venous return, however, a phasic decrease in LV stroke volume would be observed two to three beats later, usually during the expiratory phase, suggesting the right ventricle is preload responsive. These points underscore the use of LV stroke volume variation during positive-pressure ventilation to identify volume responsiveness.

MECHANICAL HEART–LUNG INTERACTIONS BECAUSE OF LUNG VOLUME

With inspiration, the expanding lungs compress the heart in the cardiac fossa,[70] increasing juxtacardiac ITP. Because the chest wall and diaphragm can move away from the expanding lungs, whereas the heart is trapped within this cardiac fossa, juxtacardiac ITP usually increases more than these external ITPs.[71,72] This effect is a result of increasing lung volume. It is not affected by the means whereby lung volume is increased. Both spontaneous[73] and positive-pressure-induced hyperinflation[56,57] induce similar compressive effects on cardiac filling. If one measured only intraluminal LV pressure, then it would appear as if LV diastolic compliance was reduced, because the associated increase in pericardial pressure and ITP would not be seen.[74–76] When LV function, however, is assessed as the relationship between end-diastolic volume and output, no evidence for impaired LV contractile function is seen[77,74] despite the continued application of PEEP.[78] These compressive effects can be considered as analogous to cardiac tamponade[79–81] and are discussed further in the "The Effect of Intrathoracic Pressure."

Effect of Intrathoracic Pressure

The heart lives within the thorax, a pressure chamber inside a pressure chamber. Thus, changes in ITP affect the pressure gradients for both systemic venous return to the right ventricle and systemic outflow from the left ventricle, independent

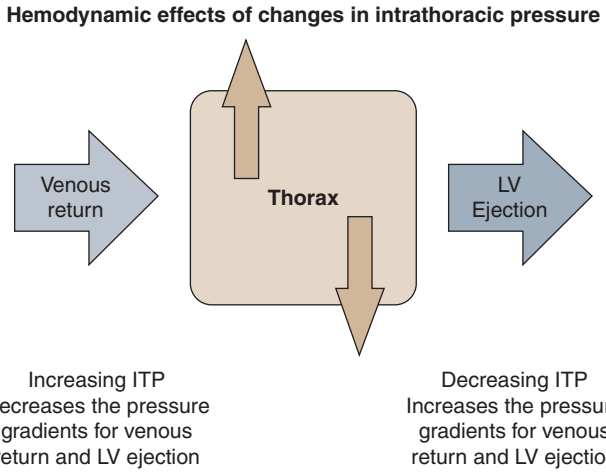

FIGURE 36-3 Schematic of the effect of increasing or decreasing intrathoracic pressure on the left-ventricular (LV) filling (venous return) and ejection pressure.

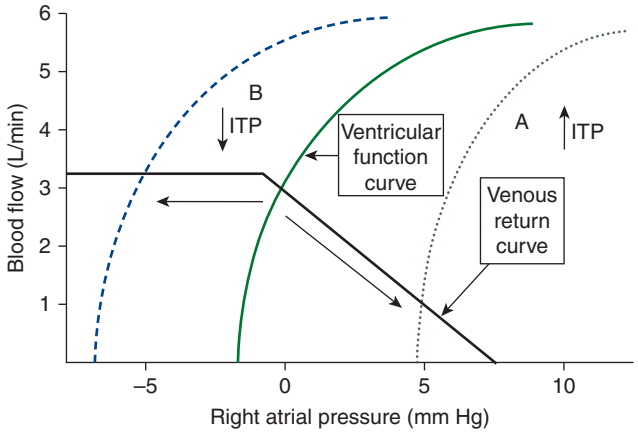

FIGURE 36-4 A venous return curve, describing the relationship between the determinants of right-ventricular preload. Right atrial pressure inversely changes the magnitude of venous return and is influenced by changes in intrathoracic pressure (ITP). Positive-pressure ventilation shifts the ventricular function curve to the right (*A*), increasing right-atrial pressure but decreasing blood flow. Spontaneous inspiration decreases ITP and shifts the ventricular function curve to the left (*B*), decreasing right-atrial pressure but increasing blood flow. As right-atrial pressure becomes negative, as may occur during forced inspiratory efforts against resistance or impedance, a maximal blood flow is reached; further decreases in right-atrial pressure no longer augment venous return.

of the heart itself (Fig. 36-3). Increases in ITP, by increasing right-atrial pressure (Pra) and decreasing transmural LV systolic pressure, will reduce the pressure gradients for venous return and LV ejection decreasing intrathoracic blood volume. Using the same argument, decreases in ITP will augment venous return and impede LV ejection, increasing intrathoracic blood volume. The increases in ITP during positive-pressure ventilation show marked regional differences; juxtacardiac ITP increases more than lateral chest wall ITP as inspiratory flow rate and tidal volume increase.[71] Interestingly, lung compliance plays a minimal role in defining the positive-pressure-induced increase in ITP. For the same increase in tidal volume, ITP usually increases similarly if tidal volume is kept constant.[82,83] If, however, chest wall compliance decreases, then ITP will increase for a fixed tidal volume.[84,85]

SYSTEMIC VENOUS RETURN

Guyton et al described the determinants of venous return more than 50 years ago.[86,87] Blood flows back from the systemic venous reservoirs into the right atrium through low-pressure, low-resistance venous conduits. Pra is the backpressure, or downstream pressure, for venous return. Pressure in the upstream venous reservoirs is called *mean systemic pressure*, and, itself, is a function of blood volume, peripheral vasomotor tone, and the distribution of blood within the vasculature.[88] Ventilation alters both Pra and mean systemic pressure. Many of the observed ventilation-induced changes in cardiac performance can be explained by these changes. Mean systemic pressure does not change rapidly during positive-pressure ventilation, whereas Pra does, owing to parallel changes in ITP (Fig. 36-4).[89,90] Positive-pressure inspiration increases both ITP and Pra, decreasing venous blood flow,[35] RV filling, and consequently, RV stroke volume.[35,89–99] During normal spontaneous inspiration, the opposite effects occur. Spontaneous inspiration decreases ITP and Pra, accelerating venous blood flow, and increasing RV filling and RV stroke volume.[35,36,64,93,96,100–102]

If changes in Pra were the only process that altered venous return, then positive-pressure ventilation would induce profound hemodynamic insufficiency in most patients. The decrease in venous return during positive-pressure ventilation, however, is often lower than one might expect based on the increase in Pra.

The reasons for this preload-sparing effect seen during positive-pressure ventilation are twofold. First, when cardiac output does decrease, increased sympathetic tone decreases venous capacitance, increasing mean systemic pressure, which tends to restore the pressure gradient for venous return, even in the face of an elevated Pra. Increases in sympathetic tone, however, would increase steady-state cardiac output and would not alter the phasic changes in venous return seen during positive-pressure ventilation. The decreased phasic reductions in venous return are caused by associated increases in mean systemic pressure during inspiration. Diaphragmatic descent and abdominal-muscle contraction increase intraabdominal pressure, decreasing intraabdominal vascular capacitance.[103,104] Because a large proportion of venous blood is in the abdomen, the net effect of both inspiration and PEEP is to increase mean systemic pressure and Pra in a parallel but unequal fashion.[105–107] Accordingly, the pressure gradient for venous return may not be reduced as much as predicted as predicted from a pure increase in Pra. This is an important adaptive response by the body to positive-pressure ventilation and PEEP, both of which produce this effect secondary to the associated increase in lung volume, which promotes diaphragmatic descent. This

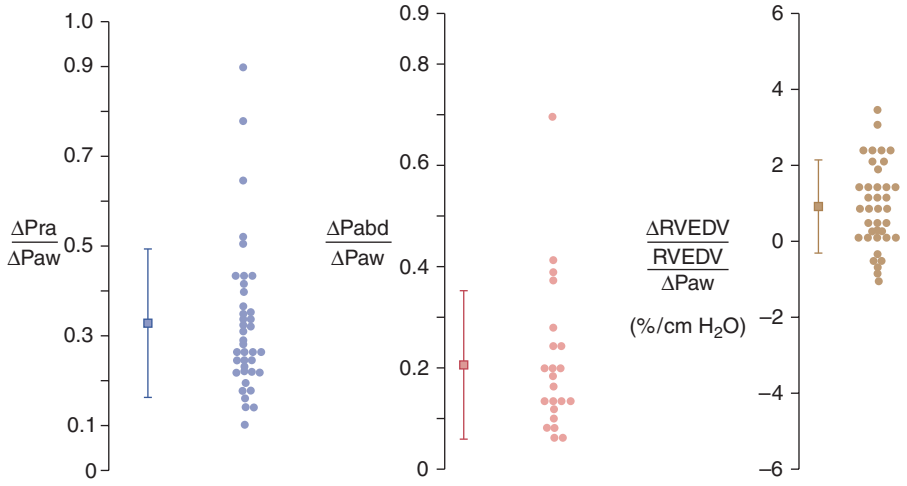

FIGURE 36-5 Effect of increasing levels of continuous positive airway pressure (CPAP) on the relations between increasing airway pressure (*Paw*) and right-atrial pressure (*Pra*) (*left graph*), *Paw* and intraabdominal pressure (*Pabd*) (*center graph*), and *Paw* and changes in right-ventricular end-diastolic volume (*RVEDV*) (*right graph*) in forty-three postoperative fluid-resuscitated cardiac surgery patients. (Data derived, with permission, from data in Van den Berg P, Jansen JRC, Pinsky MR. The effect of positive-pressure inspiration on venous return in volume loaded post-operative cardiac surgical patients. *J Appl Physiol.* 2002;92:1223–1231.)

preload-sparing effect is especially well demonstrated in patients with hypervolemia. In fact, both the translocation of blood from the pulmonary to the systemic capacitance vessels,[108] as well as abdominal pressurization secondary to diaphragmatic descent, may be the major mechanisms by which the decrease in venous return is minimized during positive-pressure ventilation.[109–113] In fact, van den Berg et al[114] documented that up to 20 cm H_2O CPAP did not significantly decrease cardiac output, as measured 30 seconds into an inspiratory-hold maneuver, in fluid-resuscitated, post-operative cardiac surgery patients. Although CPAP induced an increase in Pra, intraabdominal pressure also increased, preventing a significant change in RV volumes (Fig. 36-5). Interest in inverse-ratio ventilation has raised questions as to its hemodynamic effect, because its application includes a large component of hyperinflation.

Current data clearly show that detrimental effects of increased ITP and PEEP on venous return are far more complex than an effect on the pressure gradient between mean systemic pressure and Pra, and that geometric deformation of the venous vasculature and its flow distribution, which alter the resistance to flow, may be a better explanation.[115] Animal data suggest that compression and deformation of capacitance vessels at the entrance of the thorax[103] and compression of the portal circulation by diaphragmatic descent[115] may account for these increments in venous resistance and thus decreased venous return.

Relevance of Intrathoracic Pressure on Venous Return. It is axiomatic that the heart can only pump out that amount of blood that it receives and no more. Thus, venous return is the primary determinant of cardiac output and the two must be the same.[88] Because Pra is the backpressure to venous return and because Pra is normally close to zero relative to atmospheric pressure, venous return is maintained near maximal levels at rest,[12,87,94,98,99] because right ventricle filling occurs with minimal changes in filling pressure.[81] Spontaneous inspiratory efforts usually increase venous return because of the combined decrease in Pra[64,94–96,116] and increase in intraabdominal pressure.[103,104] For Pra to remain very low, however, RV diastolic compliance must be high and RV output must equal venous return. Otherwise, sustained increases in venous blood flow would distend the RV and increase Pra. During normal spontaneous inspiration, although venous return increases, ITP decreases at the same time, minimizing any potential increase in Pra, which might otherwise occur if ITP were not to decrease.[89] Aiding in this process of minimizing RV workload, the pulmonary arterial inflow circuit is highly compliant and can accept large increases in RV stroke volume without changing pressure.[35,117] Thus, increases in venous return proportionally increase pulmonary arterial inflow without significant changes in RV filling or ejection pressures. Accordingly, this compensatory system fails if RV diastolic compliance decreases or if Pra increases independent of changes in RV end-diastolic volume. Figure 36-6 illustrates these differential effects of negative (spontaneous inspiration) and positive (positive-pressure inspiration) swings in ITP on dynamic RV and LV performance. In RV failure states, spontaneous inspiration does not decrease Pra and Pra actually increases. This results in the physical sign of increased jugular venous distension during spontaneous inspiration.

Note further in Figure 36-6 that not only does RV stroke volume increase with spontaneous inspiration and decrease with positive-pressure inspiration, but also that LV stroke volume decreases only during spontaneous inspiration (ventricular interdependence); during positive-pressure inspiration, however, any change in LV stroke volume occurs late, as the decrease in RV output finally reaches the left ventricle. RV

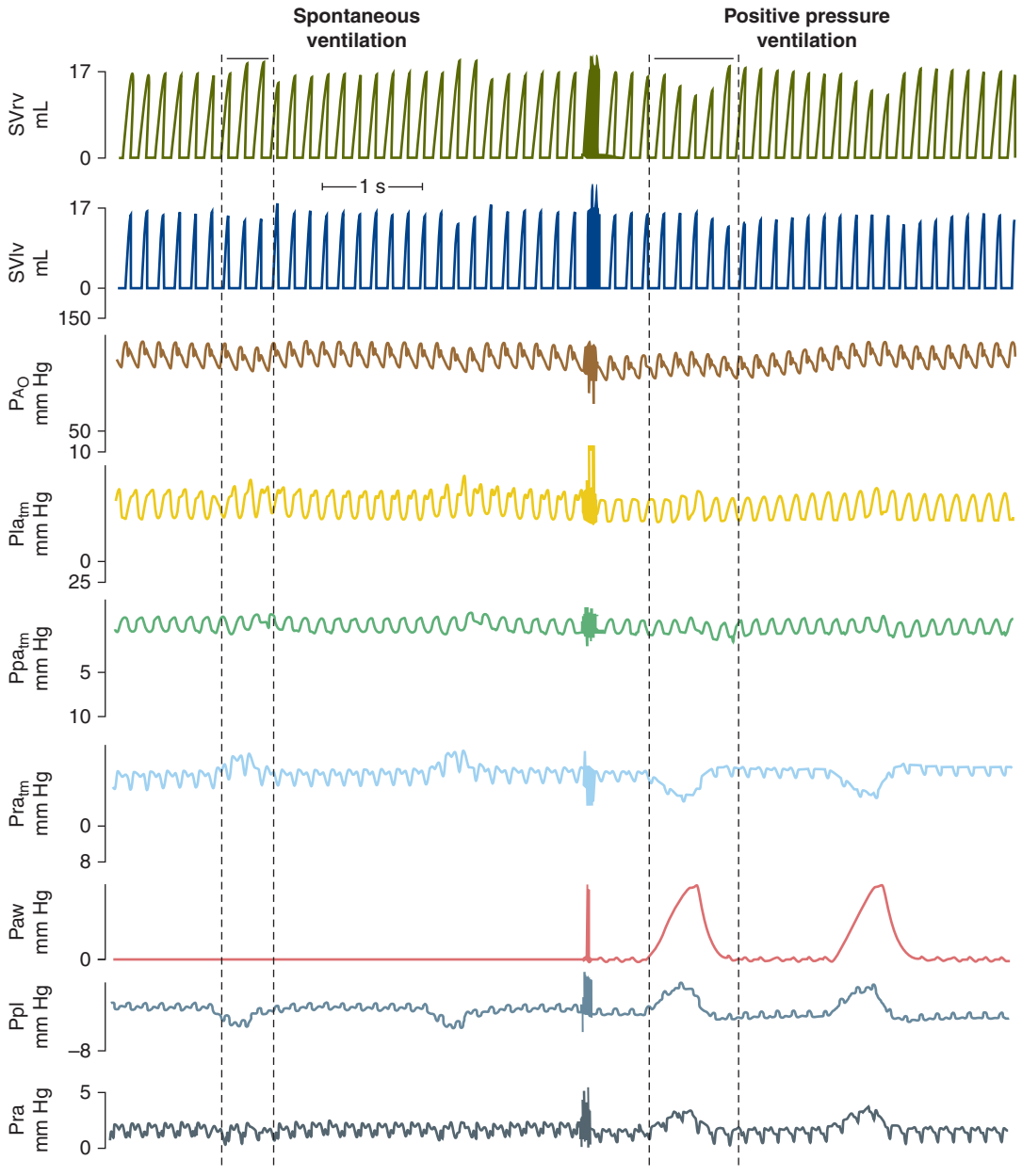

FIGURE 36-6 Strip chart recording of right and left-ventricular stroke volumes (*SVrv* and *SVlv*, respectively), aortic pressure (PA_O), left-atrial, pulmonary arterial, and right-atrial transmural pressures (Pla_{tm}, Ppa_{tm}, and Pra_{tm}, respectively), airway pressure (*Paw*), pleural pressure (*Ppl*), and right-atrial pressure (*Pra*) during spontaneous ventilation (*left*) and similar tidal volume positive-pressure ventilation (*right*) in an anesthetized, intact canine model. (Used, with permission, from Pinsky MR, Matuschak GM, Klain M. Determinants of cardiac augmentation by elevations in intrathoracic pressure. *J Appl Physiol.* 1985;58:1189–1198.)

diastolic compliance can acutely decrease in the setting of acute RV dilation or cor pulmonale (pulmonary embolism, hyperinflation, and RV infarction). Importantly, acute RV dilation and acute cor pulmonale can not only induce rapid cardiovascular collapse, but they are singularly not responsive to fluid resuscitation. Because spontaneous inspiration and inspiratory efforts cause both ITP and Pra to decrease, RV dilation may occur in patients with occult heart failure. Accordingly, some patients who were previously stable and ventilator-dependent can develop acute RV failure during weaning trials.

Finally, with exaggerated negative swings in ITP, as occur with obstructed inspiratory efforts, venous return behaves as if abdominal pressure is additive to mean systemic pressure in augmenting venous blood flow.[118–121] These findings have some investigators to suggest that obstructive breathing may be a therapeutic strategy in sustaining cardiac output in patients in hemorrhagic shock.[122] Interestingly, negative pressure ventilation, by augmenting venous return, increases cardiac output by 39% in children following repair of tetralogy of Fallot.[123] In this condition, impaired RV filling secondary to

RV hypertrophy and reduced RV chamber size are the primary factors limiting cardiac output. This augmentation of venous return by spontaneous inspiration, however, is limited,[119,120] because as ITP decreases below atmospheric pressure, venous return becomes flow-limited because the large systemic veins collapse as they enter the thorax.[87] This vascular flow limitation is a safety valve for the heart, because ITP can decrease greatly with obstructive inspiratory efforts,[13] and if not flow-limited, the RV could become overdistended and fail.[124] Finally, having subjects breathe through an airway that selectively impedes inspiration will result in exaggerated negative swings in both ITP and Pra, and associated greater increases in intraabdominal pressure secondary to recruitment of accessory muscles of respiration (to sustain a normal tidal volume).[122]

Positive-pressure ventilation tends to create the opposite effect: increase in ITP increases Pra, thus decreasing venous return, RV volumes, and ultimately LV output. The detrimental effect of positive-pressure ventilation on cardiac output can be minimized by either fluid resuscitation, to increase mean systemic pressure,[91,100,114,115,118] or by keeping both mean ITP and swings in lung volume as low as possible. Accordingly, prolonging expiratory time, decreasing tidal volume, and avoiding PEEP all minimize this decrease in systemic venous return to the right ventricle.[1,89,93–97,125,126] Increases in lung volume during positive-pressure ventilation primarily compress the two ventricles into each other, decreasing biventricular volumes.[127] The decrease in cardiac output commonly seen during PEEP is caused by a decrease in LV end-diastolic volume, because both LV end-diastolic volume and cardiac output are restored by fluid resuscitation[128,129] without any measurable change in LV diastolic compliance.[74]

A common respiratory maneuver, called a Valsalva maneuver, which is forced expiration against an occluded airway, such as one may do while straining at stool, displays most of the hemodynamic effects commonly seen in various disease states and with different types of positive-pressure ventilation.

During a Valsalva maneuver, airway pressure (Paw) and ITP increase equally, and pulmonary vascular resistance remains constant. During the first phase of the Valsalva maneuver, right ventricle filling decreases because venous return decreases with no change in left ventricle filling, LV stroke volume, or arterial pulse pressure. Although LV stroke volume does not change, LV peak ejection pressure increases equal to the amount of the increase in ITP.[30] As the strain is sustained, both LV filling and cardiac output both decrease owing to the decrease in venous return,[70,131] which results in the second phase. During this second phase of the Valsalva maneuver, both RV and LV output are decreased; arterial pulse pressure is reduced, but peak systolic pressure sustained at an elevated level owing to the sustained increase in ITP. This phase delay in LV output decrease compared to RV output decrease is also seen during positive-pressure ventilation; it is exaggerated if tidal volumes increase or if the pressure gradient for venous return was already low, as is the case in hypovolemia.[1,74–76,98,125,132–138] With release of the strain in phase three of the Valsalva maneuver, arterial pressure abruptly declines as the low LV stroke volume cannot sustain an adequate ejection pressure on its own. Furthermore, with the release of the increased ITP, venous return increases, increasing RV volume, and, through the process of ventricular interdependence, decreases LV diastolic compliance, making LV end-diastolic volume even less. Conceptually, then ventricular interdependence usually becomes apparent with sudden increases in RV volume from apneic baseline, as would occur during spontaneous inspiration, but less so when RV volumes decrease below these volumes. As described above, because RV volumes are usually decreased during positive-pressure ventilation, ventricular interdependence is not a prominent feature of this form of breathing (see Fig. 36-6).[62,136–139] Although PEEP results in some degree of right-to-left intraventricular septal shift, echocardiographic studies demonstrate that the shift is small.[77,132] It follows that positive-pressure ventilation decreases intrathoracic blood volume[94] and PEEP decreases it even more[140,141] without altering LV diastolic or contractile function.[142] During spontaneous inspiration, however, RV volumes increase transiently shifting the intraventricular septum into the LV,[63] decreasing LV diastolic compliance and LV end-diastolic volume.[48,61,139] This transient RV dilation-induced septal shift is the primary cause of inspiration-associated decreases in arterial pulse pressure, which, if greater than 10 mm Hg or 10% of the mean pulse pressure, is referred to as *pulsus paradoxus* (see Fig. 36-6).[64,143]

Left-Ventricular Preload and Ventricular Interdependence. Ventricular interdependence does not induce steady-state changes in left ventricle performance, only phasic ones. Thus, the associated rapid changes in right ventricle filling induced by phasic changes in ITP cause marked changes in LV output, which are a hallmark of ventilation-induced hemodynamic changes as described above (see Figure 36-6 Spontaneous ventilation).

LEFT-VENTRICULAR AFTERLOAD

LV afterload is defined as the maximal LV systolic wall tension, which equals the maximal product of LV volume and transmural LV pressure. Under normal conditions, maximal LV wall tension occurs at the end of isometric contraction, with the opening of the aortic valve. During LV ejection, as LV volumes rapidly decrease, LV afterload also decreases despite an associated increase in ejection pressure. Importantly, when LV dilation exists, as in CHF, maximal LV wall stress occurs during LV ejection because the maximal product of pressure and volume occurs at that time. LV ejection pressure is the transmural LV systolic pressure. This is the main reason why subjects with dilated cardiomyopathies are very sensitive to changes in ejection pressure, whereas patients with primarily diastolic dysfunction are not. Normal baroreceptor mechanisms, located in the extrathoracic carotid body, function to maintain arterial pressure constant with respect to atmosphere. Accordingly, if arterial pressure were to remain constant as ITP increased, then transmural LV pressure would decrease. Similarly, if transmural arterial pressure were to remain constant as ITP increased,

then LV wall tension would decrease.[144] Thus, increases in ITP decrease LV afterload, and decreases in ITP increase LV afterload.[130,145] These two opposing effects of changes in ITP on LV afterload have important clinical implications.

The concept that increases in ITP decrease both LV preload and LV afterload can be clearly illustrated with the use of high-frequency jet ventilation, which can increase ITP but does not result in large swings in lung volume.[135] When high-frequency jet ventilation is delivered in synchrony with the cardiac cycle, such that heart rate and ventilatory frequency are identical, one can dissect out the effects of ITP on preload and afterload. Under hypovolemic and normovolemic conditions with intact cardiovascular reserve, positive-pressure ventilation usually decreases steady-state cardiac output by decreasing the pressure gradient for venous return. When one compares the hemodynamic effects of high-frequency jet ventilation synchronized to occur during diastole (when ventricular filling occurs), cardiac output decreases to levels seen during end-inspiration for normal-to-large tidal-volume (10 mL/kg) ventilation. In the same subject, however, if the increases in ITP occur during systole, the detrimental effects of the same mean Paw, mean ITP, and tidal volume do not impede venous return (Fig. 36-7).[146,147] Furthermore, in heart failure states, positive-pressure ventilation does not impede cardiac output because the same decreases in venous return do not alter LV preload. If these increases in ITP, however, reduce LV afterload, then cardiac output will also increase. These points are illustrated in Figure 36-8, wherein synchronous high-frequency jet ventilation is delivered either during preejection systole (presystolic) or ejection (systolic). The only difference between the two ventilatory states is that arterial pulse pressure does not change despite increases in LV stroke volume with presystolic increases in Paw, consistent with a decreased LV afterload, whereas with systolic increases in Paw, arterial pulse pressure increases, and peak arterial pressure increases by an amount equal to the increase in ITP, consistent with mechanically augmented LV ejection.

Relevance of Intrathoracic Pressure on Myocardial Oxygen Consumption. Decreases in ITP increase both LV afterload and myocardial O_2 consumption. Accordingly, spontaneous ventilation not only increases global O_2 demand by its exercise component,[80,126,148] but also increases myocardial O_2 consumption. Profound decreases in ITP commonly occur during spontaneous inspiratory efforts with bronchospasm, obstructive breathing, and acute hypoxemic respiratory failure. Under these conditions, the cardiovascular burden can be great and may induce acute heart failure and pulmonary edema.[30] Because weaning from positive-pressure ventilation to spontaneous ventilation may reflect dramatic changes in ITP swings, from positive to negative, independent of the energy requirements of the respiratory muscles, weaning is a selective LV stress test.[144,148–150] Similarly, improved LV systolic function is observed in patients with severe LV failure placed on mechanical ventilation.[150] Very negative swings in ITP, as seen with vigorous inspiratory efforts in the setting of airway obstruction (asthma, upper airway obstruction, or vocal cord paralysis) or stiff lungs (interstitial lung disease, pulmonary edema, or ALI), selectively increase LV afterload, and may be the cause of LV failure and pulmonary edema,[13,30,31,151] especially if LV systolic function is already compromised.[152,153]

Pulsus paradoxus seen during spontaneous inspiration under conditions of marked pericardial restraint reflects primarily ventricular interdependence.[154–158] The negative swings in ITP, however, also increase LV ejection pressure, increasing LV end-systolic volume.[130] Other systemic factors may influence LV systolic function during loaded inspiratory efforts. These associated factors also contribute to a greater or lesser degree to the inhibition of normal LV systolic function, including increased in aortic input impedance,[159] altered synchrony of contraction of the global LV myocardium,[160] and hypoxemia-induced decreased global myocardial contractility.[161] Hypoxia also directly reduces LV diastolic compliance.[162] Experimental repetitive periodic airway obstructions induce pulmonary edema in normal animals.[30,31] Furthermore, removing the negative swings in ITP by applying nasal CPAP results in improved global LV performance in patients with combined obstructive sleep apnea and CHF.[130]

Relevance of Intrathoracic Pressure on Left-Ventricular Afterload. If arterial pressure remains constant, then increases in ITP decrease transmural LV ejection pressure, decreasing LV afterload. These points are easily demonstrated in a subject with an indwelling arterial pressure catheter during cough or Valsalva maneuvers. During a cough, ITP increases rapidly without changes in intrathoracic blood volume. Arterial pressure also increases by a similar amount, as described above for phase 1 of the Valsalva maneuver. Thus, transmural LV pressure (LV pressure relative to ITP)[130,163,164] and aortic blood flow[70] would remain constant. Sustained increases in ITP, however, must eventually decrease aortic blood flow and arterial pressure secondary to the associated decrease in venous return.[130] If ITP increased arterial pressure without changing transmural arterial pressure, then baroreceptor-mediated vasodilation would induce arterial vasodilation to maintain extrathoracic arterial pressure-flow relations constant.[134] Because coronary perfusion pressure reflects the ITP gradient for blood flow and is not increased by ITP-induced increases in arterial pressure, such sustained increases in ITP can cause decreased coronary perfusion pressure-induced myocardial ischemia.[165–167]

SPONTANEOUS BREATHING VERSUS MECHANICAL POSITIVE-PRESSURE VENTILATION

Both spontaneous and mechanical ventilation increase lung volume above resting end-expiratory lung volume or FRC. During both spontaneous and positive-pressure ventilation, end-expiratory lung volume can be artificially increased by the addition of PEEP. Thus, the primary hemodynamic

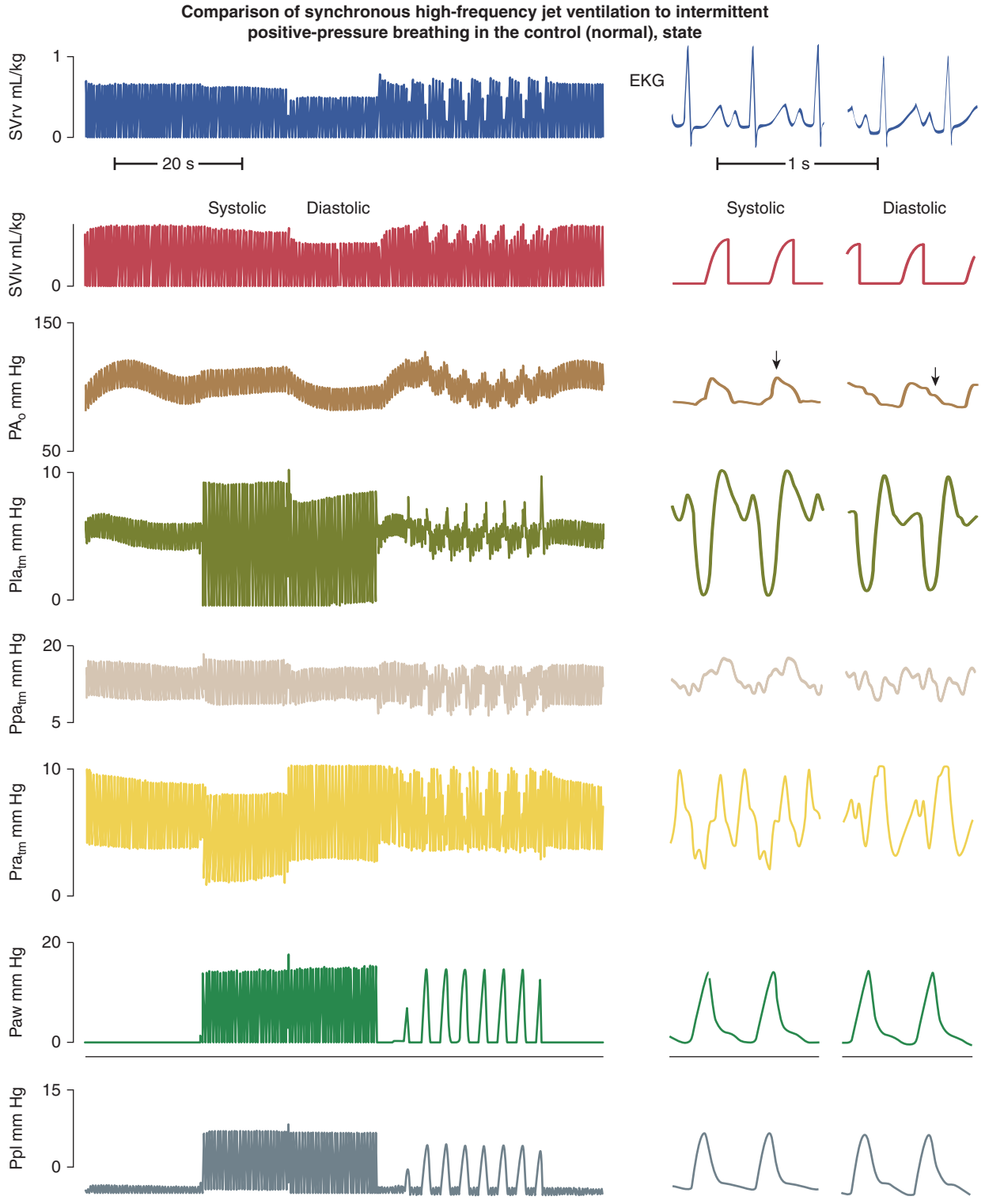

FIGURE 36-7 Strip chart recording of right- and left-ventricular stroke volumes (*SVrv* and *SVlv*, respectively), aortic pressure (PA_O), left atrial, pulmonary arterial, and right atrial transmural pressures (Pla_{tm}, Ppa_{tm}, and Pra_{tm}, respectively), airway pressure (*Paw*), and pleural pressure (*Ppl*) during apnea (*left*), and both systolic (*systole*) and diastolic (*diastole*) high-frequency jet ventilation (HFJV) (*middle*), and intermittent positive-pressure ventilation with similar mean Paw (*right*) in an anesthetized, intact canine model with normal cardiovascular function. Note that the cardiac cycle-specific increases in Paw created by systole HFJV minimally impede cardiac output, whereas diastole HFJV markedly decreases venous return (SVrv decreases first, then SVlv decreases). The rapid strip chart speed shown on the left is to illustrate the exact timing of synchronous HFJV. (Used, with permission, from Pinsky MR, Matuschak GM, Bernardi L, Klain M. Hemodynamic effects of cardiac cycle-specific increases in intrathoracic pressure. *J Appl Physiol.* 1986;60:604–612.)

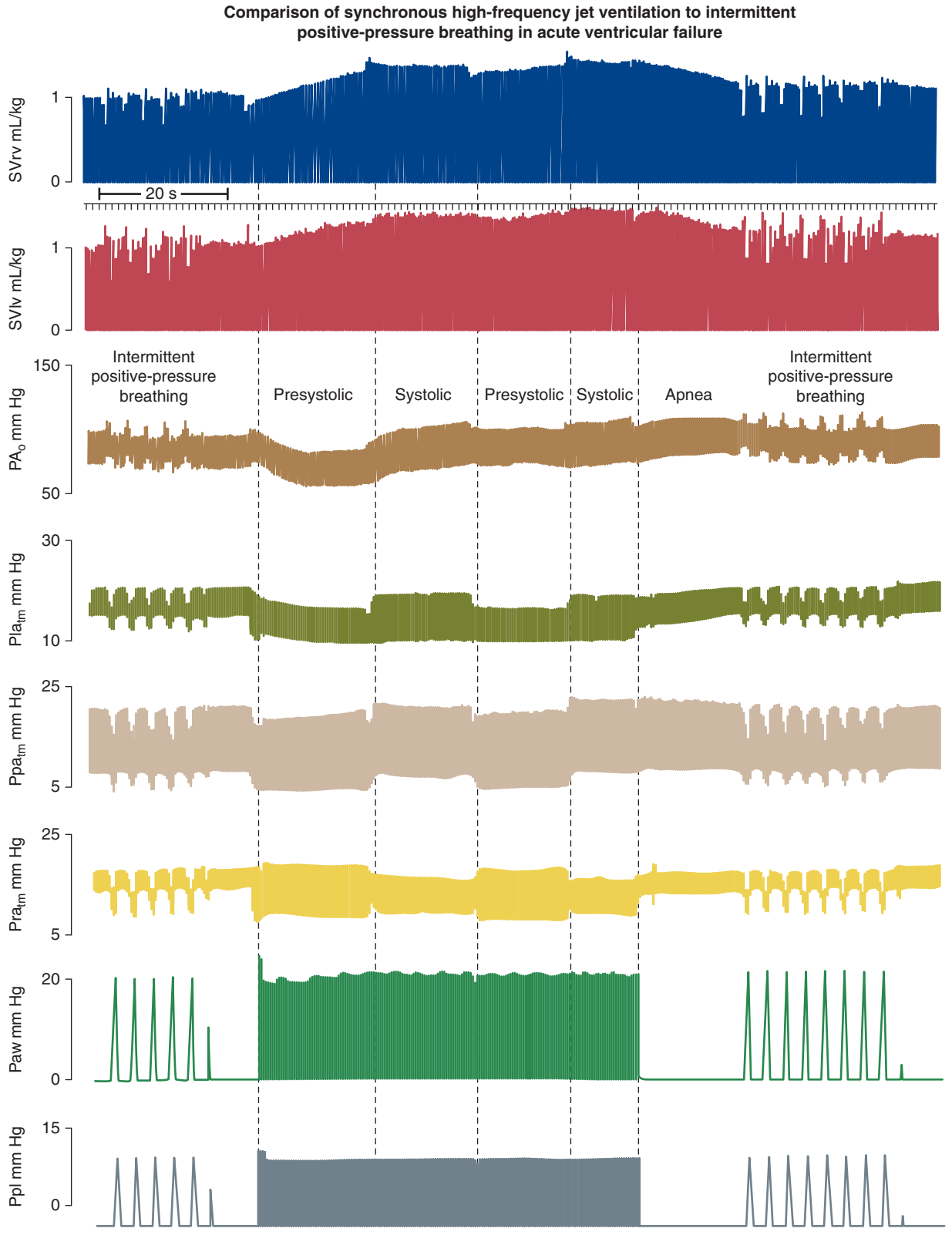

FIGURE 36-8 Continuous strip chart recording of right- and left-ventricular stroke volumes (*SVrv* and *SVlv*, respectively), aortic pressure (PA_O), left atrial, pulmonary arterial, and right-atrial transmural pressures (Pla_{tm}, Ppa_{tm}, and Pra_{tm}, respectively), airway pressure (*Paw*), pleural pressure (*Ppl*), and right-atrial pressure (*Pra*) during intermittent positive-pressure ventilation (tidal volume [V_T] 10 mL/kg), apnea (*left*), and then both preejection systole (presystolic) and LV ejection (systolic) synchronous high-frequency jet ventilation (HFJV) (*middle*), and then intermittent positive-pressure ventilation again (*right*) in an anesthetized, intact canine model with fluid-resuscitated acute ventricular failure. Note that the cardiac cycle–specific increases in Paw created by both presystolic and systolic HFJV increase steady-state SVrv and SVlv (i.e., cardiac output), but affect PA_O differently. Presystolic HFJV does not change PA_O pulse pressure despite an increase in SVlv (reduced afterload), whereas systolic HFJV increases PA_O pulse pressure for a similar increase in SVlv. (Used, with permission, from Pinsky MR, Matuschak GM, Bernardi L, Klain M. Hemodynamic effects of cardiac cycle-specific increases in intrathoracic pressure. *J Appl Physiol.* 1986;60:604–612.)

differences between spontaneous ventilation and positive-pressure ventilation are caused by the changes in ITP and the muscular contraction needed to create these changes. Importantly, even if a patient is receiving ventilator support, spontaneous respiratory efforts can persist and may result in marked increases in metabolic load, and contribute to sustained respiratory muscle fatigue.[168] Still, a primary reason for instituting mechanical ventilation is to decrease the work of breathing. Normal spontaneous ventilation augments venous return and vigorous inspiratory efforts account for most of the increased blood flow seen in exercise. Conversely, positive-pressure ventilation may impair ventricular filling and induce hypovolemic cardiac dysfunction in normal or hypovolemic subjects while augmenting LV function in patients with heart failure. Finally, heart failure, whether primary or induced by ventilation, may induce acute respiratory muscle fatigue causing respiratory failure or failure to wean from mechanical ventilation, and overtax the ability of the circulation to deliver O_2 to the rest of the body.

Fundamental to this concept is the realization that spontaneous ventilation is exercise. Spontaneous ventilatory efforts are induced by contraction of the respiratory muscles, mainly the diaphragm and intercostal muscles.[148] Although ventilation normally requires less than 5% of total O_2 delivery to meet its demand[148] (and is difficult to measure at the bedside even when using calibrated metabolic measuring devices), in lung disease states in which work of breathing is increased, the metabolic demand for O_2 can increase to 30% of total O_2 delivery.[80,125,148,169] With marked hyperpnea, muscles of the abdominal wall and shoulder girdle function as accessory muscles. Blood flow to these muscles is derived from several arterial circuits, whose absolute flow exceeds the highest metabolic demand of maximally exercising skeletal muscle under normal conditions.[148,170,171] Thus, blood flow is usually not the limiting factor determining maximal ventilatory effort. In severe heart failure states, however, blood flow constraints may limit ventilation because blood flow to other organs and to the respiratory muscles may be compromised, inducing both tissue hypoperfusion and lactic acidosis.[170–172] Aubier et al demonstrated that if cardiac output is severely limited by the artificial induction of tamponade in a canine model that respiratory muscle failure develops despite high central neuronal drive.[171] The animals die a respiratory death before cardiovascular standstill. The institution of mechanical ventilation for ventilatory and hypoxemic respiratory failure may reduce metabolic demand on the stressed cardiovascular system increasing mixed venous oxygen saturation ($S\bar{V}O_2$) for a constant cardiac output and arterial oxygen content (CaO_2).[172] Intubation and mechanical ventilation, when adjusted to the metabolic demands of the patient, may dramatically decrease the work of breathing, resulting in increased O_2 delivery to other vital organs and decreased serum lactic acid levels. Under conditions in which fixed right-to-left shunts exist, the obligatory increase in $S\bar{V}O_2$ will result in an increase in the partial pressure of arterial oxygen (Pa_{O_2}), despite no change in the ratio of shunt blood flow to cardiac output.

DETECTION AND MONITORING

Weaning Failure

Ventilator-dependent patients who fail to wean often have impaired baseline cardiovascular performance that is readily apparent,[153] but commonly patients develop overt signs of heart failure during weaning, such as pulmonary edema,[153,174] myocardial ischemia,[175–178] tachycardia, and gut ischemia.[179] Pulmonary artery occlusion pressure may rise rapidly to nonphysiologic levels within 5 minutes of instituting weaning.[153] Although all patients increase their cardiac outputs in response to a weaning trial, those that subsequently fail to wean demonstrate a reduction in mixed venous O_2 saturation, consistent with a failing cardiovascular response to an increased metabolic demand.[180] Weaning from mechanical ventilation can be considered a cardiovascular stress test. Again, investigators have documented weaning-associated electrocardiogram and thallium cardiac blood flow scan-related signs of ischemia in both patients with known coronary artery disease[175] and in otherwise normal patients.[177,178] Using this same logic, placing patients with severe heart failure and/or ischemia on ventilator support, by either intubation and ventilation[181] or noninvasive CPAP[182] can reverse myocardial ischemia. Importantly, the increased work of breathing may come from the endotracheal tube flow resistance.[183] Thus, some patients who fail a spontaneous breathing trial may actually be able to breathe on their own if extubated. There is, however, no known method of identifying this subgroup.

Using Ventilation to Define Cardiovascular Performance

Because the cardiovascular response to positive-pressure breathing is determined by the baseline cardiovascular state, these responses can be used to define such cardiovascular states. Sustained increases in airway pressure will reduce venous return, allowing one to assess LV ejection over a range of end-diastolic volumes. If echocardiographic measures of LV volumes are simultaneously made, then one can use an inspiratory-hold maneuver to measure cardiac contractility, as defined by the end-systolic pressure-volume relationship,[184] which is similar to those created by transient inferior vena-caval occlusion.[185,186] Furthermore, these measures can be made during the ventilatory cycle to define dynamic interactions.[186]

Patients with relative hypervolemia, a condition often associated with CHF, are at less risk of developing impaired venous return during initiation of mechanical ventilation, whereas hypovolemic patients are at increased risk. If positive airway pressure augments LV ejection in heart failure states by reducing LV afterload, then systolic arterial pressure should not decrease but actually increase during inspiration, so-called reverse pulsus paradoxus. This was what Abel et al[187] saw in ten postcardiac surgery patients. Perel et al[188–190] suggested that the relationship between ventilatory efforts

and systolic arterial pressure may be used to identify which patients may benefit from cardiac-assist maneuvers. Patients who increase their systolic arterial pressure during ventilation, relative to an apneic baseline, tend to have a greater degree of volume overload[189] and heart failure,[190] whereas patients who decrease systolic arterial pressure tend to be volume responsive. Perhaps more relevant to usual clinical practice is the identification of patients whose cardiac output will increase if given a volume challenge. The identification of preload responsiveness is important because only half of the hemodynamically unstable patients studied in several clinical series were actually preload-responsive.[191] Thus, nonspecific fluid loading will not only be ineffective at restoring cardiovascular stability in half the subjects, it will also both delay definitive therapy and may promote cor pulmonale or pulmonary edema. Finally, Michard et al[192] found, in a series of ventilator-dependent septic patients, that the greater the degree of arterial pulse-pressure variation during positive-pressure ventilation, the greater the subsequent increase in cardiac output in response to volume-expansion therapy. The recent literature has documented that both arterial pulse-pressure and LV stroke-volume variations[193,194] induced by positive-pressure ventilation are sensitive and specific markers of preload responsiveness. This literature was recently reviewed.[195] The greater the degree of flow or pressure variation over the course of the respiratory cycle for a fixed tidal volume, the more likely a patient is to increase cardiac output in response to a volume challenge, and the greater that increase. The overarching principles of this clinical tool have only recently been described.[173] There are several important caveats and limitations to this approach that need to be considered before the clinician proceeds to monitoring arterial pulse pressure or stroke volume variation during ventilation as a routine assessment of preload responsiveness.

First, and perhaps most importantly, being preload-responsive does not mean that the patient should be given volume. Otherwise healthy subjects under general anesthesia without evidence of cardiovascular insufficiency are also preload-responsive, but do not need a volume challenge. The presence of positive-pressure-induced changes in aortic flow or arterial pulse pressure does not itself define therapy. Independent documentation of cardiovascular insufficiency needs to be sought before the clinician attempts fluid resuscitation based on these measures. Second, these indices, which quantify the variation in aortic flow, stroke volume, and arterial systolic and pulse pressures, have routinely been demonstrated to outperform more traditional measures of LV preload, such as pulmonary occlusion pressure, Pra, total thoracic blood volume, RV end-diastolic volume, and LV end-diastolic area.[192,194] There appears to be little relation between ventricular preload and preload responsiveness. Ventricular filling pressures poorly reflect ventricular volumes, and measures of absolute ventricular volumes do not define diastolic compliance.[196,197] Patients with small left ventricles that are also stiff, as may occur with acute cor pulmonale, tamponade, LV hypertrophy, and myocardial fibrosis, will show poor volume responsiveness. Conversely, patients with large LV volumes, as often occurs with CHF and afterload reduction, may be quite volume responsive. Thus, preload does not equal preload responsiveness. Third, all the reported studies used positive-pressure ventilation to vary venous return. For such changes in venous return, however, to induce LV output changes, the changes must be of sufficient enough magnitude to cause measurable changes in preload.[69] If the increase in lung volume with each tidal breath is either not great enough to induce changes in pulmonary venous flow,[198] or if the positive-pressure breath is associated with spontaneous inspiratory efforts that minimize the changes in venous return,[199] then the cyclic perturbations to cardiac filling may not be great enough to induce the cyclic variations in LV filling needed to identify preload responsiveness. Furthermore, the degree of pressure or flow variation will be proportional to tidal volume, with greater tidal volumes inducing greater changes for the same cardiovascular state.[192,195,200] Thus, the means by which cyclic changes in lung volume and ITP are induced will affect the magnitude of arterial pressure and flow variations. Fourth, although the primary determinant of arterial pulse-pressure variation over a single breath is LV stroke-volume variation, because changes in aortic impedance and arterial tone cannot change that rapidly[201] over time, this limitation no longer applies. As arterial tone decreases, for example, then for the same aortic flow and stroke volume both mean arterial pressure and pulse pressure will be less. Accordingly, flow variation becomes more sensitive than pulse pressure variation as hemorrhage progresses.[193]

CLINICAL SCENARIOS

Initiating Mechanical Ventilation

NORMOVOLEMIC AND HYPOVOLEMIC PATIENTS

The process of initiating mechanical ventilation is a complex physiologic process for a variety of reasons. First, pharmacologic factors needed to allow for endotracheal intubation also blunt sympathetic responses, exaggerating the hemodynamic effects induced by increasing airway pressure and defining tidal volume and ventilatory frequency. This point is clearly demonstrated by comparing the relative benign impact that reinstituting ventilator support in a patient with a preexistent tracheotomy, with the impact of the initial intubation and ventilation of the same patient a few days or weeks earlier. As noted above, positive-pressure ventilation increases ITP, which must alter venous return. If the patient has reduced vasomotor tone, as commonly exists during induction of anesthesia, the associated increase in Pra will induce a proportional decrease in venous return, pulmonary blood flow and subsequently cardiac output.[1,35,152,202] If the associated tidal volumes are excessive for the duration of expiratory time available to allow for passive deflation, then dynamic hyperinflation will occur, increasing pulmonary vascular resistance and compressing the heart in the cardiac fossa, further decreasing further biventricular volumes.[127] If one were to examine the dynamic effects of ventilation on

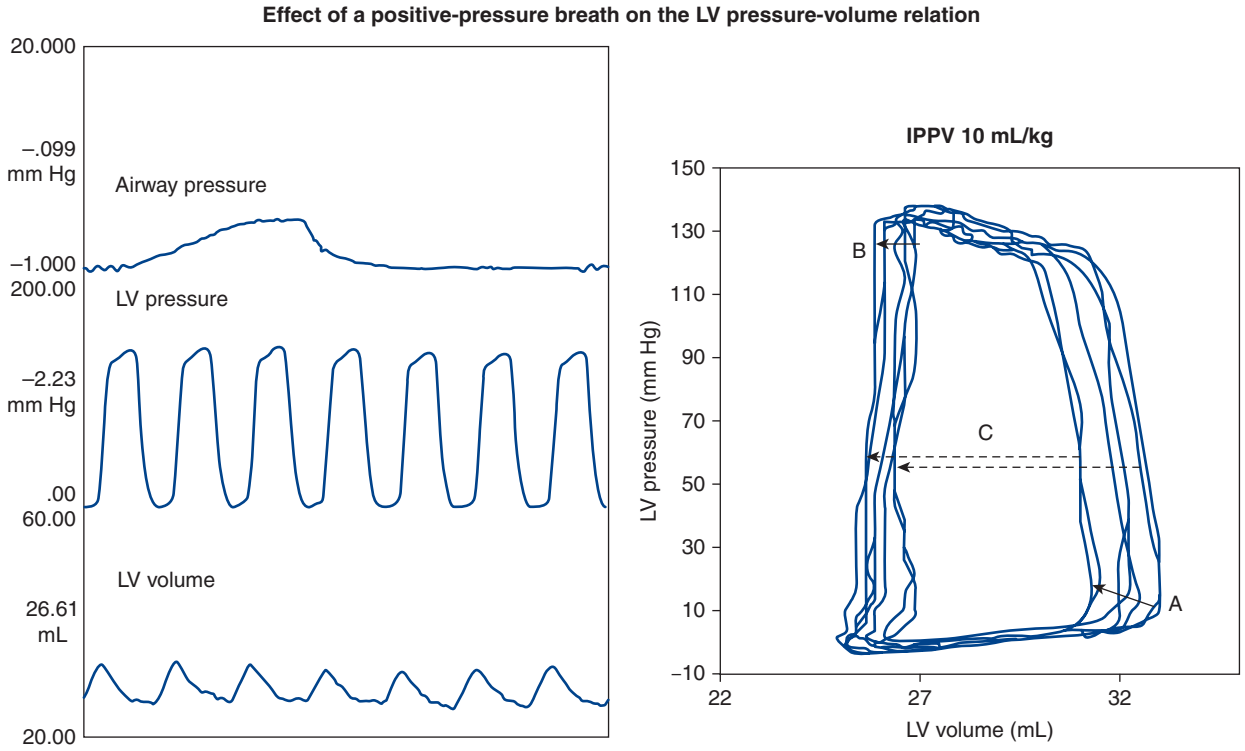

FIGURE 36-9 Dynamic effect of positive-pressure ventilation on the LV pressure-volume relation from end-expiration through a ventilatory cycle. Note the changes in LV filling (maximal end-diastolic volume), diastolic compliance (the slope of the LV pressure-volume relation as LV volume increases during filling: *lower horizontal line*), stroke volume (difference between maximal or end-diastolic volume and minimal or end-systolic volume for a given beat), and the end-systolic pressure-volume relation all change during the course of a single breath. Figure 36-10 shows how changes in tidal volume and intravascular volume alter these changes differently. *IPPV*, intermittent positive-pressure ventilation.

the LV pressure-volume relation over the course of a single breath, one would see a more complex effect, characterized by alterations in LV diastolic compliance, end-diastolic volume, stroke volume, and LV afterload (as exemplified by the leftward shift of the end-systolic pressure-volume relations; Fig. 36-9). Importantly, the impact of ventilation on LV performance, as described in the first part of this chapter, is overly simplified by this assumption that breathing alters only LV preload. Clearly, other factors also function simultaneously. The preload-reducing effects of tidal volume, however, are best described during hypovolemic states, as illustrated in the *right panel* of Figure 36-10. Note that

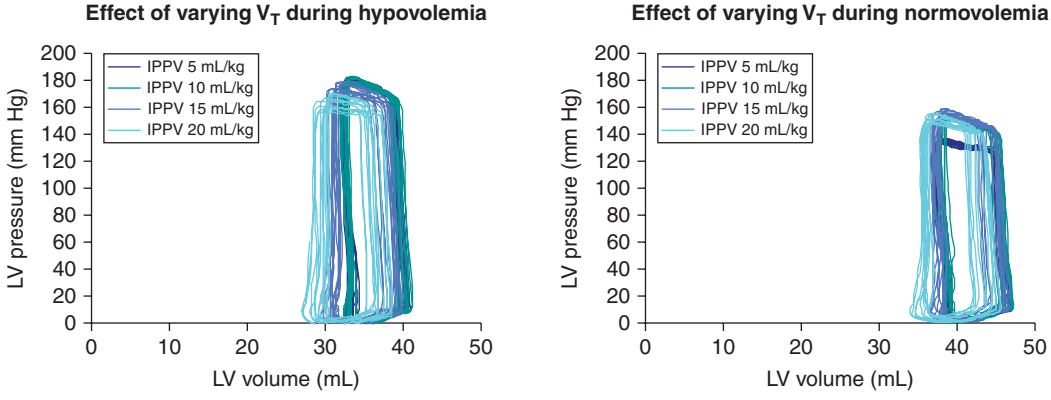

FIGURE 36-10 Effect of increasing tidal volume (V_T) on the LV pressure-volume relationship during normovolemic (*left*) and hypovolemic (*right*) conditions in an intact anesthetized canine model. Under normovolemic conditions, the preload-reducing effects of positive-pressure inspiration become more pronounced at end-inspiration as tidal volume increases. Under hypovolemic conditions, similar increases in tidal volume also tend to decrease the overall size and performance of the heart along lines consistent with pure reductions in LV preload (end-diastolic volume); that is, steady-state LV end-diastolic and end-systolic volumes decrease, end-systolic pressure decreases, and stroke volume decreases with increasing tidal volumes and airway pressures. *IPPV*, intermittent positive-pressure ventilation.

increasing tidal volumes limit ventricular filling, decreasing LV stroke volume under both normovolemic (*left panel*) and hypovolemic (*right panel*) conditions (Fig. 36-10), but this effect is markedly exaggerated by hypovolemia.

HYPERVOLEMIC AND HEART-FAILURE PATIENTS

Initiating mechanical ventilation in hypervolemic patients has far less effect on cardiac output than seen during normovolemic or hypovolemic conditions, because the impact of ventilation on venous return is much less (see *right-hand panel* of Fig. 36-7). Moreover, if such patients also have a component of acute RV volume overload, one may actually see LV diastolic compliance increase and LV output markedly improve. It is not clear, however, if these often-seen improvements in LV performance and cardiac output in hypervolemic conditions represents improved LV filling, reduced metabolic demands, or improved LV contraction. Regrettably, no clinical trials have examined the mechanisms by which such improvement occurs.

Comparing Different Ventilator Modes

Any hemodynamic differences between different modes of total mechanical ventilation at a constant airway pressure and PEEP are a result of differential effects on lung volume and ITP.[203] When two different modes of total or partial ventilator support have similar changes on ITP and respiratory effort, their hemodynamic effects are also similar, despite markedly different airway waveforms. Partial ventilator support with either intermittent mandatory ventilation or pressure-support ventilation give similar hemodynamic responses when matched for similar tidal volumes.[204] Similar tissue oxygenation occurred in ventilator-dependent patients when switched from assist-control, intermittent mandatory ventilation, and pressure-support ventilation with matched tidal volumes.[205] Numerous studies document cardiovascular equivalence when different ventilator modes are matched for tidal volume and level of PEEP.[206,207] Different ventilator modes will affect cardiac output to a similar extent for similar increases in lung volume.[112,208,209] When pressure-controlled ventilation with a smaller tidal volume was compared to volume-controlled ventilation, however, pressure-controlled ventilation was associated with a higher cardiac output.[209,210] Davis et al[211] studied the hemodynamic effects of volume-controlled ventilation versus pressure-controlled ventilation in twenty-five patients with ALI. When matched for the same mean Paw, both modes gave the same cardiac outputs. When Paw, however, was increased during volume-controlled ventilation from a sine-wave to a square-wave flow pattern, cardiac output fell. Furthermore, Kiehl et al found[212] cardiac output better during biphasic positive-airway pressure than during volume-controlled ventilation, leading to an increased $S\bar{V}O_2$ and indirectly increasing Pa_{O_2}. In eighteen ventilator-dependent but hemodynamically stable patients, Singer et al[213] showed that the degree of hyperinflation, not the Paw, determined the decrease in cardiac output. Finally, in an animal model of ALI, Mang et al[214] demonstrated that if total PEEP (intrinsic PEEP plus additional extrinsic PEEP) was similar, no hemodynamic differences were observed between conventional ventilation and inverse-ratio ventilation.

Upper Airway Obstruction

The cardiovascular effects of upper airway obstruction have been reviewed.[215] To understand the effects, it is useful to examine the effect of spontaneous inspiratory efforts against an occluded airway, referred to as a *Mueller maneuver*. This maneuver is easy to create in a graded fashion in the laboratory by having a subject inspire against an occluded airway connected to a manometer; the negative swings in Paw can be controlled by the subject. Based on the above physiologic discussion, it is clear that a Mueller maneuver will result in an increase in both venous return and LV afterload. The hemodynamic effects, however, of positive and negative swings in ITP may not be mirrored opposites of each other; the interactions are nonlinear. As ITP becomes more negative, venous return becomes flow limited as the veins collapse because their transmural pressure becomes negative. LV afterload, however, increases progressively and linearly.[182] Figure 36-4 illustrates these nonlinear effects. Changes in ITP will appear to shift the LV Frank-Starling curve to the left or right, with Pra on the *x* axis, equal to the change in ITP, because the heart is in the chest and acted upon by ITP, whereas venous return is from the body, which is outside of this pressure chamber. Accordingly, large negative swings in ITP will selectively increase LV ejection pressure without greatly increasing RV preload or LV diastolic compliance. This concept is important. Removing large negative swings in ITP without inducing positive swings in ITP, as would occur by endotracheal intubation or tracheotomy to bypass any upper airway obstruction, should selectively reduce LV ejection pressure (LV afterload) and not reduce venous return (LV preload).

Large negative swings in ITP commonly occur in critically ill patients. Upper airway obstruction is a medical emergency. The most common cause of upper airway obstruction is pharyngeal obstruction secondary to loss of muscle tone, which is manifest as snoring or obstructive sleep apnea. Laryngeal edema or vocal cord paralysis following extubation commonly present as acute upper airway obstruction immediately following extubation. Other causes of upper airway obstruction include epiglottis, retropharyngeal hematomas, tumors of the neck and vocal cords, and foreign-body aspiration. Because the site of obstruction is in the extrathoracic airway, increasing inspiratory efforts only cause the obstruction to become more pronounced. By markedly increasing LV afterload, inspiration against an occluded airway rapidly leads to acute pulmonary edema.[130,216–223] During an acute asthmatic attack in a child, peak negative ITP can be −40 cm H_2O and mean tidal ITP

maintained between −24 and −7 cm H_2O,[13] increasing both LV afterload[130,131] and promoting pulmonary edema.[216]

Chronic Obstructive Pulmonary Disease

The hemodynamic consequences of COPD reflect complex issues related to hyperinflation, a propensity to further dynamic hyperinflation and increased airway resistance. Hyperinflation within the context of preexisting reduced pulmonary vascular cross-sectional area and increased pulmonary vasomotor tone, are the primary reasons for ventilation-induced pulmonary hypertension and RV failure. RV afterload is often increased owing to loss of pulmonary parenchyma and hyperinflation. Ventilation–perfusion mismatch can promote further increases in pulmonary vasomotor tone through hypoxic pulmonary vasoconstriction. The ultimate effects of this process are to impede RV ejection and induce by RV dilation, and, if pulmonary hypertension persists, induce RV hypertrophy. An immediate increase in lung volume may decrease RV end-diastolic volume because of cardiac compression and an associated increase in Pra. Neurohumoral reflex mechanisms, however, acting through right atrial stretch receptors cause salt and water retention, causing blood volume and Pra to increase. The goal of this exercise is to restore venous return to its baseline level. Accordingly, the elevated Pra commonly seen in COPD patients reflects a survival strategy analogous to LV dilation in heart failure.

During exacerbations of COPD, hypoxemia, respiratory acidosis, increased intrinsic sympathetic tone, and increased, but inefficient, respiratory efforts combine to increase the work of breathing. The net result is often unpredictable, but certain scenarios often present themselves, which suggests the dominance of one process over the others. These differences are relevant because these identify specific, and often opposite, therapeutic strategies that are used to reverse the associated cardiovascular insufficiency. On a global level, however, any treatments that can reduce airway obstruction and bronchospasm will reduce work of breathing, minimize hyperinflation, and reverse respiratory acidosis and hypoxemia, decreasing RV afterload. Accordingly, the aggressive use of supplemental O_2, bronchodilating agents, and antibiotics to reduce airway infection and the volume and viscosity of secretion will all improve cardiovascular function. If mechanical ventilation can reverse hyperinflation and alveolar hypoxia, one will see reductions in Pra, increases in cardiac output, and less radical arterial pressure swings during ventilation. If, however, hyperinflation persists or is exaggerated by mechanical ventilation, then acute RV failure may occur.

ACUTE COR PULMONALE

Hyperinflation, in the setting of preexisting pulmonary hypertension or decreased pulmonary vessel cross-sectional area, can induce profound increases in pulmonary arterial pressure, promoting acute cor pulmonale. With the initiation of mechanical ventilation, it is easy to set tidal volume too large and inspiratory time too long, promoting dynamic hyperinflation.[224,225] Every effort should be made to minimize this life-threatening complication. Importantly, the cardiovascular management of this life-threatening process is to reduce RV wall strain and maintain or improve RV coronary perfusion. These considerations are briefly summarized. First, one almost always sees acute elevations of Pra, often accompanied by acute tricuspid regurgitation at end-inspiration. If a pulmonary arterial catheter is present, Pra equal or exceed pulmonary artery occlusion pressure. Furthermore, if the catheter has the ability to measure RV ejection fraction, it almost always reduced (<40%). Importantly, acute volume infusions will only compromise the dilated right ventricle further, such that both stroke volume and RV ejection fraction are decreased. These are clear signs of impending or existing cardiovascular collapse secondary to acute cor pulmonale. Because most of RV myocardial blood flow occurs in systole, maintaining aortic pressure higher than pulmonary arterial pressure to sustain RV myocardial perfusion is an essential aspect of the initial cardiovascular management.

LEFT-VENTRICULAR FAILURE

Although COPD is usually characterized by right-sided dysfunction owing to the alterations in pulmonary vascular biology, these subjects also tend to be smokers, elderly, and male, three demographic qualities that place them at high risk of coronary artery disease. With the exception of intubation-induced hypotension and reactive tachycardia, the risk of LV ischemia during intubation and sustained mechanical ventilation is relatively low in these patients. Because they are usually volume overloaded and have a reduced cardiac reserve before intubation, these patients usually benefit from a reduction in metabolic demands and reduced ventricular interdependence owing to the smaller RV volumes. Patients with COPD may fail weaning attempts because their work of breathing exceeds their cardiovascular reserve.[226,227] Just as these patients cannot climb two flights of stairs, they may wean because of impaired cardiovascular reserve. The combination of occult impaired cardiovascular reserve and the stress of spontaneous ventilation, with associated negative swings in ITP and positive swings intraabdominal pressure, which augment venous return, provide a primary reason for cases of weaning failure characterized by hypoxemia or transient pulmonary edema. Beach et al demonstrated many years ago that heart-failure patients who are ventilator-dependent may be weaned if pharmacologic support of the heart is subsequently introduced.[152]

Auto–Positive End-Expiratory Pressure

The hemodynamic effects of positive-pressure ventilation are caused by changes in ITP, not airway pressure. This concept greatly influences the analysis of heart–lung interactions in patients with lung disease. As discussed above (see the

section "Physiology of Heart-Lung Interactions"), the primary determinants of the hemodynamic responses to ventilation are secondary to changes in ITP and lung volume,[3] not Paw. The relation between Paw, ITP, pericardial pressure, and lung volume varies with spontaneous ventilatory effort, lung compliance, and chest wall compliance. Lung and thoracic compliance determine the relation between end-expiratory Paw and lung volume in the sedated paralyzed patient. If a ventilated patient, however, actively resists lung inflation or sustains expiratory muscle activity at end-inspiration, then end-inspiratory Paw will exceed resting Paw for that lung volume. Similarly, if the patient activity prevents full exhalation by expiratory braking, then for the same end-expiratory Paw, lung volume may be much higher than predicted from end-expiratory Paw values alone. Finally, even if inspiration is passive and no increased airway resistance is present, Paw may rapidly increase over minutes as chest wall compliance decreases. During inspiration, positive-pressure Paw increases as a function of both total thoracic compliance and airway resistance. Patients with marked bronchospasm will display a peak Paw greater than end-inspiratory (plateau) Paw. The difference between measured Paw and Palv is called *auto-PEEP*.[224,225] Changes in transpulmonary pressure and total thoracic compliance alter FRC, and FRC is the primary volume about which all hemodynamic interactions revolve.

FRC is a nefarious value. When one reclines from a standing position, FRC may decrease by as much as 500 mL in a 70-kg healthy male. PEEP and CPAP increase FRC by offsetting Palv. If a subject does not have sufficient time to exhale completely to FRC, however, then the next breath will stack upon the extra lung volume present. Bergman described this concept of dynamic hyperinflation many years ago.[224] Pepe and Marini coined the term "auto-PEEP" to connote the similarities between dynamic hyperinflation (also called occult PEEP) and extrinsically applied PEEP.[225] Auto-PEEP is not measured by the ventilator, as part of its usual parameters, and may go unappreciated. Yet, it functions identically to extrinsic PEEP in altering pulmonary vascular resistance and recruiting alveoli. The hemodynamic effect of this hyperinflation is to increase ITP and pulmonary vascular resistance, and compress the heart within the cardiac fossa. Thus, one may see Pra and pulmonary artery occlusion pressure progressively increase as arterial pulse pressure and urine output decrease. One may then make the erroneous diagnosis of acute heart failure, when all that is occurring is hyperinflation and the unaccounted increase in ITP. If one adds extrinsic PEEP to the ventilator circuit of patients with auto-PEEP, no measurable hemodynamic effects are seen until extrinsic PEEP exceeds auto-PEEP levels.[228] These data suggest that auto-PEEP and extrinsic PEEP have identical hemodynamic effects during controlled mechanical ventilation.

During assisted ventilator support, however, or spontaneous breathing, auto-PEEP adds an additional elastic workload on the respiratory muscles. This increased workload is often the cause of failure to wean because spontaneous breathing trials are often associated with tachypnea, which prevents adequate time for complete exhalation. Clinical signs and symptoms suggestive of hemodynamically significant auto-PEEP include increased anxiety and agitation during spontaneous breathing associated with a marked increase in respiratory efforts and paradoxical chest wall motion. Because changes in ITP are occurring even though no air movement initially takes place, an arterial pressure recording will show immediate decreases in diastolic arterial pressure without changes in pulse pressure until the inspiratory breath finally occurs. Finally, by adding progressive increases in extrinsic PEEP to the ventilator circuit during a spontaneous breathing trial, changes in arterial diastolic pressure and pulse pressure will start to occur in unison as ventilatory efforts recouple with the ability to cause airflow.

Acute Respiratory Distress Syndrome and Acute Lung Injury

Patients with ALI have decreased aerated lung volumes owing to alveolar collapse and flooding. Because lung expansion during positive-pressure inspiration pushes on the surrounding structures, distorting them, this expansion causes thoracic surface pressures to increase. The degree of lateral chest wall, diaphragmatic or juxtacardiac ITP increase, relative to each other as lung volume increases, will be a function of the compliance and inertance of their opposing structures.[71] Changes in pleural pressure (Ppl) induced by positive-pressure inflation are different among differing lung regions (Fig. 36-11). Pleural pressure close to the diaphragm increases least during inspiration, and juxtacardiac Ppl increases most, presumably because the diaphragm is very compliant whereas the mediastinal contents are not. If abdominal distension develops, however, then the diaphragm will become relatively noncompliant and ITP will increase similarly across the entire thorax. Increasing Paw to overcome chest wall stiffness (abdominal distension) in secondary acute respiratory distress syndrome should produce a greater increase in ITP, with greater hemodynamic consequences, but it should not improve gas exchange, because the alveoli are not damaged. Conversely, if lung compliance is reduced, as in primary acute respiratory distress syndrome, then for a similar increase in Paw, ITP will increase less, creating fewer hemodynamic effects, but also recruiting more collapsed and injured alveolar units, improving gas exchange. If lung injury induces alveolar flooding or increased pulmonary parenchyma stiffness, then greater increases in Paw will be required to distend the lungs to a constant end-inspiratory volume. Romand et al[82] demonstrated that although Paw increased more during ALI than under control conditions for a constant tidal volume, the increases in lateral chest wall Ppl and pericardial pressure were equivalent for both conditions if tidal volume was held constant (see Fig. 36-11). The primary determinant of the increase in Ppl and pericardial pressure during positive-pressure ventilation is lung volume change, not Paw change.[84]

The distribution of alveolar collapse and lung compliance in ALI is nonhomogeneous. Accordingly, lung distension

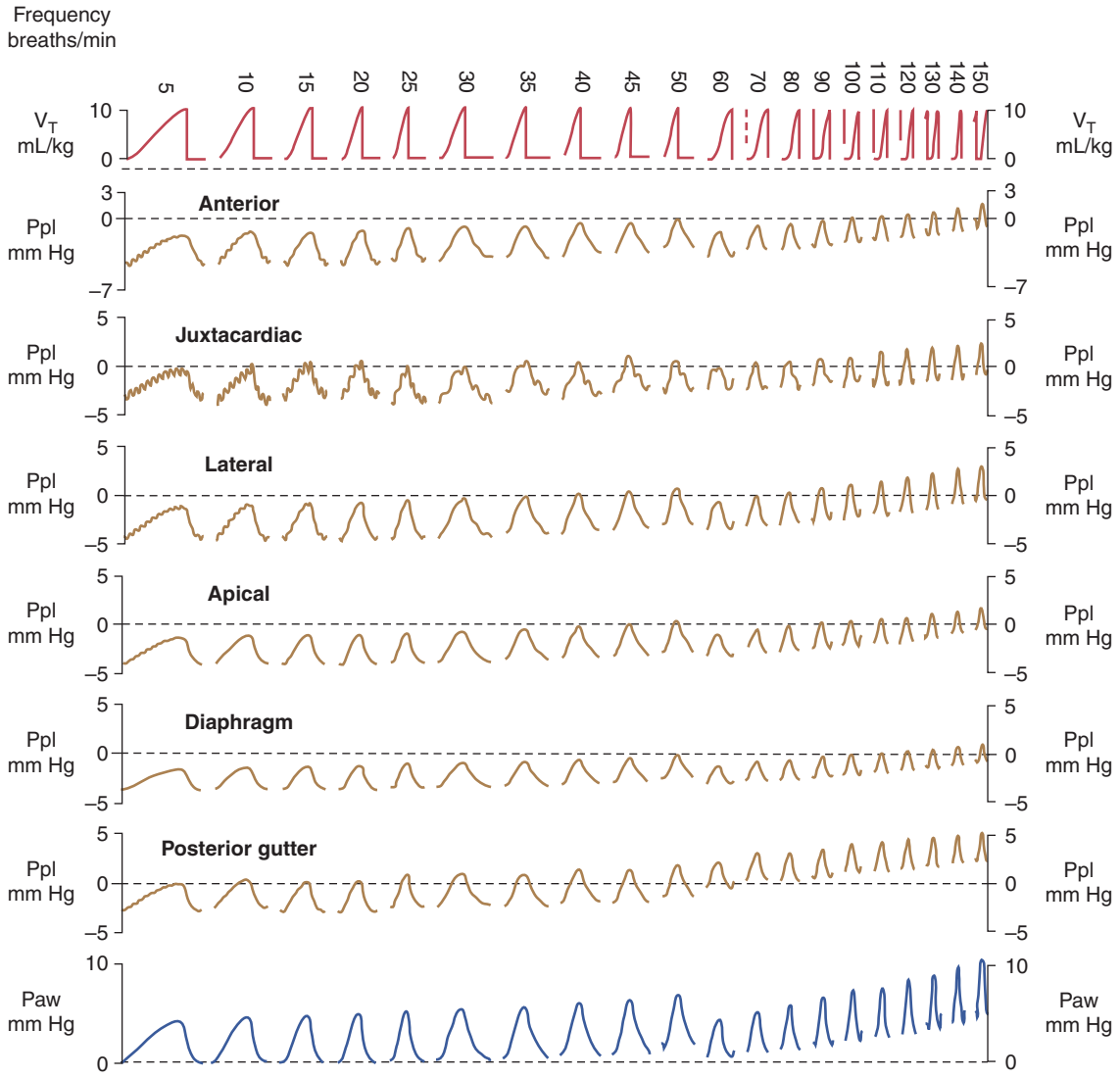

FIGURE 36-11 Effect of increasing ventilatory frequency on regional pleural pressure (Ppl) changes in the lung of an intact dog. Ppl (mean ± standard error [SE]) for six pleural regions of the right hemothorax of an intact supine canine model. *Paw*, airway pressure; V_T, tidal volume. (Reproduced, with permission, from Novak, et al. Effect of positive-pressure ventilatory frequency on regional pleural pressure. *J Appl Physiol.* 1988;65:1314–1323.)

during positive-pressure ventilation must reflect overdistension of some regions at the expense of poorly compliant regions because aerated lung units display a normal specific compliance.[85] Accordingly, Paw will reflect distension of lung units that were aerated before inspiration, but may not reflect the degree of lung inflation of nonaerated lung units. Pressure-limited ventilation assumes that this is the case and aims to limit Paw in ALI states so as to prevent overdistension of aerated lung units, with the understanding that tidal volume, and thus minute ventilation, must decrease. Thus, pressure-limited ventilation will hypoventilate the lungs, leading to "permissive" hypercapnia. In an animal model of ALI, when tidal volume was either kept constant at preinjury levels or reduced to match preinjury plateau pressure, both Ppl and pericardial pressure increased less as compared with either the pre–lung injury states or the ALI state, but with tidal volume set at the preinjury levels.[82] These points underlie the fundamental hemodynamic differences seen when different ventilator modes are compared to each other. Important for the hemodynamic effects of ventilation in ALI, vascular structures that are distended will have a greater increase in their surrounding pressure than collapsible structures that do not distend.[229] However, both Romand et al [82] and Scharf and Ingram[83] demonstrated that, despite this nonhomogeneous alveolar distension, if tidal volume is kept constant, then Ppl increases equally, independently of the mechanical properties of the lung. Thus, under constant tidal volume conditions, changes in peak and mean Paw will reflect changes in the mechanical properties of the lungs and patient coordination, but may not reflect changes in ITP.

Similarly, these changes in Paw may not alter global cardiovascular dynamics.

Positive-pressure ventilation can also have beneficial effects on hemodynamics in ALI patients. Intentional hyperinflation in subjects with ALI, induced by the use of supplemental PEEP to treat hypoxemia, may reduce pulmonary vascular resistance, if lung recruitment and aeration of hypoxic alveolar units reduces hypoxic pulmonary vasoconstriction; eventually, however, increase pulmonary vascular resistance must increase as all lung units are expanded above their normal resting volumes.[230] Applying the least amount of PEEP necessary to achieve an adequate Pa_{O_2} and fractional inspired oxygen concentration (FI_{O_2}) combination should be associated with the least-detrimental hemodynamic effects.

Congestive Heart Failure

Patients with CHF are difficult to wean from the ventilator because the increases in work of breathing, venous return, and intrathoracic blood volume during the transition from assisted to spontaneous ventilation may cause acute pulmonary edema. Rasanen et al documented that decreasing levels of ventilator support in patients with myocardial ischemia and acute LV failure worsened ischemia and promoted the development of pulmonary edema.[181,231] These effects could be minimized by preventing effort-induced negative swings in ITP by the use of CPAP while allowing the patient to continue to breathe spontaneously.[182] Thus, in these patients, it is not the work-cost of breathing that is inducing heart failure, but the negative swings in ITP. Presumably, the ability of CPAP to decrease ventricular explains the beneficial effects of CPAP during weaning trials.

If increases in ITP during positive-pressure ventilation decrease LV afterload, why then does positive-pressure ventilation not induce an increase in cardiac output in patients with CHF? The answer is that it does. Increases in cardiac output with Paw increases suggest the presence of CHF.[182,187] Grace and Greenbaum[232] noted that adding PEEP in patients with heart failure did not decrease cardiac output; cardiac output actually increased if pulmonary artery occlusion pressure exceeded 18 mm Hg. Similarly, Calvin et al[233] noted that patients with cardiogenic pulmonary edema had no decrease in cardiac output when given PEEP.[234] Finally, Pinsky et al demonstrated that ventilator-induced increases in ITP, using ventilatory frequencies of 12 to 20 breaths/min (phasic high intrathoracic pressure support; see Fig. 36-11) and increases in ITP synchronized to occur with each cardiac systole (cardiac cycle-specific where ventilator frequency equals heart rate; Fig. 36-12) greatly increased cardiac output in cardiomyopathy.[235,236] Note the similarities in the increase in mean cardiac output seen with systolic synchronized ventilation with the cardiovascular responses to similar systolic synchronized ventilation (see Fig. 36-8), which was derived in an acute animal model, wherein many more hemodynamic measures were made.

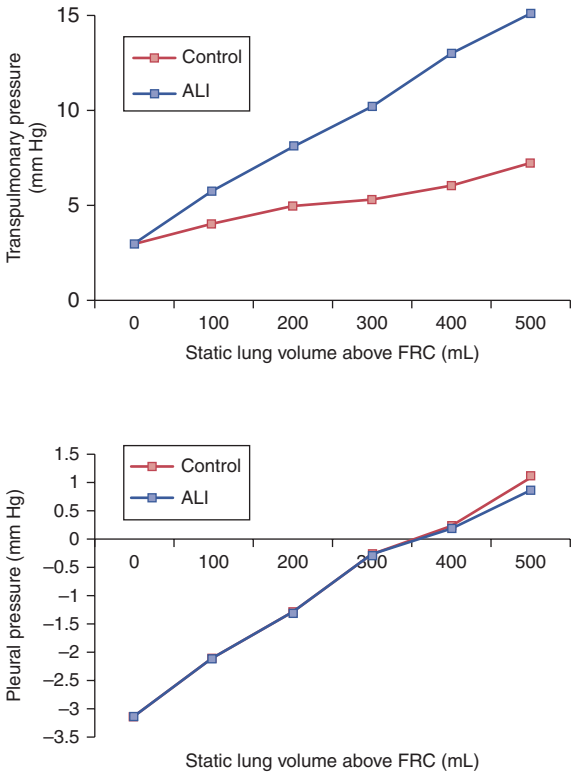

FIGURE 36-12 Relation between transpulmonary pressure (*top*) and pleural pressure (*bottom*) and lung volume as lung volume is progressively increased above functional residual capacity (FRC) in control and oleic acid-induced acute lung injury (ALI) conditions in a canine model. Note that despite greater increases in transpulmonary pressure for the same increase in lung volume during ALI as compared to control conditions, pleural pressure increases similarly during both control and ALI conditions for the same increase in lung volume. (Reproduced, with permission, from Romand, et al. Cardiopulmonary effects of positive pressure ventilation during acute lung injury. *Chest.* 1995;108:1041–1048.)

These beneficial effects do not required endotracheal intubation. They are realized with the use of mask CPAP. In fact, CPAP levels as low as 5 cm H_2O can increase cardiac output in patients with CHF. Cardiac output, however, decreases with similar levels of CPAP in both normal subjects and in patients with heart failure who are not volume overloaded. Nasal CPAP can also accomplish the same results in patients with obstructive sleep apnea and heart failure,[237] although the benefits do not appear to be related to changes in obstructive breathing pattern.[238] Prolonged nighttime nasal CPAP can selectively improve respiratory muscle strength and LV contractile function in the patients who have preexisting heart failure.[239,240] These benefits are associated with reductions of serum catecholamine levels.[241] There is no special effect of nonintubated CPAP on cardiac performance. In patients with hypovolemic CHF, as manifested by a pulmonary artery occlusion pressure equal to or less than 12 mm Hg, CPAP and biphasic positive airway pressure, at the same mean airway pressure, decrease cardiac outputs equally.[242]

If noninvasive ventilation improves LV performance in patients with both obstructive sleep apnea and CHF, can noninvasive ventilation then be useful in treating acute cardiogenic pulmonary edema? Several workers have asked this question. Rasanen et al[182] used mask CPAP to treat patients with acute coronary insufficiency and cardiogenic pulmonary edema. They demonstrated that myocardial ischemia was reversed by CPAP, but only after the level of CPAP was adjusted to prevent negative swings in ITP. CPAP levels below this threshold did not improve LV performance. The amount of CPAP needed to abolish negative swings in ITP, however, varied among patients. This is important, because subsequent clinical trials of CPAP to treat cardiogenic pulmonary edema used only fixed levels of CPAP, not CPAP levels titrated to abolish negative swings in ITP. Several early studies demonstrated that mask CPAP improved gas exchange and reduced the need for endotracheal intubation.[243,244] Mortality and hospital length of stay, however, were usually similar among patients on CPAP and conventional O_2,[245–247] suggesting that prevention of intubation is not a determinant of outcome from cardiogenic pulmonary edema. Consistent with an afterload-sparing effect of blocking negative swings in ITP, both CPAP and biphasic positive airway pressure, which decrease equally the negative swings in ITP, demonstrated similar improvement in oxygenation without changing long-term outcome.[248] The lack of long-term benefit from CPAP in acute cardiogenic pulmonary edema underscores the importance of separating outcome from acute processes characterized by symptoms (cardiogenic pulmonary edema) from underlying pathology (CHF). In fact, it would be surprising if mask CPAP had improved outcome as long as endotracheal intubation remained the default option for CHF. Still, abolishing negative swings in ITP acutely improves cardiac function in heart-failure patients.

One cannot, however, readily apply increasing ITP to augment LV performance because the effect rapidly becomes self-limited as venous return declines. This is analogous to phase 3 of the Valsalva maneuver. The effect of removing large negative levels of ITP, however, does not have the same effect on venous return as does increasing ITP. Because venous return if flow-limited below an ITP of zero, removing large negative swings in ITP will not alter venous return. The effect, however, of removing negative ITP swings on LV afterload will be identical millimeter of mercury for millimeter of mercury to adding positive ITP. Thus, any relative increase in ITP from very negative values to zero, relative to atmosphere, will minimally alter venous return, but markedly reduce LV afterload. Removing large negative swings in ITP by either bypassing upper airway obstruction (endotracheal intubation) or instituting mechanical ventilation or PEEP-induced loss of spontaneous inspiratory efforts, should selectively reduce LV afterload, without significantly decreasing either venous return or cardiac output.[87,100,117,131,166,182,249] The cardiovascular benefits of positive airway pressure on nonintubated patients can be seen by withdrawing negative swings in ITP, as created by using increasing levels of CPAP.[250,251]

Intraoperative State

Most elective surgery patients are kept relatively hypovolemic before surgery because of the risk of aspiration pneumonia during induction. They are not allowed food for 8 to 12 hours, nor anything by mouth for 6 hours before surgery, and they rarely are given intravenous fluids before coming into the operating room. Moreover, with the induction of general anesthesia, basal sympathetic tone is markedly reduced. Thus, it is amazing how little cardiovascular compromise occurs in this setting. Two factors may explain the lack of significant cardiovascular compromise. First, almost all patients are supine, and do not have to perform work; thus, venous return is maximized, and metabolic demand reduced. Second, almost all anesthesiologists insert an intravenous catheter to infuse anesthetic agents; usually they use this port to rapidly infuse large volumes of saline solutions as part of the induction. Nevertheless, to the extent that vasomotor tone is compromised, venous return will decrease, causing cardiac output to become a limiting cardiovascular variable.

Independent of these initial blood volume and vasomotor tone effects, other events can profoundly alter cardiovascular status. Both laparotomies and thoracotomies cause cardiac output to decrease by altering heart–lung interactions. Recall that the primary determinant of venous return is the pressure gradient between the venous reservoirs and Pra (see Fig. 36-4). Because a little over half of the venous blood resides in the abdomen, intraabdominal pressure represents a significant determinant of mean systemic pressure.[114] This point was illustrated earlier, when it was shown that diaphragmatic descent during positive-pressure inspiration pressurized the intraabdominal compartment, minimizing the decrease in venous return predicted by the associated increase in Pra (see Fig. 36-5). During abdominal surgery, however, the act of opening the abdomen and keeping it open abolishes the effect of diaphragmatic descent on intraabdominal pressure. Accordingly, an open laparotomy induces a fall in cardiac output by making the pressure gradient for venous return dependent only on changes in Pra. From the opposite side of the venous return curve, changes in Pra are dependent on changes in ITP. Thus, an open thoracotomy, by abolishing the end-expiratory negative ITP, induces an immediate increase in Pra, causing cardiac output to decrease.

During general anesthesia, most intubated patients have their ventilation completely controlled by the ventilator. Under these conditions, assuming that tidal volume and PEEP remain constant, the hemodynamic effects of ventilation remain remarkably constant. One can use this phasic-forcing function to assess preload responsiveness, as discussed above (see the Clinical scenarios, Initiating mechanical ventilation and Figure 36-9). Specifically, positive-pressure ventilation induces a cyclic change in LV end-diastolic volume, owing to complex and often different processes. But these ventilation phase-specific changes in LV end-diastolic occur anyway. Thus, in patients whose global cardiovascular system is preload-responsive, they will also manifest ventilation-induced

changes in LV stroke volume and arterial pulse pressure. When quantified as a pressure-induced stroke-volume variation or pulse-pressure variation, numerous studies show that these measures reflect robust and profoundly simple means to assess preload responsiveness.[192–194,200,252,253]

STEPS TO LIMIT OR OVERCOME DETRIMENTAL HEART–LUNG INTERACTIONS

Two major approaches can be used to minimize deleterious cardiovascular interactions while augmenting the beneficial ones: those focusing on ventilation and those focusing on cardiovascular status. All these approaches, however, are relative.

Minimize Work of Breathing

The most obvious technique for minimizing work of breathing during spontaneous ventilation is to decrease airway resistance and recruit collapsed alveolar units. Because ventilation is exercise, minimizing the metabolic load on the respiratory muscles allows blood flow to be diverted to other organ systems in need of O_2. Bronchodilator therapy and recruitment maneuvers accomplish these effects.

Minimize Negative Swings in Intrathoracic Pressure

It is important to minimize the negative swings in ITP during spontaneous breathing because these swings account for the increased intrathoracic blood volume and increased LV afterload, and can induce acute LV failure and pulmonary edema. Still, allowing normal negative swings in ITP at end-expiration promotes normal venous return and maintains cardiac output higher than during positive-pressure ventilation in patients with hemorrhagic shock. Although promoting inspiratory strain to augment cardiac output is the logical extension of this concept,[122] this logic is self-limiting because the associated increase in metabolic demand exceeds the associated increase in blood flow. Numerous studies, cited above, document the improvements in myocardial O_2 demand, ischemia, and cardiovascular reserve achieved by this strategy. All these effects can be realized in nonintubated patients using noninvasive mask CPAP and biphasic positive airway pressure (Figs. 36-13 and 36-14).

Prevent Hyperinflation

Third, by preventing overdistension of the lungs, pulmonary vascular resistance will not increase, cardiac filling will not be impeded, and venous return will remain at or near maximal levels. Several important caveats, however, need to be listed. First, hyperinflation is not PEEP. Recruitment

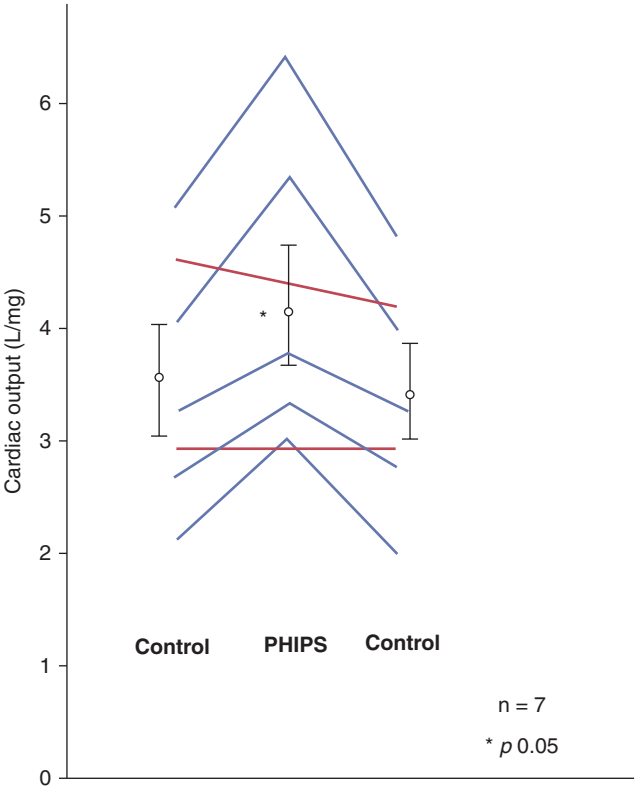

FIGURE 36-13 Effect of phasic high intrathoracic pressure support (PHIPS) on cardiac output in ventilator-dependent patients. (Used, with permission, from Pinsky MR, Summer WR. Cardiac augmentation by phasic high intrathoracic pressure support (PHIPS) in man. *Chest*. 1983;84:370–375.)

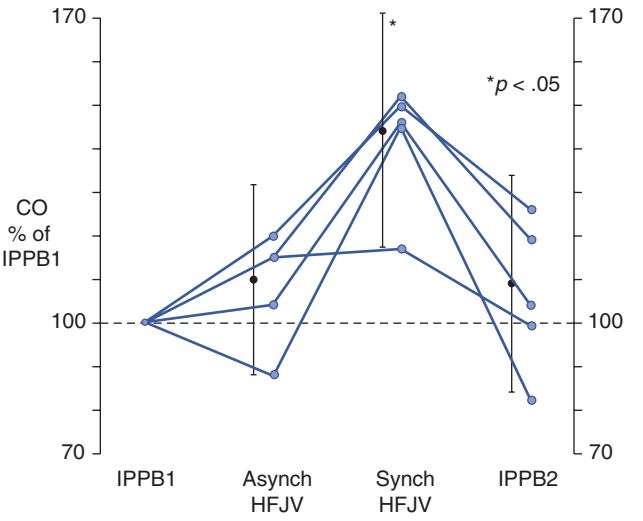

FIGURE 36-14 Effect of cardiac cycle–specific increases in airway pressure, delivered by a synchronized high-frequency jet ventilator in intraoperative patients with congestive heart failure. Note that for the same mean airway pressure, tidal volume, and ventilatory frequency, the placement of the inspiratory pulse within the cardiac cycle has profoundly different effects. (Used, with permission, from Pinsky et al. Ventricular assist by cardiac cycle-specific increases in intrathoracic pressure. *Chest*. 1987,91:709–715.).

of collapsed alveoli and stabilization of injured alveoli in an aerated state often requires the use of PEEP, which itself may reduce pulmonary vascular resistance. Although overdistension of aerated alveoli will improve gas exchange further, it will also increase pulmonary vascular resistance. Thus, one should use the lowest level of PEEP required to create adequate oxygenation. Second, in CHF, lung inflation improves LV ejection effectiveness[254] and may itself reflect a type of ventricular support.

Fluid Resuscitation during Initiation of Positive-Pressure Ventilation

The act of endotracheal intubation is often accompanied by complex manipulations, including the use of anesthetic and analgesic agents, and institution of positive-pressure ventilation. The consequent reduction in sympathetic tone and increase in Pra act synergistically to reduce venous return. These combined effects can be lifesaving in patients with cardiogenic pulmonary edema. In otherwise healthy subjects or in patients with hypovolemia (e.g., trauma), however, these additive effects can induce hypovolemic cardiovascular collapse. Thus, the bedside caregiver should be prepared to rapidly infuse intravascular volume to potentially hypovolemic patients during the act of endotracheal intubation.

Prevent Volume Overload during Weaning

The transition from positive-pressure to spontaneous ventilation must reduce ITP and increase oxygen consumption. Thus, patients are at risk of developing or worsening pulmonary edema, myocardial ischemia, and acute LV failure during weaning trials. Before initiating a spontaneous breathing trial, it is important to ensure that a patient is not volume overloaded. Steps to minimize volume overload include limiting fluids before weaning trials, forced diuresis in the setting of overt volume overload and pleural effusion, and gradual reduction in the level of positive-pressure through the use of partial support modes, so as to allow fluid shifts to be excreted in urine. Furthermore, in patients with markedly increased total-body water, fluid resorption often accelerates as Pra decreases. Thus, attention to subsequent fluid overload over the days following extubation and the use of limited intravascular fluids or forced diuresis is often needed to prevent reintubation. A clinician cannot presume that a patient with clear evidence of increased extravascular water has been successfully extubated when an endotracheal tube has been removed or even several hours later. Although detailed studies on the pathophysiology of extubation failure have not been conducted, and while failure may be multifactorial, cardiovascular compromise secondary to subsequent volume overload from either fluid resorption or intravascular volume loading (often manifested by increased secretions, wheezing, and hypoxemia) is likely to be one important cause.

Augment Cardiac Contractility

Because spontaneous breathing trial is exercise, it may precipitate acute coronary insufficiency, even in patients who are successfully weaned. Almost 40 years ago, Beach et al demonstrated that many ventilator-dependent patients can be successfully weaned if they are simultaneously given a positive inotropic agent, such as dobutamine.[152] Although no prospective clinical trial has ever been done to address this issue, many physicians support such patients with dobutamine infusions for 12 to 24 hours before a spontaneous breathing trial. If one were to use this approach, then the inotropic agent may still be needed following extubation and weaned thereafter, because the work of breathing may remain high even if the endotracheal tube is not contributing to the increase in airway resistance.

IMPORTANT UNKNOWNS

Perhaps the most important unknown in assessing the hemodynamic effect of ventilation is the assessment of cardiovascular reserve and the effects of breathing on hyperinflation and the swings in ITP. To date, no set of physiologic variables derived from measures of respiratory performance or ventilatory reserve have proven reliable in predicting weaning outcome in the setting of acute ventricular failure. In large part, we believe, this failure reflects an underappreciation of the role that cardiovascular responsiveness plays in weaning and the inadequate methods for assessing cardiovascular reserve. In essence, physicians have chosen an oversimplistic approach, and now institute blind daily spontaneous breathing trials to define when a patient is capable of weaning. Although this approach is commendable in its simplicity, it still places patients who would obviously fail such trials at risk of coronary ischemia, ongoing respiratory muscle fatigue, and impaired gas exchange secondary to LV failure and hydrostatic pulmonary edema. Because the breathing pattern can change in just one breath, and physiologically significant hyperinflation can occur in a single breath, it is probably impossible to predict with accuracy whether one can wean or not from mechanical ventilatory trials using static measures.

THE FUTURE

The future of heart–lung interactions is wedded to both new and evolving methods of mechanical ventilation and our increasing reliance on clinical techniques, like the spontaneous breathing trial, to predict weaning success and the need for supplemental cardiovascular support. To the extent that new techniques of ventilator support follow the principle of proportional assist ventilation, they will limit the detrimental effects of positive-pressure ventilation and patient–ventilator dyssynchrony, minimizing the work of breathing. Mask CPAP will need to be titrated to minimize negative swings in

ITP. To the extent that mask CPAP abolishes swings in ITP, it promotes LV ejection efficiency and minimizes LV failure. The use of pressure-limited ventilation in patients with ALI has resulted in decreases delivered tidal volume. Because increases in ITP are linked to changes in lung volume, these newer ventilatory strategies must result in less cardiovascular dysfunction than were seen with use of higher tidal volumes and peak airway pressures used in the past.

Acute care medicine is evolving from a static treatment and monitoring center into a proactive diagnostic and treatment center. We now use pulse pressure and stroke volume variation during positive-pressure ventilation to identify those hemodynamically unstable patients who are likely to respond to a volume challenge with an increase in cardiac output, and by how much. In the future, patients would be better served if clinicians were to examine the immediate hemodynamic effects of spontaneous breathing trials before patients progressed to ventilatory and cardiovascular deterioration. Invasive and noninvasive measures of tissue oxygenation using data derived from pulmonary artery catheters, central venous catheters, pulse oximetry, and newer evolving noninvasive technologies will result in a dynamic assessment of impending respiratory failure and its causes. The future is upon us, and will be led by the firms that are developing newer noninvasive technologies that address these specific issues.[255]

SUMMARY AND CONCLUSIONS

Our understanding of clinically relevant cardiopulmonary interactions has advanced far over the past 50 years. What was once cloaked with much mystery, now seems obvious. Still, complacency in the application of these principles at the bedside should be avoided. Just as we thought we knew all there was to know about COPD 20 years ago, the entire management scheme was altered with a better understanding of dynamic hyperinflation and auto-PEEP.[224,225] Similarly, the exact nature by which heart–lung interactions define myocardial ejection efficiency and myocardial O_2 requirements in both ALI states and severe airflow obstruction remain to be defined.

The hemodynamic effects of ventilation are multiple and complex, but can be grouped into four clinically relevant concepts. First, spontaneous ventilation is exercise. In patients' increased work of breathing, initiation of mechanical ventilation improves O_2 delivery to the remainder of the body by decreasing O_2 consumption. To the extent that mixed venous P_{O_2} increases, arterial P_{O_2} will also increase without any improvement in gas exchange. Similarly, weaning from mechanical ventilatory support is a cardiovascular stress test. Patients who fail weaning exhibit cardiovascular insufficiency during the failed weaning attempts. Improving cardiovascular reserve or supplementing support with inotropic therapy may allow patients to wean.

Second, changes in lung volume alter autonomic tone and pulmonary vascular resistance, and high lung volumes compress the heart in the cardiac fossa, similarly to cardiac tamponade. As lung volume increases, so does the pressure difference between airway and Ppl. When this pressure difference exceeds pulmonary artery pressure, pulmonary vessels collapse as they pass from the pulmonary arteries into the alveolar space, increasing pulmonary vascular resistance. Thus, hyperinflation increases pulmonary vascular resistance and pulmonary artery pressure, which impede RV ejection. Decreases in lung volume below FRC, as occurs in ALI and alveolar collapse, also increase pulmonary vasomotor tone by the process of hypoxic pulmonary vasoconstriction. Recruitment maneuvers, PEEP, and CPAP may reverse hypoxic pulmonary vasoconstriction and reduce pulmonary artery pressure.

Third, spontaneous inspiratory efforts decrease intrathoracic pressure. Because diaphragmatic descent increases intraabdominal pressure, these combined effects cause Pra inside the thorax to decrease but venous pressure in the abdomen to increase, which markedly increases the pressure gradient for systemic venous return. Furthermore, the greater the decrease in intrathoracic pressure, the greater the increase in LV afterload for a constant arterial pressure. Mechanical ventilation, by abolishing the negative swings in intrathoracic pressure, selectively decreases LV afterload, as long as the increases in lung volume and intrathoracic pressure are small.

Finally, positive-pressure ventilation increases ITP. Because diaphragmatic descent increases intraabdominal pressure, the decrease in the pressure gradient for venous return is less than would otherwise occur if the only change were an increase in Pra.[3] In hypovolemic states, however, positive-pressure ventilation can induce profound decreases in venous return. Increases in intrathoracic pressure decreases LV afterload and will augment LV ejection. In patients with hypervolemic heart failure, this afterload reducing effect can result in improved LV ejection, increased cardiac output, and reduced myocardial O_2 demand.

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37

EFFECT OF MECHANICAL VENTILATION ON GAS EXCHANGE

Roberto Rodriguez-Roisin
Antoni Ferrer

The major function of the lung is to exchange physiologic (respiratory) gases, namely oxygen (O_2) and carbon dioxide (CO_2). Once the lungs fail as a gas exchanger, arterial hypoxemia, hypercapnia, or both appear and respiratory failure ensues. Arterial P_{O_2} (Pa_{O_2}) and P_{CO_2} (Pa_{CO_2}) are the measurable end-point variables used routinely by clinicians to manage patients with acute respiratory failure. When the latter is severe, mechanical ventilation is then considered the final strategy for treating patients.

RELEVANCE

Classically, the mechanisms of hypoxemia are alveolar hypoventilation, limitation of alveolar to end-capillary O_2 diffusion, intrapulmonary shunt, and ventilation–perfusion ($\dot{V}_A/\dot{Q}$) imbalance; the major causes of hypercapnia are alveolar hypoventilation and $\dot{V}_A/\dot{Q}$ mismatching.[1] Ideally, it would be of great interest to solely manage respiratory blood-gas measurements, such as alveolar-arterial P_{O_2} difference $P(A\text{-}a)O_2$, venous admixture ratio ($\dot{Q}_S/\dot{Q}_T$), and physiologic dead space (dead-space-to-tidal-volume ratio [V_D/V_T]), as a general marker of the overall function of the lung. Thus, impaired or improved results of these variables, whose principal merits are their simplicity and relative ease of measurement, could reflect impaired or improved pulmonary gas exchange. Unfortunately, all these variables reflect not only the state of the lung, but also the conditions under which the lung is operating. These conditions, which uniquely determine the P_{O_2} and P_{CO_2} in any single gas-exchange unit of the lung, are the $\dot{V}_A/\dot{Q}$ ratio, the composition of inspired gas, and the composition of mixed venous blood heavily modulated by the behavior of the cardiac output.[2,3] It is important to appreciate the key role played by these three factors governing the respiratory gases in any single gas-exchange unit.[3]

PHYSIOLOGY: MULTIPLE INERT GAS ELIMINATION TECHNIQUE

This chapter reviews the effect of ventilator support on pulmonary gas exchange using the multiple inert gas elimination technique (MIGET), an approach that represents a major conceptual breakthrough in our understanding of pulmonary medicine pathophysiology in disease states.[4–7] MIGET has three major advantages. First, it estimates the pattern of pulmonary blood flow and alveolar ventilation and calculates the mismatch of $\dot{V}_A/\dot{Q}$ relationships. Second, it partitions the $P(A\text{-}a)O_2$ into determinants of intrapulmonary shunt, $\dot{V}_A/\dot{Q}$ inequality, and diffusion limitation to O_2. Third, it apportions and unravels arterial oxygenation into intrapulmonary, namely the latter three factors, and extrapulmonary components, that is, inspired P_{O_2}, overall ventilation, cardiac output, and O_2 consumption. Of paramount importance is the ability to perform measurements at any

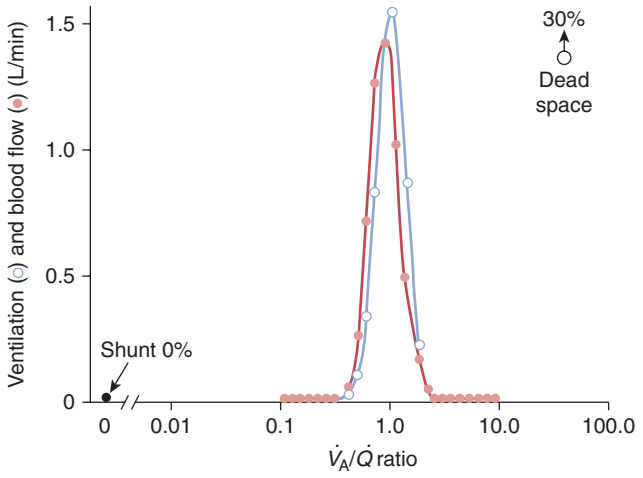

FIGURE 37-1 Distributions of alveolar ventilation and pulmonary blood flow plotted versus $\dot{V}_A/\dot{Q}$ ratio. For further explanation, see text.

fractional inspired oxygen concentration (FI_{O_2}) without perturbing the vascular and bronchomotor tones.[8]

Figure 37-1 illustrates the $\dot{V}_A/\dot{Q}$ distribution obtained with MIGET in a healthy, young individual at rest breathing ambient air. Each data point represents a particular amount of blood flow or alveolar ventilation. Both overall pulmonary perfusion and total ventilation correspond to the sum of the respective data points (the lines have been drawn for clarity only). These quantities (distributions) are plotted against a broad range (50) of $\dot{V}_A/\dot{Q}$ ratios, from zero (intrapulmonary shunt) to infinity (dead space), on a log scale. The unimodal profile of each distribution has three main characteristics: symmetry, location around a $\dot{V}_A/\dot{Q}$ ratio of 1, and narrowness (very little dispersion). Note that there is no inert-gas shunt (contrasted with the concept of venous admixture ratio), because the tracer nature of inert gases utilized for MIGET is insensitive to the presence of postpulmonary shunt (i.e., the bronchial and thebesian circulations). Inert-gas physiologic dead space is also slightly lower than Bohr dead space because it does not include the alveolar units, which have an alveolar P_{CO_2} that is lower than Pa_{CO_2}.

NATURE OF GAS EXCHANGE IN DISEASE STATES

From a clinical standpoint, the three principal mechanisms of altered arterial respiratory gases during spontaneous breathing in any pulmonary disease state are $\dot{V}_A/\dot{Q}$ mismatching, increased intrapulmonary shunt, and alveolar hypoventilation. The role of diffusion limitation to O_2 is modest and plays a role in patients with pulmonary fibrosis[9] and in healthy individuals under very extreme conditions at high altitude.[10] During mechanical ventilation, however, alveolar hypoventilation is controlled in such a way that Pa_{CO_2} does not represent a problem. $\dot{V}_A/\dot{Q}$ inequalities play a pivotal role in disorders characterized by chronic lung disease ("dry lung"), namely during exacerbations of chronic obstructive pulmonary disease (COPD) and bronchial asthma, which have in common expiratory airflow limitation and large pulmonary volumes. Increased intrapulmonary shunt is a key determinant of hypoxemia in conditions characterized by acute lung injury ("wet lung"), such as acute lung injury (ALI), and its most severe form, acute respiratory distress syndrome (ARDS), and life-threatening pneumonia, all of which have small lung volumes.[11]

The main mechanisms of pulmonary gas exchange are extensively reviewed (see the section Acute Respiratory Failure "Wet Lung") during mechanical ventilation in ALI or ARDS, pneumonia, COPD, and asthma—the most common conditions in the critical care setting. In each condition, the gas-exchange abnormalities at maintenance FI_{O_2} and while breathing 100% O_2 are addressed. Likewise, the effects of external positive end-expiratory pressure (PEEP) and intrinsic PEEP (PEEPi) on gas exchange, and the effects of several ventilator settings are considered.

Acute Respiratory Failure ("Wet Lung")

This section reviews the two most frequent disorders seen in the intensive care unit, ARDS and severe life-threatening pneumonia, together with a short review of gas exchange in patients with head trauma and following cardiac surgery. It can be difficult to differentiate ALI or ARDS from the other disorders—after all, ALI or ARDS is a constellation of many entities, among which pneumonia and the other conditions of acute respiratory failure are common causes. From a gas-exchange viewpoint, however, ALI or ARDS and pneumonia show different functional findings. Furthermore, the response to high FI_{O_2} differs substantially.

ACUTE LUNG INJURY OR ACUTE RESPIRATORY DISTRESS SYNDROME

Severe acute respiratory failure in previously healthy subjects may result from a primary infectious lung process or a more widespread, noninfectious process, namely either ALI or ARDS. The latter entity is characterized by severe hypoxemia refractory to high FI_{O_2}, and differences are related to the severity of gas-exchange abnormalities.[12]

MECHANISMS OF HYPOXEMIA

The main cause of hypoxemia in patients with ALI or ARDS is a characterized by an increased intrapulmonary shunt, averaging 20% or more of cardiac output. In approximately half the patients, however, there are considerable additional areas with low $\dot{V}_A/\dot{Q}$ ratios: A moderate percentage of total pulmonary blood flow is distributed to areas of the lung with reduced ventilation.[13]

Figure 37-2 illustrates the profiles of two representative $\dot{V}_A/\dot{Q}$ distributions of patients with ARDS during mechanical ventilation with PEEP (at FI_{O_2}, 0.5).[14] Although both

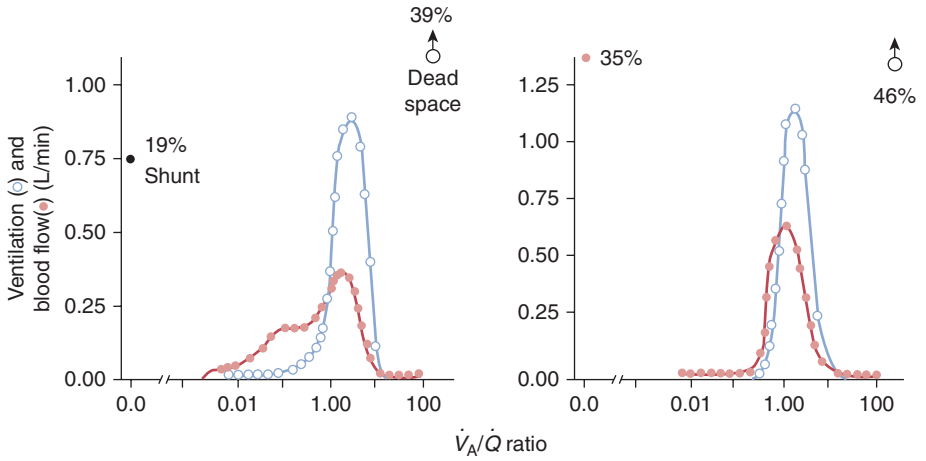

FIGURE 37-2 Two patterns of $\dot{V}_A/\dot{Q}$ distributions in patients with ARDS (with PEEP). Note that intrapulmonary shunt and dead space were considerably increased in both individuals. Notice also the presence of some amount of blood flow distributed to units with low $\dot{V}_A/\dot{Q}$ (*left panel*). (Reprinted with permission of the American Thoracic Society. Copyright © 2012 American Thoracic Society. Reyes A, Roca J, Rodriguez-Roisin R, et al. Effect of almitrine on ventilation-perfusion distribution in adult respiratory distress syndrome. *Am Rev Respir Dis.* 1988;137:1062–1067. Official Journal of the American Thoracic Society. Modified with permission of the American Thoracic Society.)

patterns show marked amounts of shunt and dead space, the main body of the dispersion of blood flow is different. In one patient, the dispersion is narrowly unimodal (*right panel*). In the other, the pattern of perfusion is broadly unimodal, that is, blood flow is distributed to areas with low $\dot{V}_A/\dot{Q}$ ratios (usually less than 10% of cardiac output) (*left panel*). The former profile reflects an "all-or-none" phenomenon: pulmonary perfusion is essentially diverted to two lung areas, those with ventilation that is normal and proportional to blood flow, and those that are completely unventilated.[15] The presence of areas with low $\dot{V}_A/\dot{Q}$ ratios suggests the coexistence of areas with partially filled alveolar spaces or alveolar units in which ventilation is reduced compared to blood flow (because of increased airways resistance) or both. A few patients showed an increase of alveolar ventilation distributed to high $\dot{V}_A/\dot{Q}$ ratios, including a bimodal pattern of the dispersion of ventilation; in contrast, dead space was increased in most patients. These two findings may reflect areas with reduced pulmonary blood flow secondary to the effects of external PEEP, although an additional influence of pulmonary vascular derangement cannot be ruled out.[16]

There was no limitation to the diffusion of O_2, as reflected by the close agreement between predicted Pa_{O_2} (according to MIGET, this reflects the underlying amount of intrapulmonary shunt and $\dot{V}_A/\dot{Q}$ mismatch only) and measured Pa_{O_2} (Fig. 37-3).[15,17] When measured Pa_{O_2} is not significantly different from the predicted Pa_{O_2}, this suggests that other potential causes of hypoxemia, namely diffusion limitation for O_2, increased postpulmonary shunt, and/or augmented intrapulmonary O_2 consumption,[18] are not occurring.

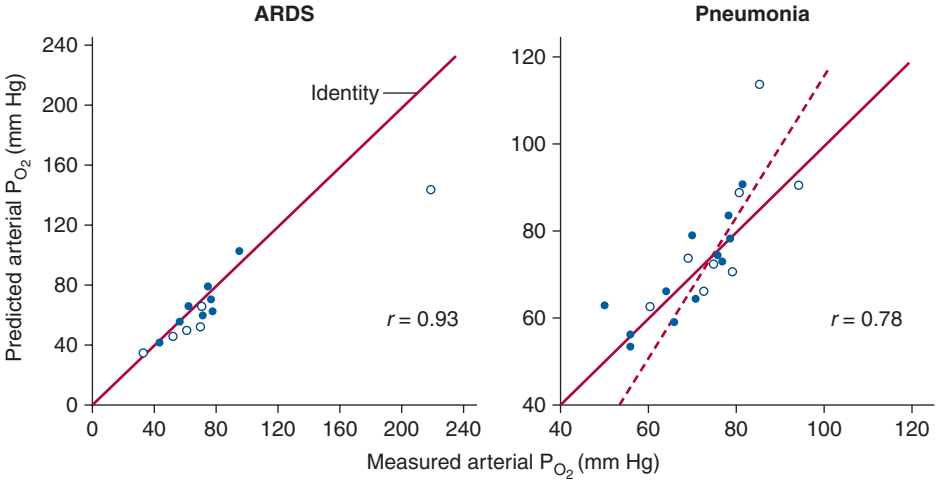

FIGURE 37-3 Plots of predicted (estimated by MIGET) Pa_{O_2} versus measured Pa_{O_2} in patients with ARDS (*left panel; open symbols* = without PEEP; *closed symbols* = with PEEP) and with severe pneumonia (*right panel; open symbols* = with mechanical ventilation; *closed symbols* = without mechanical support). Note the good agreement between both variables in each clinical condition (*dashed line* = regression line). (Used, with permission, from Dantzker et al.[15] and Gea et al.[17])

BREATHING 100% OXYGEN

The concept of an increase in intrapulmonary shunt while breathing 100% oxygen in patients with acute respiratory failure is old.[19,20] Earlier data using MIGET, however, did not support this view.[16] It was considered that areas with critical inspiratory $\dot{V}_A/\dot{Q}$ ratios may remain partly open and facilitate O_2 transfer; potential mechanisms include the efficiency of collateral ventilation, interdependence of surrounding lung parenchyma, or the interaction of mechanical forces exerted during artificial ventilation.[8] No studies, however, properly addressed this question.

We have shown that Pa_{O_2} increases modestly (≤300 mm Hg) and intrapulmonary shunt increases considerably (approximately 35%) during hyperoxic breathing over 1 hour, suggesting the development of reabsorption atelectasis (Fig. 37-4).[8,21] The increase in intrapulmonary shunt was noticed within less than half an hour, confirming the theoretical analysis on the minimum time required for collapse of alveolar units with various fixed inspired $\dot{V}_A/\dot{Q}$ ratios according to the different levels of FI_{O_2}.[8] The limited increase in Pa_{O_2} while breathing 100% O_2 indicates that increased intrapulmonary shunt is the key determinant of hypoxemia in ALI and ARDS. Furthermore, the increments in shunt persisted for 1 hour after resuming maintenance FI_{O_2}, indicating the persistence of atelectasis. Of note, this worsening of shunt was also accompanied by a small but significant increase in Pa_{CO_2}, possibly explained by the Haldane effect (Fig. 37-5). The Haldane effect is the increase in Pa_{CO_2} at a given arterial CO_2 content that occurs in response to an increase in arterial O_2 saturation. The dispersions of blood flow and alveolar ventilation remained unchanged.

The increase in shunt not accompanied with release of hypoxic pulmonary vasoconstriction in patients with ALI or ARDS is compatible with the concept that, at any level of FI_{O_2}, units with low $\dot{V}_A/\dot{Q}$ cannot redistribute blood flow from areas of intrapulmonary shunt or very low $\dot{V}_A/\dot{Q}$ ratios, because their vascular resistance remains unchanged.[8]

EFFECTS OF POSITIVE END-EXPIRATORY PRESSURE

The gas-exchange response to external PEEP illustrates one of the best examples of the complex interplay between intrapulmonary and extrapulmonary determinants of respiratory gases.[5,16] Several studies have assessed this action in patients with ALI or ARDS.

In a seminal study,[15] which measured $\dot{V}_A/\dot{Q}$ distributions at increasing levels of PEEP, two distinct patterns were shown (Fig. 37-6). In some patients, the $\dot{V}_A/\dot{Q}$ pattern remained unchanged despite progressive increases of PEEP. In others, there was a broadening of the dispersion of ventilation because areas with high $\dot{V}_A/\dot{Q}$ ratios increased and ventilation was redistributed to infinity $\dot{V}_A/\dot{Q}$ ratios. In each patient, however, PEEP led ultimately to a marked decrement in cardiac output distributed to unventilated (shunt) areas or poorly ventilated $\dot{V}_A/\dot{Q}$ units and to a considerable increase in dead space. The final result was a substantial optimization of Pa_{O_2}.

Subsequently, the $\dot{V}_A/\dot{Q}$ response to external PEEP was investigated while cardiac output was kept constant at control values with dopamine.[22] During PEEP, Pa_{O_2}, mixed venous P_{O_2}, and oxygen delivery increased significantly, whereas the venous admixture ratio decreased markedly. Similarly, shunt decreased substantially, and pulmonary blood flow was redistributed from nonventilated units with zero $\dot{V}_A/\dot{Q}$ ratios to areas with normal $\dot{V}_A/\dot{Q}$ ratios. Dead space increased slightly, but the dispersion of the alveolar ventilation did not vary. Because PEEP causes redistribution of extravascular lung water from alveoli to peribronchial and perivascular spaces,[23] these data suggest that the improvement in pulmonary gas exchange with external levels of PEEP results from the reopening of collapsed airways and alveoli. The key message from this study is that the avoidance of the reduction of cardiac output during PEEP application enhances a more optimal gas exchange.

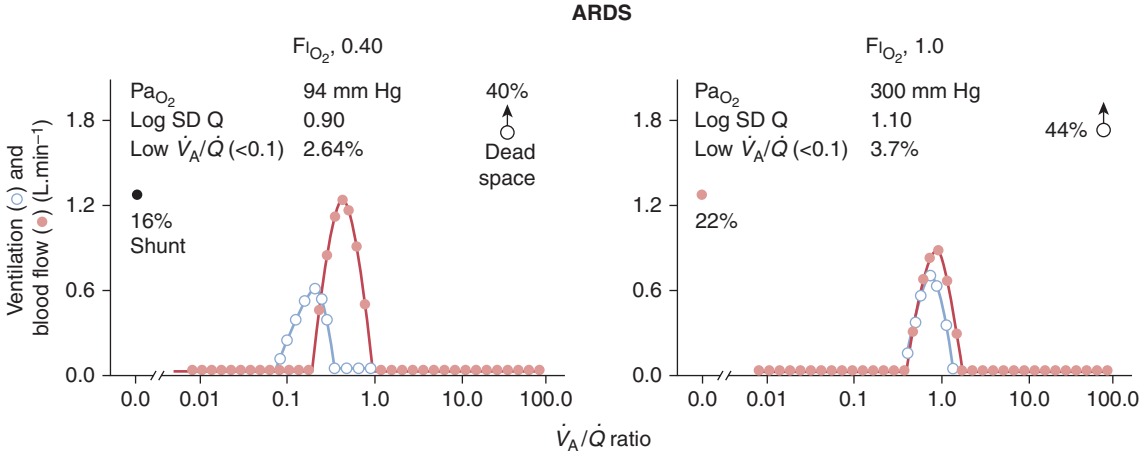

FIGURE 37-4 Effect of breathing 100% oxygen (*right panel*) in a representative patient with ARDS (with PEEP). Compared with low FI_{O_2} (*left panel*), Pa_{O_2} increased modestly (approximately 300 mm Hg), but intrapulmonary shunting increased moderately; in contrast, both the dispersion of blood flow (*Log SD Q*) and the amount of blood flow distributed to areas with low $\dot{V}_A/\dot{Q}$ ratios remained unchanged. This suggests the development of reabsorption atelectasis without release of hypoxic vasoconstriction. Dead space tended to increase.

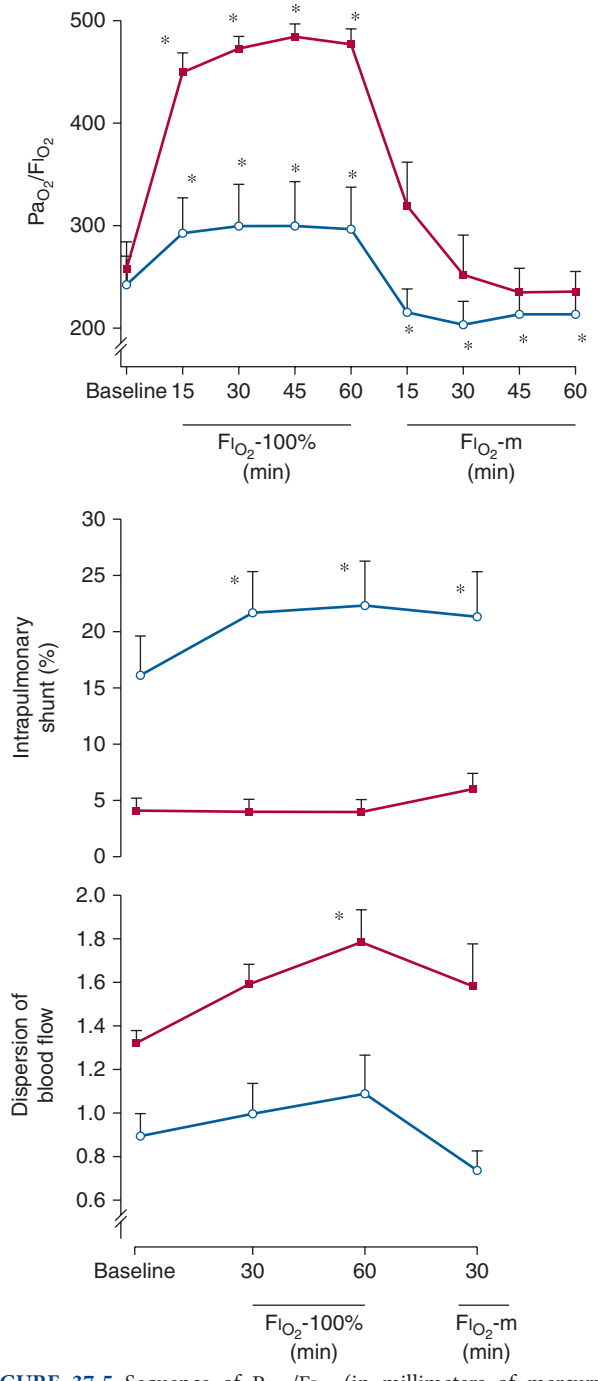

FIGURE 37-5 Sequence of Pa_{O_2}/FI_{O_2} (in millimeters of mercury), shunt (in percentage of cardiac output), and Log SD Q (dimensionless). In patients with ALI (*open circles*) arterial oxygenation and Log SD Q remained almost unchanged, whereas shunt increased significantly, suggesting reabsorption atelectasis. In contrast, in patients with COPD (*solid squares*), Log SD Q and arterial oxygenation substantially increased whereas shunt remained low and unvaried, indicating release of hypoxic vasoconstriction. For further explanation, see text. (Used, with permission, from Santos et al.[21])

In another study,[24] the gas-exchange response to increments in PEEP was studied. In most patients, Pa_{O_2} improved substantially because of a decrease in intrapulmonary shunt or in the zone of low $\dot{V}_A/\dot{Q}$ ratio, or a derecruitment of blood flow from areas with shunt to those with low or normal $\dot{V}_A/\dot{Q}$ ratio; blood flow reductions to low $\dot{V}_A/\dot{Q}$ areas were less predictable. When Pa_{O_2} did not vary in response to PEEP, there were no variations in the $\dot{V}_A/\dot{Q}$ relationships. An increase either in poorly perfused $\dot{V}_A/\dot{Q}$ units or in dead space was shown in only a few individuals. The beneficial effect of PEEP on Pa_{O_2} could not be predicted by the etiology of ARDS or the severity of abnormal gas exchange. As expected, cardiac output and mixed venous P_{O_2} decreased progressively as PEEP was increased. The mean change in cardiac output was essentially similar between PEEP trials irrespective of the improvement in Pa_{O_2}.

Experimentally, low levels of PEEP (5 to 10 cm H_2O) decrease physiologic dead space by reducing both shunt and $\dot{V}_A/\dot{Q}$ mismatch.[25] At higher levels of PEEP, however, physiologic dead space increases because both ventilation to high $\dot{V}_A/\dot{Q}$ regions and anatomic dead space increase while the efficiency of CO_2 elimination by the lungs is diminished.

All in all, these studies are of interest for two reasons. First, these findings indicate that the beneficial effects of PEEP in ALI and ARDS essentially result from a redistribution of blood flow from severely injured (shunt) areas to poorly or normally ventilated alveolar units. This seems to be related to the reopening of collapsed alveoli and airways rather than to a decrease of cardiac output by itself. Alternatively, the depression of cardiac output may reduce shunt or blood flow distributed to units with poorly ventilated $\dot{V}_A/\dot{Q}$ ratios.[2] It has been shown both clinically and experimentally, using pharmacologic and mechanical techniques, that changes in cardiac output lead to directionally similar changes in shunt. Likewise, in many instances, the shunt fraction also changes in a similar direction to changes in the mixed venous P_{O_2} and negatively with pulmonary vascular resistance.[26]

Second, in two of the studies in which the values of mixed venous P_{O_2} were reported, this variable either increased[22] or remained stable[24] when cardiac output was reduced. Arterial P_{O_2} increased during PEEP because the beneficial effects on gas exchange, essentially secondary to the reduction in shunt (intrapulmonary factor), were not offset by the simultaneous deleterious effect on Pa_{O_2} secondary to decreased cardiac output (extrapulmonary factor), which had allowed mixed venous P_{O_2} to decrease, other factors being equal. If the reduction in cardiac output had been more severe, Pa_{O_2} would have remained unaltered or even decreased despite the reduction in shunt.[16] Alternatively, the observation that mixed venous P_{O_2} values did not always vary in the same direction as cardiac output raises the question of the pathologic supply dependence between O_2 delivery and the O_2 consumption.[27] Such patients may respond to the depression of cardiac output during PEEP by reducing O_2 consumption.

The development of high $\dot{V}_A/\dot{Q}$ peaks and the moderate-to-severe increments of dead space during PEEP are consistent with experimental data indicating that the reduction of

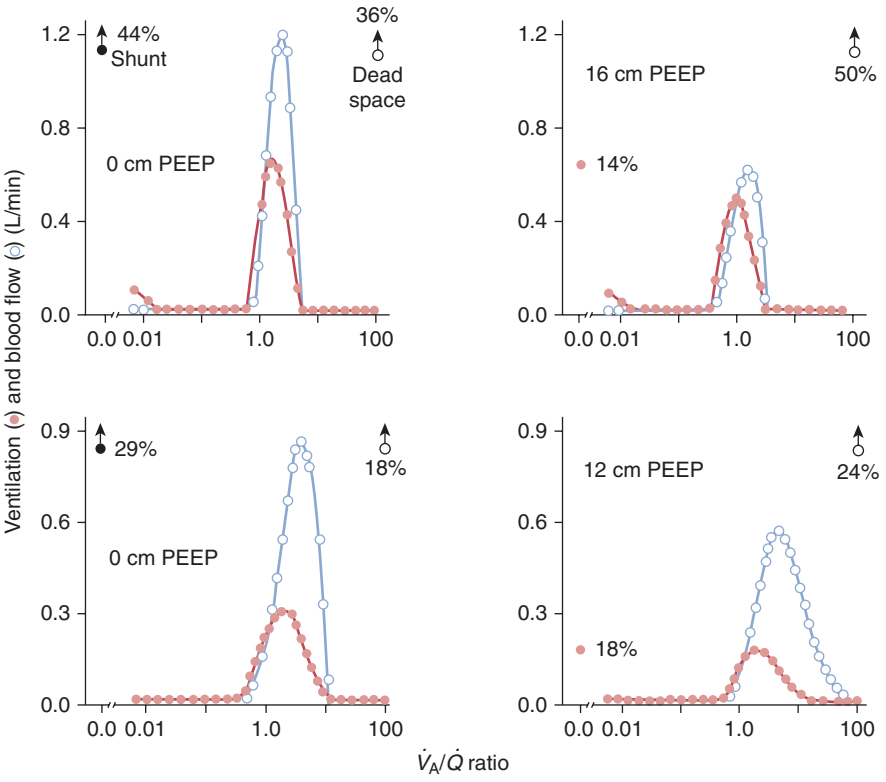

FIGURE 37-6 The application of 16 cm H_2O of PEEP in a patient with ARDS induced a reduction of shunt and an increase of dead space, whereas $\dot{V}_A/\dot{Q}$ distributions remain essentially unaltered (*top, from left to right*). In another patient, 12 cm H_2O of PEEP caused similar effects on shunt and dead space, but $\dot{V}_A/\dot{Q}$ distributions are broadened (*bottom, from left to right*). For further explanation, see text. (Reprinted with permission of the American Thoracic Society. Copyright © 2012 American Thoracic Society. Dantzker DR, Brook CJ, Dehart P, et al. Ventilation-perfusion distributions in the adult respiratory distress syndrome. *Am Rev Respir Dis.* 1979;120:1039–1052. Official Journal of the American Thoracic Society. Modified with permission of the American Thoracic Society.)

cardiac output and the depression of perfusion in the uppermost regions of the lung determine changes in the pattern of ventilation with PEEP.[28]

VENTILATOR MODALITIES

Over the last 10 years, increasing emphasis has been placed on avoiding ventilator-associated lung injury and the use of a protective ventilator strategy, accepting an increase in Pa_{CO_2} if necessary (permissive hypercapnia), in patients with ALI or ARDS. Ventilator-associated lung injury[29] is defined as lung damage with characteristic features of ARDS that can occur in patients receiving mechanical ventilation. The two most important factors responsible for ventilator-associated lung injury are thought to be: (a) the association of alveolar overdistension and high transpulmonary pressure; and (b) repeated alveolar collapse and reopening owing to ventilation at inappropriate tidal ranges of transpulmonary pressure. The prevention of alveolar overdistension by reducing tidal volume has been investigated in combination with relatively low levels of PEEP and high levels of PEEP. We describe them separately.

Permissive Hypercapnia with Low Tidal Volume and Low Positive End-Expiratory Pressure. Four recent controlled studies[13,30–32] have compared the outcome with use of low (6 to 7 mL/kg) versus high (10 to 12 mL/kg) tidal volumes with standard levels of PEEP (8 to 11 cm H_2O). Only one study[13] showed a significant (20%) decrease in mortality, likely because of a superior statistical power and a larger difference between the low-tidal-volume and high-tidal-volume branches. Use of low tidal volume, however, can worsen pulmonary gas exchange, necessitating higher FI_{O_2} requirements, secondary to reduction in alveolar ventilation and increased shunt caused by both alveolar collapse and increased cardiac output, which may further worsen intrapulmonary shunt in patients with ARDS.[15]

The induction of permissive hypercapnia by reducing tidal volume and maintaining constant standard levels of PEEP was shown to increase cardiac output, decrease Pa_{O_2}, and increase shunt, but had no effect on the dispersion of blood flow (Log SD Q).[33] When baseline tidal volume was reinstated and cardiac output was maintained with use of dobutamine, both shunt and Pa_{O_2} remained unchanged. Thus, low tidal volume with standard PEEP increased intrapulmonary shunt and the deterioration in gas exchange was caused by the combined effects of increased cardiac output and decreased alveolar ventilation. In another study,[34] the effects of permissive hypercapnia were compared in two groups of patients with ARDS, with and without hyperdynamic sepsis. Permissive hypercapnia was induced by decreasing tidal volume and increasing PEEP to prevent alveolar recruitment. In both groups of

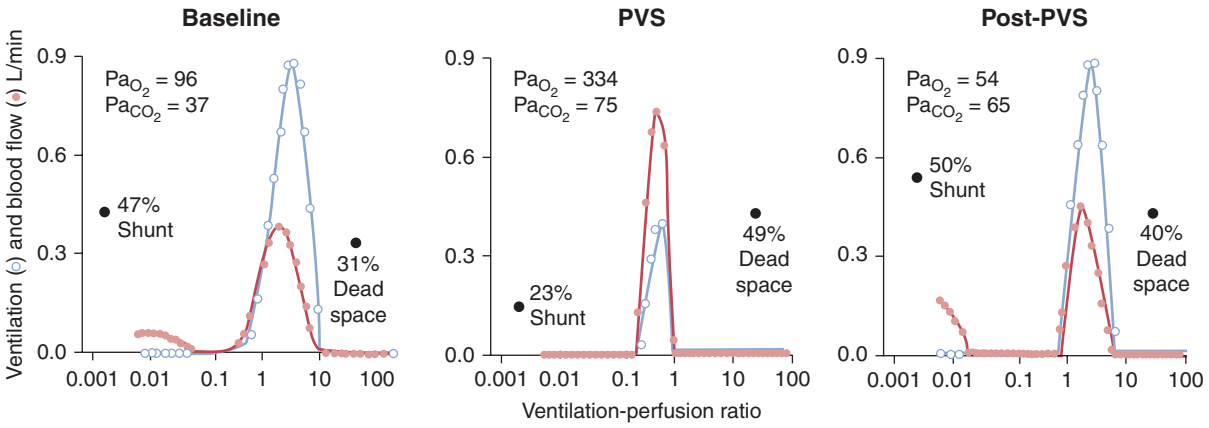

FIGURE 37-7 Representative patient with ARDS at baseline (*left*), during protective ventilator support (PVS) (*center*), and after PVS (*right*). During PVS, shunt decreased and arterial oxygenation improved; dead space increased as a result of low tidal volume and high PEEP. (Reproduced, with permission, from Mancini et al.[37])

patients, permissive hypercapnia increased shunt but did not worsen Pa_{O_2} because of an increase in mixed venous P_{O_2} secondary to an increased cardiac output. In septic patients, Pa_{O_2} remained unchanged, and in nonseptic patients, it increased. Dead space and the descriptors of $\dot{V}_A/\dot{Q}$ imbalance remained unchanged in both subsets of patients.

Permissive Hypercapnia with Low Tidal Volume and High Positive End-Expiratory Pressure. The combination of low tidal volume, to avoid alveolar overdistension, and high PEEP, to prevent sequential collapse and reopening of alveolar units throughout the ventilatory cycle, has been advocated as an alternative strategy to decrease ventilator-associated lung injury. In patients with ARDS,[35] this approach achieved a significant reduction in mortality at 4 weeks, but hospital mortality was not decreased. The protective ventilation group had a higher rate of weaning from mechanical ventilation and a lower rate of barotrauma. This type of permissive hypercapnia produced an acute hyperdynamic state,[36] with transient systemic vasodilation and increased cardiac output. The acute hemodynamic effects were in part related to acute respiratory acidosis, and progressively attenuated during the first 36 hours of ventilation despite persisting hypercapnia. The gas-exchange response to this ventilator strategy[37] revealed superior efficacy in early ARDS (Fig. 37-7), mainly through recruitment of previously collapsed alveoli and redistribution of pulmonary blood flow from unventilated alveolar units to normal units. Arterial P_{O_2} improved and intrapulmonary shunt decreased. Recruitment of previously collapsed alveolar units was the key factor underlying the decreased intrapulmonary shunt. The beneficial effects of this approach on gas exchange fully overcame the deleterious effect of permissive hypercapnia on arterial oxygenation (i.e., reduced alveolar P_{O_2}). Moreover, the increase in cardiac output secondary to systemic vasodilatation[36] did not result in a proportional increase in intrapulmonary shunt, as one might expect in patients with ARDS,[15] likely because pulmonary blood flow was appropriately redistributed to normal alveolar units secondary to the concomitant efficiency of alveolar recruitment (Fig. 37-8). The substantial improvement in

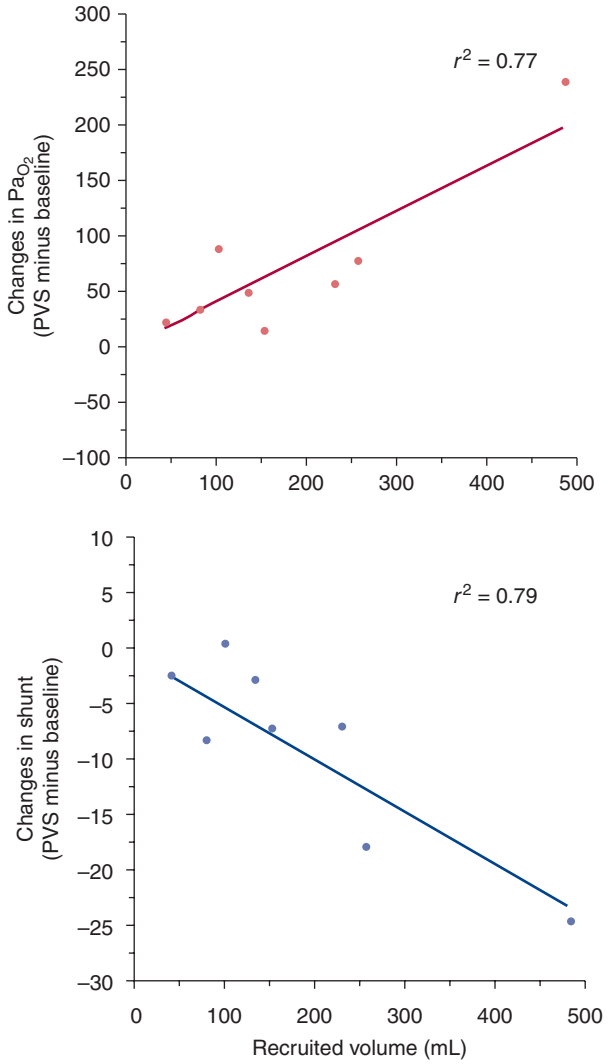

FIGURE 37-8 Correlations between increased Pa_{O_2} (*top*) and decreased shunt (*bottom*) and recruited lung volume during protective ventilator support (PVS) in patients with ARDS (*dots,* individual patients; *lines,* regression lines). (Reproduced, with permission, from Mancini et al.[37])

$\dot{V}_A/\dot{Q}$ imbalance, indicated by decreased blood flow dispersion (Log SD Q), may have been caused by the reduction of the overall $\dot{V}_A/\dot{Q}$ ratio secondary to the concomitant effects of both decreased alveolar ventilation and increased cardiac output (induced by this ventilator modality). Under these circumstances, a more efficient distribution of pulmonary blood flow toward areas with normal $\dot{V}_A/\dot{Q}$ ratios cannot be ruled out. Likewise, the marked increase in dead space observed with the protective strategy can be explained by the combination of a decrease in alveolar ventilation and an increase in functional residual capacity induced by high levels of PEEP. This study showed a strong relationship between improvement of alveolar gas exchange and the amount of PEEP-induced alveolar recruitment. Overall, these findings strongly support the combination of low tidal volumes and high PEEP levels as the most appropriate approach, at least in early ARDS, although further studies are warranted. The growing knowledge that therapeutic hypercapnia per se may prevent pulmonary and systemic damage in patients with ARDS[38,39] adds further complexities.

Inverse Inspiratory-to-Expiratory Ratio Ventilation. Before the advantages of protective ventilation with permissive hypercapnia were known, inverse inspiratory-to-expiratory (I:E) ratio ventilation was used in ARDS to improve oxygenation at lower-than-conventional peak airway pressures. Because of discrepant results in several studies, the gas-exchange response was investigated.[40] Compared to conventional volume-controlled ventilation with PEEP, the application of equivalent levels of PEEP during inverse-ratio ventilation did not result in a superior Pa_{O_2}. Pressure-controlled ventilation with inverse I:E ratio did not affect Pa_{O_2} either, although it decreased Pa_{CO_2} because of a concomitant decrease in dead space with a shift to the right of $\dot{V}_A/\dot{Q}$ distributions.

Postural Changes. The $\dot{V}_A/\dot{Q}$ distributions during pressure-controlled ventilation in the prone position[41] revealed an improvement in Pa_{O_2} of more than 10 mm Hg after 30 minutes in two-thirds of patients (responders), whereas the remaining patients showed no change in Pa_{O_2} (nonresponders). In the responders, the prone position caused a substantial decrease in shunt regions with a concomitant increase of areas with normal $\dot{V}_A/\dot{Q}$ ratios in the dorsal zones, which were now less gravitationally dependent. Returning the patient to the supine position reversed the improvement in gas exchange. These changes suggest that the redistribution of blood flow away from shunt areas is most likely caused by efficient recruitment of previously atelectatic, but nondiseased, zones induced by altered gravitational forces. Continuous axial rotation might be another method for acutely reducing $\dot{V}_A/\dot{Q}$ imbalance in patients with ALI or ARDS[42]; continuous axial rotation on a kinetic-treatment table reduced intrapulmonary shunt and improved Pa_{O_2}. The positive response to continuous rotation was only demonstrated in patients with mild-to-moderate ALI; in patients with progressive ARDS, the acute response was limited.

Partial Ventilator Support. A study comparing the effects of airway pressure release ventilation, with and without spontaneous breathing, and pressure support ventilation, in which both modalities were delivered with equal airway pressure limits or minute ventilation, on pulmonary gas exchange in patients with ARDS,[43] showed that spontaneous breathing with airway pressure release ventilation improved $\dot{V}_A/\dot{Q}$ mismatching, as revealed by decreases in intrapulmonary shunt, dead space, and the dispersions of blood flow and ventilation. Pressure support did not improve $\dot{V}_A/\dot{Q}$ imbalance when compared with airway pressure release ventilation without spontaneous breathing. These findings indicated that uncoupling of spontaneous and mechanical ventilation during airway pressure release ventilation improves $\dot{V}_A/\dot{Q}$ inequalities in ARDS, presumably by recruiting nonventilated lung units. As compared with controlled ventilation, inspiratory assistance during pressure support is not sufficient to counteract the $\dot{V}_A/\dot{Q}$ imbalance caused by alveolar collapse in patients with ARDS, and does not provide any complementary advantage in cardiopulmonary function or pulmonary gas exchange.

PNEUMONIA

Mechanisms of Hypoxemia. In pneumonia, arterial hypoxemia is basically determined by the presence of a considerable shunt (average: 20% of cardiac output) together with moderate to severe amounts (range: 10% to 20% of cardiac output) of blood flow distributed to units with low $\dot{V}_A/\dot{Q}$. In general, the pattern of the dispersion of perfusion is bimodal (Fig. 37-9).[17,44] These functional findings are consistent with the main pathologic findings, namely extensive consolidation of areas of the lungs, with alveoli completely or partially filled with edema, leukocytes and other cells, causative bacteria, and fibrin.[45] Dead space is, by and large, slightly increased, and some patients can exhibit areas wherein ventilation is diverted to high $\dot{V}_A/\dot{Q}$ ratios. The latter findings may reflect the use of PEEP, which is commonly used in these patients. There is good agreement between predicted Pa_{O_2} and measured Pa_{O_2}, suggesting therefore that additional intrapulmonary factors determining hypoxemia (diffusion limitation to O_2, increased intrapulmonary O_2 uptake, and postpulmonary shunt), other than shunt and $\dot{V}_A/\dot{Q}$ mismatch, can be ruled out.[17,44] The coexistence of increased intrapulmonary O_2 consumption within the parenchyma[18] and increased postpulmonary shunt,[46] previously suggested as an additional mechanism contributing to hypoxemia, was not observed in patients with severe pneumonia.[17]

Breathing 100% Oxygen. Breathing 100% O_2 induced no changes in inert-gas shunt or in venous admixture ratio, as might be expected, at least theoretically, in patients whose lungs contain abundant critical alveolar units at risk of undergoing collapse, thereby developing reabsorption atelectasis.[8,21] This suggests that, in lungs with more localized lung injury, low $\dot{V}_A/\dot{Q}$ areas are less liable to collapse during oxygen breathing, probably because of the efficiency of

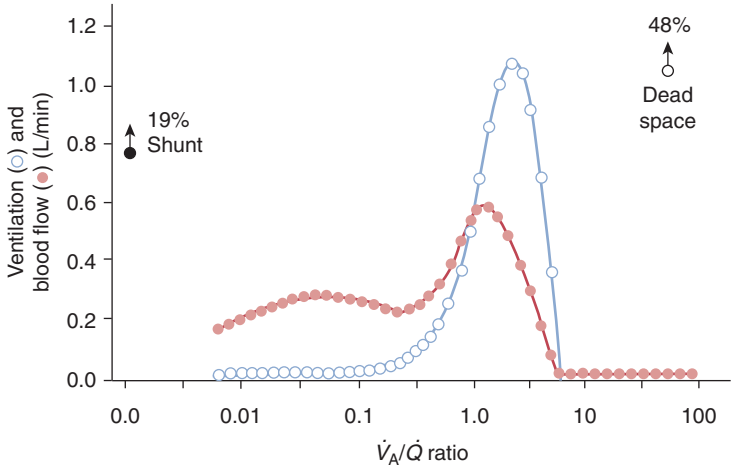

FIGURE 37-9 Ventilation–perfusion distributions in a patient with severe pneumonia requiring mechanical ventilation with PEEP. Note that shunt and dead space are markedly increased; likewise, a considerable amount of blood flow is distributed to a zone with low $\dot{V}_A/\dot{Q}$ ratios (below 0.1). Compared with patients with ARDS (see Fig. 37-2), the bimodal pattern of pulmonary perfusion is more accentuated. (Reproduced, with permission, from Gea et al.[17])

collateral ventilation and the interaction between mechanical forces within the lung. Nevertheless, there was further $\dot{V}_A/\dot{Q}$ deterioration, as assessed by the marked increase in the dispersion of blood flow, indicating release of hypoxic pulmonary vasoconstriction. This finding indicates a considerable hypoxic vascular response of the lung, which may play a protective role against further worsening of gas exchange. In contrast, the dispersion of ventilation tended to decrease (improve) and dead space remained unaltered (Table 37-1). Conceivably, this mild reduction in the dispersion of alveolar ventilation might reflect blood flow redistribution from high- to low-$\dot{V}_A/\dot{Q}$ regions, where hypoxic vasoconstriction takes place.

Postural Changes. Ventilation–perfusion distributions have been studied in a few patients with unilateral lung disease (presence of infiltrates) needing mechanical ventilation.[47] Two patients displayed a predominant decrease in intrapulmonary shunt and two other patients showed an improvement in $\dot{V}_A/\dot{Q}$ distributions when the uninvolved lung side was dependent. Although this difference in response may be related to the lack of clinical uniformity in the small number of patients studied, both responses resulted in increases in Pa_{O_2} when the healthy lung was dependent.

TABLE 37-1: CHARACTERISTICS OF PULMONARY GAS EXCHANGE IN ACUTE LUNG INJURY "WET LUNG"

	ALI or ARDS	Pneumonia
Principal mechanisms		
Shunt	Severe ≥20%	Severe ≥20%
$\dot{V}_A/\dot{Q}$ mismatch	Absent/mild	Mild/moderate
O_2 diffusion limitation	Absent	Absent
100% Oxygen effects		
Increase in Pa_{O_2}	Mild/moderate (≤300 mm Hg)	Marked (≥300 mm Hg)
Increase in shunt	Mild/moderate	Absent
Hypoxic vascular response	Absent	Increased

HEAD TRAUMA

Patients with head trauma with normal chest radiology and without clinical neurogenic pulmonary edema show mild-to-severe $\dot{V}_A/\dot{Q}$ mismatch, essentially characterized by the presence of areas of low $\dot{V}_A/\dot{Q}$ ratios and mild shunt (less than 10% of cardiac output) (without PEEP). Although no satisfactory explanation has been given for such gas-exchange abnormalities,[48] subclinical pulmonary edema on days before admission, atelectasis, and/or decreased lung compliance have been suggested as potential mechanisms.

When mechanical ventilation was discontinued, shunt remained almost unchanged, while $\dot{V}_A/\dot{Q}$ distributions were less homogeneous and less unimodal, with a substantial increase in perfusion to regions of low $\dot{V}_A/\dot{Q}$ ratio units. Functional residual capacity, minute ventilation, and cardiac output were no different between both conditions, but pulmonary arterial pressures increased significantly when patients were removed from the ventilator. Two patients improved dramatically in a few days with considerable, although incomplete, restoration of $\dot{V}_A/\dot{Q}$ mismatch to normal. This suggested the return of normal hypoxic pulmonary vasoconstriction.

CARDIAC SURGERY

Gas exchange has been studied in patients on the day after coronary bypass surgery for myocardial revascularization[49–51] or aortic valvular replacement.[52] Overall, shunt was mildly to moderately increased (less than 15% to 20% of cardiac output) and $\dot{V}_A/\dot{Q}$ distributions showed a variable degree of

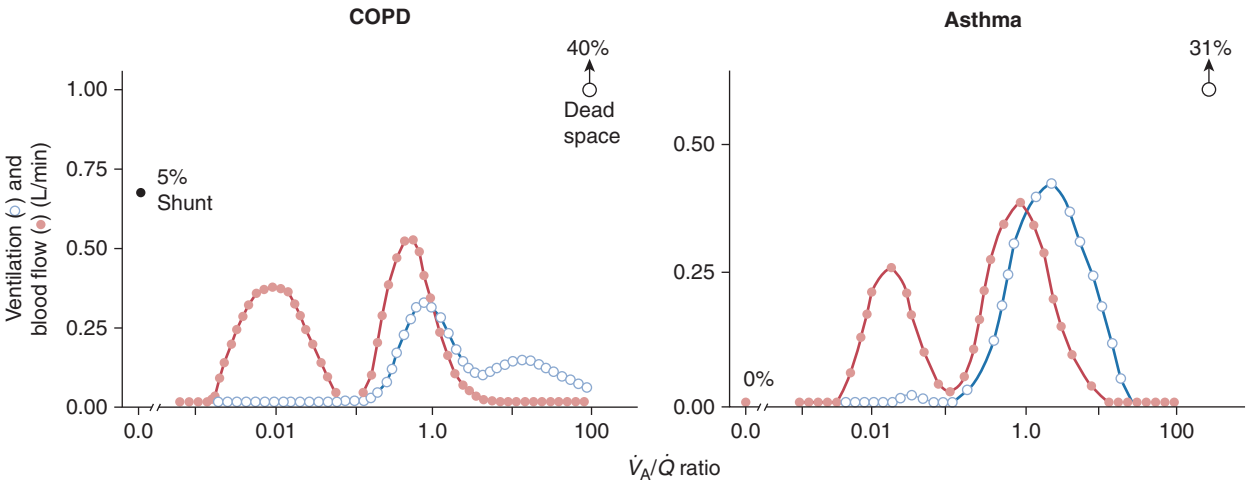

FIGURE 37-10 *Left panel.* Typical bimodal patterns of both blood flow and alveolar ventilation in a representative patient with COPD needing mechanical ventilation. Both shunt and dead space are modestly increased. (*Right panel*) Typical bimodal pattern of blood flow in a representative patient with asthma needing mechanical ventilation. At variance with the COPD patients shunt is absent and dead space is modestly decreased. For further explanation, see text. (Reproduced, with permission, from Rodriguez-Roisin.[16])

severity, in general akin to preoperative findings, with variable patterns (broadly unimodal or clearly bimodal) of $\dot{V}_A/\dot{Q}$ abnormalities. The presence of relatively abundant shunt was also consistent with the presumed underlying multifactorial pathology in these patients. Shunt has been attributed to noncardiogenic pulmonary edema related to cardiopulmonary bypass, reduced functional residual capacity, surfactant alterations, increased closing volume secondary to retained secretions, abnormal hypoxic pulmonary vasoconstriction, and reabsorption atelectasis from a high FI_{O_2}. Breathing 100% O_2 increased the dispersion of blood flow, but neither intrapulmonary shunt nor dispersion of alveolar ventilation increased.[49] These findings were interpreted as release of hypoxic pulmonary vasoconstriction.

In one study,[52] measurements were repeated while the uninvolved (good) right lung was down. Gas-exchange abnormalities in these patients had been previously reported to be more common in the left lung.[52] The improvement of Pa_{O_2} on moving the patient from supine to the right lateral decubitus position was associated with an improvement in $\dot{V}_A/\dot{Q}$ relationships but not in shunt, although a beneficial effect on overall gas exchange, secondary to a simultaneous increase of cardiac output, could not be ruled out. These results are at variance with those in patients with unilateral lung disease, in whom either intrapulmonary shunting or $\dot{V}_A/\dot{Q}$ mismatch improved when the uninvolved (good) lung was down.[47]

Chronic Airflow Limitation ("Dry Lung")

Although exacerbations of COPD and acute severe asthma have a common functional hallmark, chronic airflow obstruction with or without associated reversibility, they show substantial pathophysiologic differences. A contrasting feature of pulmonary gas exchange in patients with "dry lung" and in patients with "wet lung" is that the functional findings observed during exacerbations can be better interpreted in light of the findings observed during the stable state.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE EXACERBATIONS

Patients with COPD show up to four different patterns of $\dot{V}_A/\dot{Q}$ distributions (Fig. 37-10). One pattern may be characterized by a mode that includes a substantial amount of blood flow diverted to lung units with very low $\dot{V}_A/\dot{Q}$ regions, known as "low $\dot{V}_A/\dot{Q}$ mode" (type L).[53,54] Another profile may include alveolar units with high $\dot{V}_A/\dot{Q}$ regions, named "high $\dot{V}_A/\dot{Q}$ mode" (type H). This pattern likely suggests that most of the alveolar ventilation is distributed to zones with higher $\dot{V}_A/\dot{Q}$ ratios. A third profile is a mixed high-low $\dot{V}_A/\dot{Q}$ mode (type H-L), which consists of additional modes above and below the main body of $\dot{V}_A/\dot{Q}$ ratios. A fourth pattern has only two broadly unimodal dispersions. All in all, the dispersions of blood flow or ventilation, or both, tend to be severely increased. Intrapulmonary shunting is slightly elevated and dead space is mildly to moderately increased. The minimal amount of shunt suggests that the efficiency of collateral ventilation is very active or that complete airway obstruction does not occur functionally except in a few airways that are completely occluded, possibly by inspissated bronchial secretions.

An important concept is that patients with a COPD exacerbation, whether requiring or not requiring ventilator support, exhibit mild amounts of shunt (usually less than 10% of cardiac output) although quantitatively more severe $\dot{V}_A/\dot{Q}$ patterns than do patients with stable COPD.[53,54] If a patient with an exacerbation of COPD shows moderate-to-severe amounts of shunt (i.e., 20% of cardiac output) despite normal chest radiology—which excludes collapse, consolidation, or

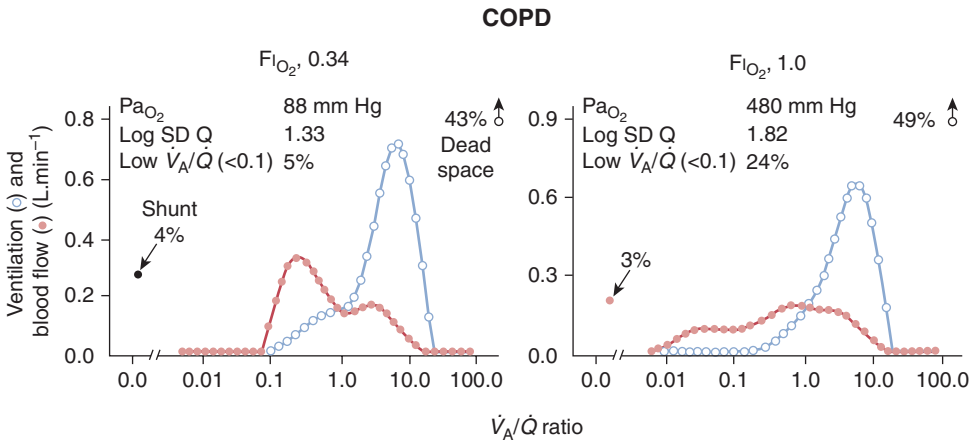

FIGURE 37-11 Effects of breathing 100% oxygen (*right panel*) in a representative patient with COPD. Compared with low FI_{O_2} (*left panel*), Pa_{O_2} increased substantially (≥400 mm Hg) but intrapulmonary shunt remained unaltered; in contrast, the dispersion of blood flow (Log SD Q) and the amount of blood flow distributed to areas with low $\dot{V}_A/\dot{Q}$ ratios increased markedly. This suggests release of hypoxic vasoconstriction without developing reabsorption atelectasis. Dead space tended to increase. Compare these data with those in patients with ARDS (see Fig. 37-2).

edema within the lung—then the possibility of a reopening of the foramen ovale should be considered.[55,56]

Breathing 100% Oxygen. During COPD exacerbations, administration of 100% O_2 rapidly produces full nitrogen washout of alveolar units, even in patients with low or very low $\dot{V}_A/\dot{Q}$ ratios. A steady state is reached by approximately half an hour, resulting in Pa_{O_2} values close to 500 mm Hg.[21,57] These data indicate that shunt is trivial (less than 10% of cardiac output) or negligible.

Breathing 100% O_2 always worsens $\dot{V}_A/\dot{Q}$ relationships, as assessed by a significant increase in the dispersion of blood flow (Log SD Q). In addition, there is a discrete decrease of the dispersion of alveolar ventilation, and dead space tends to increase (Fig. 37-11). As discussed above, the further worsening in $\dot{V}_A/\dot{Q}$ relationships suggests attenuation of hypoxic pulmonary vasoconstriction, even though both pulmonary arterial pressure and vascular resistance remain essentially unaltered. This $\dot{V}_A/\dot{Q}$ deterioration results in a slight but significant increase in Pa_{CO_2}, which also can be influenced by the Haldane effect. The latter was more strongly demonstrated in patients with COPD exacerbations while spontaneously breathing 100% O_2.[58] Alternatively, the slight decrease in the ventilation dispersion could reflect some redistribution of blood flow, from areas of high to areas of low $\dot{V}_A/\dot{Q}$, induced by the accentuated hypoxic vascular response. The lack of increase of shunt in patients with COPD, unlike in patients with ALI or ARDS, indicates that reabsorption atelectasis does not take place. This suggests that either collateral ventilation is very efficient or regional airway occlusion is never functionally complete.

Another striking finding is that when maintenance FI_{O_2} is resumed, Pa_{O_2} rapidly (in less than half an hour) regains the values observed before the institution of breathing 100% O_2.[21] This indicates that nitrogen washout of alveolar units rapidly ceases, even in patients with severe airflow limitation, an observation at variance with ARDS (see Fig. 37-5).[21]

Effects of Positive End-Expiratory Pressure. The potential effects of PEEPi (auto-PEEP)[59] on gas exchange should be kept in mind in patients with COPD requiring mechanical ventilation. In these patients, alveolar pressure can remain positive throughout the respiratory cycle despite the absence of PEEP set on the ventilator.[59]

Because low levels of external PEEP may offset the deleterious effects of PEEPi, investigators assessed the effects of both PEEP and PEEPi on $\dot{V}_A/\dot{Q}$ relationships in patients with chronic airflow obstruction (all but one patient with acute severe asthma had COPD).[60] At low levels of external PEEP (approximately 50% of PEEPi), arterial blood gases improved secondary to an overall optimization of $\dot{V}_A/\dot{Q}$ relationships without changes in pulmonary mechanics or hemodynamics. With further increases in external PEEP so that PEEP was equal to PEEPi, airway pressures slightly increased without further $\dot{V}_A/\dot{Q}$ improvement. The investigators also showed that the use of "permissive" or "controlled" hypoventilation[61] to deliberately reduce PEEPi (by 50%) optimized O_2 delivery secondary to a simultaneous increase in cardiac output. Accordingly, the use of low levels of external PEEP together with "permissive" hypoventilation may be advantageous in patients with COPD needing ventilator support. PEEP may improve gas exchange with less risk of barotrauma. These findings have been strengthened by a study[62] in patients with expiratory flow limitation (i.e., COPD and asthma exacerbations) and PEEPi that showed that application of external PEEP below measured PEEPi did not cause hyperinflation or increased intrathoracic pressure, and resulted in no alteration in lung mechanics, hemodynamics, or gas exchange.

Weaning. $\dot{V}_A/\dot{Q}$ relationships in patients with COPD during weaning from mechanical ventilation has been investigated (Fig. 37-12).[57] No major differences in pulmonary and systemic hemodynamics were shown between mechanical and spontaneous breathing, although cardiac output increased

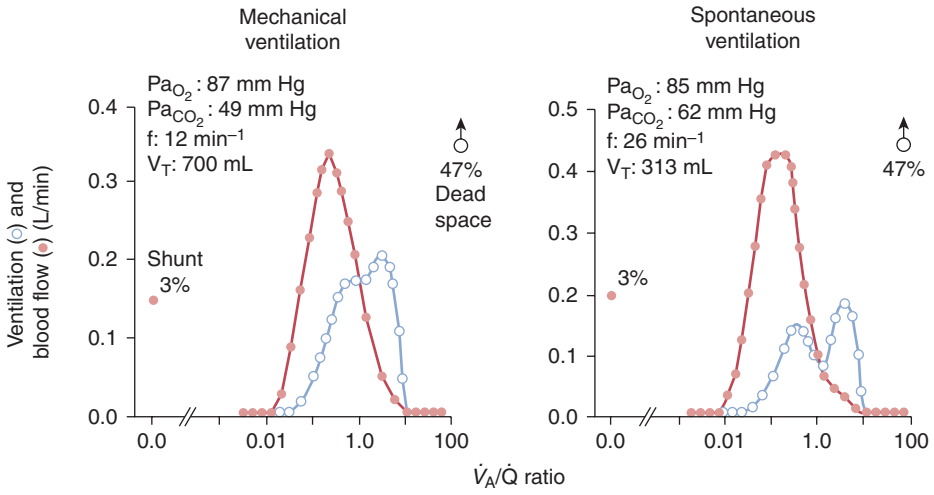

FIGURE 37-12 Effect of ventilator weaning in a representative patient with COPD. Compared with mechanical ventilation (*left panel*), weaning (*right panel*) induced rapid and shallow breathing resulting in increased Pa_{CO_2}. Arterial P_{O_2} did not decrease because the simultaneous increase in cardiac output (not shown) when mechanical ventilation was removed tended to improve Pa_{O_2}, the final result being an unaltered Pa_{O_2}. (Reprinted with permission of the American Thoracic Society. Copyright © 2012 American Thoracic Society. Torres A, Reyes A, Roca J, et al. Ventilation-perfusion mismatching in chronic obstructive pulmonary disease during ventilator weaning. *Am Rev Respir Dis.* 1989;140:1246–1250. Official Journal of the American Thoracic Society. Modified with permission of the American Thoracic Society.)

significantly when patients were removed from the ventilator. Arterial P_{O_2} and O_2 consumption did not change between the two conditions, but mixed venous P_{O_2} and O_2 delivery increased significantly when patients were weaned from the ventilator. During spontaneous breathing, minute ventilation remained essentially unchanged, but respiratory frequency increased and tidal volume fell, resulting in rapid shallow breathing, increased Pa_{CO_2}, and decreased pH.

A considerable increase in the percentage of blood flow to areas of low $\dot{V}_A/\dot{Q}$ was observed during spontaneous ventilation. In contrast, shunt, dispersion of blood flow, and dead space did not change. Therefore, there was further $\dot{V}_A/\dot{Q}$ worsening during spontaneous ventilation after removal of ventilator support. This worsening can be explained by alterations in the breathing pattern and also by changes in cardiac output. Yet, Pa_{O_2} did not undergo major changes, indicating that arterial blood gases were not sufficiently sensitive to detect $\dot{V}_A/\dot{Q}$ changes because other factors, such as minute ventilation and cardiac output were modulating pulmonary gas exchange. Indeed, cardiac output increased substantially after cessation of mechanical ventilation because of a simultaneous abrupt increase in venous return. Similarly, there were increases in mixed venous P_{O_2} and O_2 delivery secondary to the increased cardiac output. Nevertheless, the resulting beneficial effect of the increased cardiac output on Pa_{O_2} was counterbalanced by the simultaneous $\dot{V}_A/\dot{Q}$ worsening, induced in turn by a less-efficient breathing pattern and an increased overall blood flow. Furthermore, using pressure-support ventilation during weaning in patients with exacerbations of COPD prevented worsening of $\dot{V}_A/\dot{Q}$ relationships during the transition from positive-pressure ventilation to spontaneous breathing.[63] Gas-exchange and hemodynamic abnormalities were no different between assist-control and pressure-controlled ventilation when both strategies provided similar levels of ventilator assistance.

Similar results, although without further $\dot{V}_A/\dot{Q}$ worsening, were observed during weaning from mechanical ventilation in patients following coronary artery bypass (half of whom had chronic airflow limitation).[64] Patients with head trauma[48] showed a similar gas-exchange response upon discontinuation of mechanical ventilation, although without associated changes in ventilation and cardiac output.

The key role played by hemodynamic changes has been also emphasized during unsuccessful weaning in patients with COPD.[64] Additional factors contributing to weaning failure include preexisting cardiovascular disease, which may be aggravated by dramatic changes in venous return. An increase of gastric pressure during spontaneous ventilation with subsequent increased splanchnic flow could be an additional mechanism.[65] Oxygen consumption also increases significantly. Inert gas and isotopic studies subsequently revealed that the critical alteration of the ventilation during weaning caused the development of basal regions with very low $\dot{V}_A/\dot{Q}$ ratios.[66]

The increased metabolic demands in these patients could have further negatively influenced the final Pa_{O_2}, thus offsetting the positive effects of the increased cardiac output. In patients with COPD, switching mechanical ventilation to either continuous positive-pressure ventilation or pressure support, increased O_2 consumption and decreased minute ventilation, with marked increments Pa_{CO_2} and no change in Pa_{O_2}.[67] Conceivably, the simultaneous increase in cardiac output (not measured) prevented a fall in Pa_{O_2}. Subsequently, it was observed that patients needing mechanical ventilation (mostly with COPD and cardiac disorders) who failed a trial of spontaneous breathing developed a progressive reduction of mixed venous O_2 saturation secondary to the combined effect of a relative decrease in O_2 transport, possibly related to a decreased right-ventricular and left-ventricular afterload, and an increase in O_2 extraction by the tissues.[68]

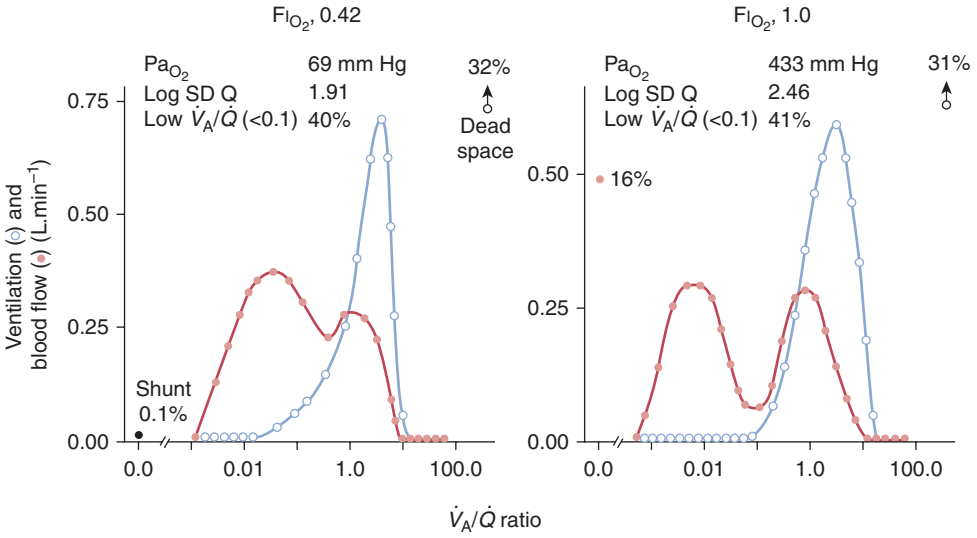

FIGURE 37-13 Effect of breathing 100% O_2 (*right panel*) in a representative patient with acute severe asthma. Compared with low $F_{I_{O_2}}$ (*left panel*), Pa_{O_2} increased substantially (≥400 mm Hg) associated with increases in intrapulmonary shunt, the dispersion of blood flow (Log SD Q), and the amount of blood flow distributed to areas of low $\dot{V}_A/\dot{Q}$ ratios. This suggests the development of reabsorption atelectasis (or selective redistribution of pulmonary blood flow) accompanied with the release of hypoxic vasoconstriction. Compare these data with those seen in patients with COPD (see Fig. 37-12).

Noninvasive Ventilation. The short-term effect of noninvasive ventilation for an exacerbation of COPD has been investigated by our group.[69] The beneficial effect on pulmonary gas exchange—decreased Pa_{CO_2} and increased Pa_{O_2} and pH—was essentially achieved by a more efficient ventilatory pattern (slower and deeper breathing) without a favorable influence on $\dot{V}_A/\dot{Q}$ imbalance. A significant decrease in cardiac output during mechanical support, because of increased intrathoracic pressure, did not decrease Pa_{O_2}.

Acute Severe Asthma

In postmortem studies in patients with sudden fatal asthma, bronchioles reveal increased amounts of luminal occlusion, increased smooth-muscle thickness, and inflammatory infiltrate with both mononuclear cells and eosinophils. Muscular pulmonary arteries adjacent to occluded and inflamed peripheral airways showed a marked inflammatory process in their walls more noticeably when close to airways.[70]

MECHANISMS OF HYPOXEMIA

Patients with life-threatening status asthmaticus who need mechanical ventilation show the most abnormal $\dot{V}_A/\dot{Q}$ pattern in patients with asthma: a marked bimodal blood flow profile that may include 50% or more of cardiac output (Fig. 37-13).[71,72] Severe airways obstruction produces regions of low $\dot{V}_A/\dot{Q}$ that remain perfused but poorly ventilated. This must increase blood flow dispersion more than ventilation dispersion. Conceivably, the high $F_{I_{O_2}}$, together with high doses of bronchodilators with potential vasodilating effects, may attenuate hypoxic pulmonary vasoconstriction, hence contributing to the increase in perfusion of areas with low $\dot{V}_A/\dot{Q}$ ratios. The relatively well-preserved Pa_{O_2} in the presence of such severe $\dot{V}_A/\dot{Q}$ mismatch is noteworthy. This can be attributed to the inordinately high levels of both cardiac output and overall ventilation, which reinforce the major role played by the extrapulmonary determinants of Pa_{O_2} in modulating gas exchange.[5,11,16]

Unexpectedly, shunt was negligible or trivial in these patients. Given the presence of abundant, tenacious, and viscous secretions, one would expect alveolar units distal to narrowed airways to be collapsed. This, however, need not be the case. Collateral ventilation and hypoxic pulmonary vasoconstriction are exceptionally efficient. Moreover, airway occlusion is never functionally complete. Another unexpected finding was the presence of normal dead space, the mechanism of which remains unsettled. The coexistence of diffusion limitation for O_2 was also ruled out (Table 37-2).

TABLE 37-2: CHARACTERISTICS OF PULMONARY GAS EXCHANGE IN CHRONIC AIRFLOW LIMITATION ("DRY LUNG")

	COPD	Asthma
Principal mechanisms		
Shunt	Mild (<10% of Q_T)	Absent
$\dot{V}_A/\dot{Q}$ mismatch	Severe (nonuniform pattern)	Severe (uniform pattern)
O_2 Diffusion limitation	Absent	Absent
100% Oxygen effects		
Increase in Pa_{O_2}	Marked (≥500 mm Hg)	Marked (≥500 mm Hg)
Increase in shunt	Absent	Mild/moderate
Hypoxic vascular response	Increased	Increased

BREATHING 100% OXYGEN

Breathing 100% O_2 induced mild amounts of shunt (less than 10% of cardiac output) in patients with asthma (see Fig. 37-13), suggesting either the presence of critical alveolar units leading to reabsorption atelectasis, or redistribution of pulmonary blood flow of preexisting small shunts, or both.[71] In addition, $\dot{V}_A/\dot{Q}$ mismatch substantially deteriorated, as shown by a considerable increase of the dispersion of pulmonary blood flow. This suggests that hypoxic pulmonary vasoconstriction was decreased. These data are consistent with the morphologic postmortem findings[70] showing that muscular pulmonary arteries adjacent to occluded peripheral airways had marked inflammatory wall involvement that was not characteristic of that associated with chronic hypoxia. Conceivably, these structural abnormalities may reflect pulmonary vascular leakage related to the release of inflammatory mediators.[73] In contrast, the dispersion of alveolar ventilation decreased significantly. A redistribution of blood flow from areas with units of high to areas with units of low $\dot{V}_A/\dot{Q}$ ratio is a potential explanation. A tendency toward an increase in dead space, also shown during 100% O_2 breathing, could reflect hyperoxic bronchodilation.

EFFECTS OF POSITIVE END-EXPIRATORY PRESSURE

The use of PEEP in patients with severe asthma is controversial. Anecdotal reports in patients with life-threatening asthma show conflicting results. Although some studies showed improvement in gas exchange and lung mechanics,[74,75] others found marked increases in Pa_{O_2} associated with gas trapping and increased airway and intrathoracic pressures with decreased cardiac output.[76] From a therapeutic viewpoint, a study by our group[60] of patients with COPD and acute respiratory failure suggests that low levels of PEEP, combined with some degree of "permissive" hypoventilation, might help in optimizing gas exchange in patients with acute severe asthma needing mechanical ventilation.

EFFECT OF SPECIAL MODES OF VENTILATION

High-Frequency Ventilation

During the 1980s there was much interest in mechanical ventilation using small tidal volumes combined with very high frequencies. Few techniques of mechanical ventilation have stimulated as much excitement in the minds of investigators as high-frequency ventilation (HFV), resulting in hundreds of research studies. A reduction in complications such as hemodynamic depression and barotrauma associated with conventional modes was invoked as one of the major advantages.[77]

A comparison of HFV and controlled mechanical ventilation (CMV) in a canine model showed that the efficiency of Pa_{O_2} was no different, but the amount of areas of high $\dot{V}_A/\dot{Q}$ was increased.[78,79] Additional experiments showed that there was an enhanced transport of high-solubility inert gases (approximately twice that for other inert gases) along the airways during HFV. It was suggested that this enhanced transport was dependent on the wet luminal surface of conducting airways.[78]

Although the mechanism of gas delivery by HFV remains to be elucidated, one of the hypotheses is based on augmented dispersion.[80] The theory posits that augmented dispersion during HFV should be less dependent on airway resistance and pulmonary compliance than during CMV. Accordingly, regions of low $\dot{V}_A/\dot{Q}$ might be better ventilated than during CMV. In a canine model of extensive areas of low $\dot{V}_A/\dot{Q}$ but little shunt associated with bronchoconstriction and mucus secretion, HFV was no more effective in delivering fresh gas to such areas than was CMV.[81]

Continuous-Flow Ventilation

Continuous-flow ventilation (CFV) is achieved by delivering continuous streams of gas through cannulas directed down the two main bronchi, in the absence of tidal excursions in lung volume. When CFV was compared to CMV in an animal model,[82] CFV caused significant deterioration in $\dot{V}_A/\dot{Q}$ matching secondary to an increase in the amount of dispersion of pulmonary blood flow. This suggested that CFV induced a nonuniform ventilation distribution and a redistribution of pulmonary perfusion.

In supine dogs, CO_2 elimination was more efficient with endotracheal insufflation than with tracheal insufflation, but the $P(a\text{-}a)O_2$ was larger during CFV than during CMV irrespective of the type of insufflation.[83] Conversely, elimination of CO_2 and $P(a\text{-}a)O_2$ was lower when prone than when supine. In the prone position, gas distribution was uniform with both modes of ventilation. The increased $P(a\text{-}a)O_2$ when supine during CFV was negatively correlated with the decreased ventilation of the dependent zones of the lung, suggesting further $\dot{V}_A/\dot{Q}$ inequalities. The improved gas exchange during CFV in dogs lying prone reflects a more efficient $\dot{V}_A/\dot{Q}$ matching, presumably because the distribution of pulmonary blood flow is nearly uniform.

IMPORTANT UNKNOWNS

The lung is a complex system deriving its chief function from the interaction of two very complicated networks that respectively determine regional perfusion and ventilation. It is now well accepted that the normal lung is exquisitely sensitive to gravity, which normally causes regional differences in blood flow, alveolar ventilation, pleural pressures, and parenchymal stress.

The most common model of pulmonary gas exchange proposes a gravity-induced vertical distribution of perfusion and ventilation, and regional matching of ventilation and

perfusion is accomplished primarily by the shared effects of gravity. Radioactive gases and chest wall scintillation counters were used by a number of investigators in the early 1960s to estimate regional ventilation and perfusion within anterior–posterior cores of lung tissue.

Despite being quantitative, studies using MIGET could not identify the topographical distribution or size of low $\dot{V}_A/\dot{Q}$ units or determine the extent to which the distribution of pulmonary perfusion changes in different experimental and clinical interventions. There have been, however, a few complex attempts to interpret pulmonary perfusion heterogeneity within the context of the gravitational model as random noise. Fractal analysis, a revolutionary mathematical science, demonstrated that this "error" can be analyzed as a fundamental property of the biologic system. Fractal analysis permits characterization of processes or structures that are not easily represented by traditional analytical tools and provides insights and tools for constructing new models. The primary incentive for developing a fractal model of pulmonary blood flow distribution was to explore a unifying mechanism that explains the heterogeneity of perfusion as well as the observation that neighboring lung regions have similar magnitudes of flow.[84]

Another approach has been the use of positron emission tomography imaging of intrapulmonary kinetics of intravenously infused tracer nitrogen-13 (^{13}NN) to measure the regional distribution of ventilation and perfusion.[85]

Ideally, one would like to have a tool to timely measure both ventilation and perfusion taking into account many of the alluded-to caveats. This should include the overcoming of the great difficulties of achieving real steady-state conditions while invasiveness is minimized to cope with cost and time investments.

THE FUTURE

Until the development of some completely new noninvasive, simple technique, it is difficult to anticipate what the future holds for research on pulmonary gas exchange. Over the past three decades, we have witnessed hundreds of elegant studies, of both an experimental and clinical nature. These studies have extensively, and complementarily, unravelled the basic mechanisms of gas exchange across a spectrum of acute and chronic respiratory conditions. Key to the gains in knowledge has been parallel advances that have broadened and deepened our understanding of the clinical management of these conditions. Given this high level of research excellence, it is difficult to predict what will come next. Nevertheless, several worthwhile questions remain to be addressed, particularly in the area of clinical management.

One recent MIGET study was undertaken in patients experiencing a severe exacerbation of COPD,[86] and it addressed the gas-exchange response to a common therapy. It has long been recognized that nebulized, short-acting β_2-agonists can induce mild arterial hypoxemia in patients with COPD, but most of the published work was conducted in the setting of stable COPD. The new study, conducted in patients experiencing a severe exacerbation of COPD requiring hospitalization, revealed no significant gas-exchange abnormalities after use of nebulized salbutamol. During convalescence, however, the same patients experienced small decrements in Pa_{O_2}, secondary to $\dot{V}_A/\dot{Q}$ worsening, on administration of a β_2-agonist. This study addressed not only the salbutamol-induced interplay between extrapulmonary (ventilatory, metabolic, and vascular effects) and intrapulmonary mechanisms (consequences of $\dot{V}_A/\dot{Q}$ mismatching), providing a better insight into the role of gas-exchange pathophysiology in the management of COPD exacerbations. It further confirmed that short-acting bronchodilators are safe when used in the therapy of life-threatening exacerbations of COPD.

CONCLUSION

Arterial P_{O_2} and P_{CO_2} are the end-point outcomes of the gas-exchange state and are governed by the interplay of several intrapulmonary and extrapulmonary components. The most remarkable intrapulmonary factors are $\dot{V}_A/\dot{Q}$ mismatching and intrapulmonary shunt; in contrast, diffusion limitation to O_2 plays a marginal role. Among the extrapulmonary factors, inspired P_{O_2}, overall ventilation, cardiac output, and O_2 consumption are viewed as the most influential.

While breathing 100% O_2, despite substantial Pa_{O_2} improvements, $\dot{V}_A/\dot{Q}$ relationships worsen characteristically according to the underlying nature of acute respiratory insufficiency. In patients with "wet lung" (ALI or ARDS), shunt increases secondary to the development of reabsorption atelectasis without release of hypoxic pulmonary vasoconstriction. In patients with "dry lung" (COPD or asthma), hypoxic vasoconstriction is ultimately released while shunt remains unchanged. Gas-exchange abnormalities may be influenced by changes in cardiac output depending on different ventilator modalities, in particular during weaning from mechanical ventilation.

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ARTIFICIAL AIRWAYS AND MANAGEMENT

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38

AIRWAY MANAGEMENT

Aaron M. Joffe
Steven Deem

"Airway management" implies the provision of assistance to a patient in maintaining a patent airway. This chapter will review airway anatomy and basic airway management techniques.

AIRWAY ANATOMY

The Nose and Nasopharynx

The nose is lined with vessel-rich mucosa designed to warm and humidify the air. Bypassing the nose causes dry gases to reach the respiratory tract and necessitates warming and humidification of gases during mechanical ventilation.

The two nares are divided by a nasal septum that is often not midline. In each naris are three turbinates (Fig. 38-1) that help to condition the inspired gases. Underneath each turbinate lies the opening of perinasal sinus. When these openings are occluded by nasogastric or nasotracheal tubes, fluid tends to accumulate in the sinuses as reflected by a high incidence of radiographic sinus opacification.[1]

The floor of the nose leading to the nasopharynx is in the same plane as the nasal orifices. When a tube is introduced into the nose, it should be directed straight back rather than caudad (Fig. 38-2), and advanced carefully to avoid injuring the turbinates.

Mouth

Oral structures relevant to airway management include the lips, teeth, and tongue as each may either impede introduction of airway devices into the pharynx or diminish upper airway patency or both during artificial breathing.

Pharynx

The pharynx is shaped like a cone (Fig. 38-3) and includes the nasopharynx and the oropharynx, which join to form the hypopharynx. The walls of the pharynx are typically soft and compliant, but may become stiff, increase in volume, or both when inflamed from any cause.

The digestive and respiratory tracts share a common lumen in the pharynx. The posterior portion of the pharynx continues to form the esophagus whereas the anterior portion ends in a series of pouches or fossae surrounding the larynx. The epiglottis forms the posterior wall of the anterior pouch. The region anterior to the epiglottis is called the vallecula and is an important landmark for endotracheal intubation as the tip of a curved laryngoscope blade is typically placed in this fossa.

The epiglottic cartilage is shaped like a leaf and is attached to the posterior surface of the thyroid cartilage.

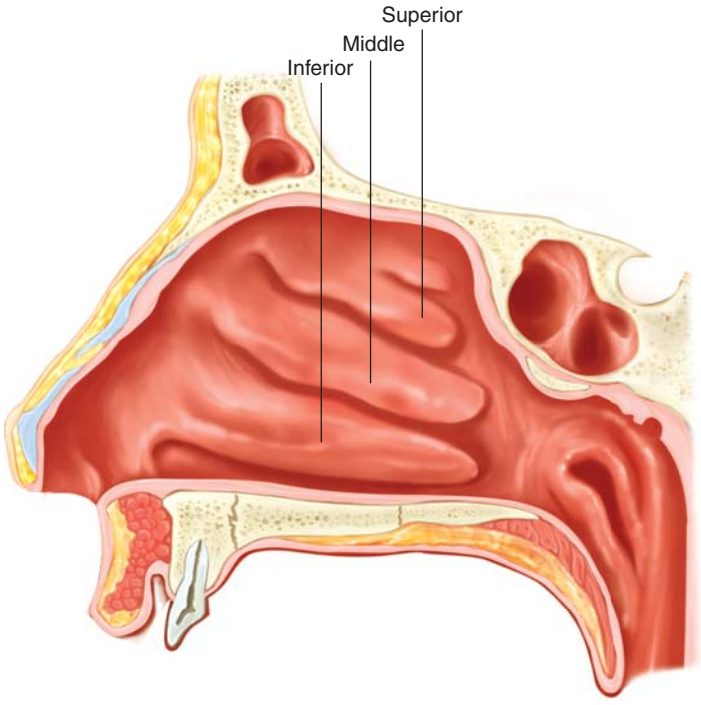

FIGURE 38-1 The nasal turbinates. Note that these are easily traumatized during nasal instrumentation. (Used, with permission, from Pierson DJ, Kacmarek R, eds. *Foundations of Respiratory Care.* New York, NY: Churchill Livingstone; 1992.)

Functionally, the epiglottis directs food away from the larynx by sitting like a tent over the epiglottic opening. This represents an impediment to visualization of the laryngeal aperture and must be lifted out of the way, either by traction or direct lifting from underneath.

FIGURE 38-2 Insertion of a catheter in the nose. The catheter should be directed in parallel with the floor of the nose. (Used, with permission, from Pierson DJ, Kacmarek R, eds. *Foundations of Respiratory Care.* New York, NY: Churchill Livingstone; 1992.)

Larynx

The laryngeal skeleton consists of a group of cartilages extending between the fourth and sixth cervical vertebrae. The major portion of the laryngeal body consists of the thyroid cartilage anteriorly and the cricoid cartilage posteriorly. The cricoid cartilage is actually a complete ring with a wide posterior portion and a narrow anterior portion, which is palpable just inferior to the thyroid cartilage. Between the two cartilages is a small depression that represents the cricothyroid membrane.

The arytenoid cartilages sit posteriorly atop the cricoid cartilage. These small paired cartilages provide support to the posterior portions of the true vocal cords. The mucosa of the vocal cords covers these cartilages, and movement of the cartilages occurs during respiration. The arytenoids are an important landmark insofar as they may be the only portion of the glottic inlet visible during attempted laryngoscopy.

AIRWAY MANAGEMENT WITHOUT INTUBATION

Face-mask ventilation, commonly referred to as bag-valve-mask ventilation, is an essential airway management skill. Although considered a "basic" skill, it is not always easy and requires considerable practice, best mastered in a controlled setting such as the operating room. Face-mask ventilation

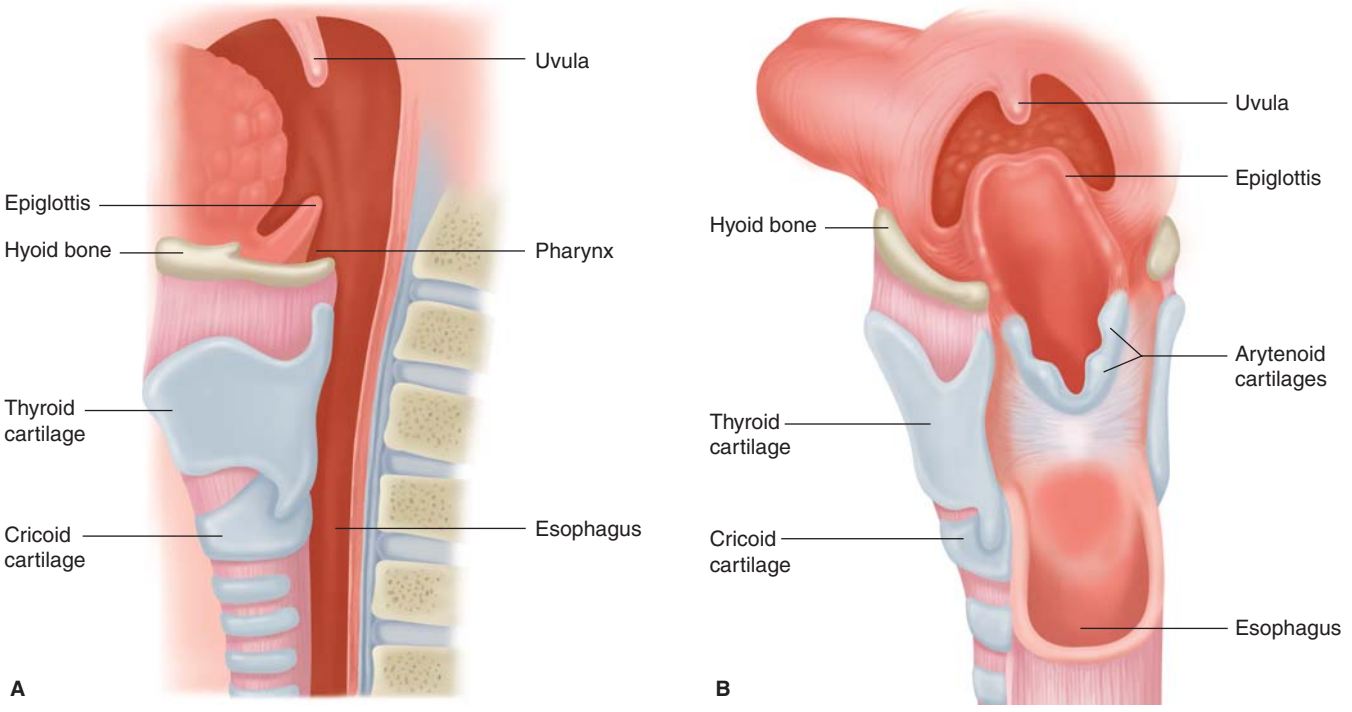

FIGURE 38-3 Lateral (**A**) and posterior oblique (**B**) views of the pharynx and larynx, including the laryngeal skeleton. (Reproduced, with permission, from Pierson DJ, Kacmarek R, eds. *Foundations of Respiratory Care.* New York, NY: Churchill Livingstone; 1992.)

may be required as an initial resuscitative measure, when the need for ventilation is very brief, or when tracheal intubation proves difficult or impossible. Face-mask ventilation may be difficult or impossible because of imperfect patient–face-mask interface or airways obstruction, chiefly of the upper airways but also of the lower airways. If there is high risk of regurgitation of gastric contents ("full stomach"), active vomiting, or bleeding that might result in massive aspiration, face-mask ventilation should only be used as a rescue technique when severe hypoxemia is present.

Risk Factors for Difficult and Impossible Mask Ventilation

Currently, there is no accepted, single definition of what constitutes difficult mask ventilation. Lack of clinical signs of gas exchange, such as "adequate chest rise" or an oxygen saturation by pulse oximetry less than 90%, and the need for oral or nasal airways or the use of a second operator to help with face-mask ventilation are the most referenced surrogates for difficulty.[2] Using these definitions, difficult mask ventilation has been reported in less than 2% of patients.[3] Impossible mask ventilation is a rare event, reported in only 1.5/1000 patients.[4] Caution is advised, however, as these data come from the operating room environment, chiefly in the setting of elective surgery, in patients with stable, managed, or anticipated comorbidities who have been well preoxygenated, rather than in the emergency setting. Risk factors may be segregated by considering operator-dependent factors and patient-related factors, which themselves can be split into those that inhibit proper mask fit and those that may result in upper or lower airways obstruction. Table 38-1 summarizes reported risk factors for difficult and impossible mask ventilation; these factors are highly predictive of difficult mask ventilation, in contrast to the poor positive and negative predictive value of external exams to predict difficult laryngoscopy.[3–6] When a patient exhibits multiple risk factors for difficult mask ventilation, immediate tracheal intubation ("rapid-sequence") or an alternative to facemask ventilation, such as placement of a supraglottic airway, should be performed, preferentially at the outset of airways management.

Most modern face masks are teardrop shaped, made of clear plastic with large, highly compliant, inflatable borders that conform to a wide variety of faces. A tight seal between the mask and the patient's face is critical to achieve adequate ventilation. This is most commonly attempted using a generic left-handed technique in which the operator grips with the fifth finger at the left mandibular angle and the third and fourth fingers on the left mandibular ramus while controlling the mask with their first finger and thumb (Fig. 38-4). In the event that initial face-mask ventilation is difficult or impossible, knowledge of the common anatomic locations of upper airway obstruction allows the airway manager to rapidly perform a variety of maneuvers to relieve the obstruction specific to the site.

TABLE 38-1: RISK FACTORS FOR DIFFICULT OR IMPOSSIBLE MASK VENTILATION

Difficult Mask Ventilation
Increased BMI
History of snoring/OSA
Presence of a beard
Lack of teeth
Age older than 55 years
Mallampati III or IV
Limited mandibular protrusion
Male gender
Cervical spine limitation
Airway masses/tumors
Impossible Mask Ventilation
Neck radiation changes
Male gender
OSA
Mallampati III or IV
Presence of a beard

Abbreviations: BMI, body mass index; *OSA,* obstructive sleep apnea.
Data from Kheterpal et al,[3,4] Langeron et al,[5] and Yildiz et al.[6]

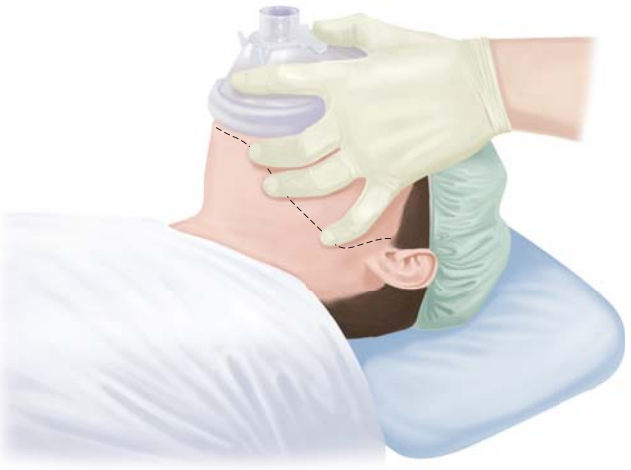

FIGURE 38-4 The generic, single, left-handed mask-hold technique. The operator grips with the fifth finger at the left mandibular angle and the third and fourth fingers on the left mandibular ramus (in the shape of a letter E) while controlling the mask with his or her first finger and thumb (in the shape of a letter C). The *dotted line* represents the line of the jaw. (Image courtesy A. Joffe.)

Head Position

As consciousness is lost, upper airway caliber diminishes and obstruction may occur. The so-called sniffing position, used to optimize visualization during direct laryngoscopy, is ideal for providing face-mask ventilation because it decreases the passive collapsibility of the pharynx and pulls the epiglottis and tongue away from the posterior pharynx.[7] Another maneuver that may open the glottis is to advance the mandible so that the bottom teeth are anterior to the upper teeth.

Nasopharyngeal and Oral Airways

The insertion of an oropharyngeal airway maintains the mouth in an open position and bypasses the nasopharynx and base of the tongue. Hypopharyngeal patency may also be augmented. Nasopharyngeal airways relieve obstruction at the level of the nares and soft palate with the potential to improve the patency of the airway at the level of the base of the tongue and hypopharynx (Fig. 38-5). Oropharyngeal airways are tolerated by anesthetized patients, whereas a nasopharyngeal airway is better tolerated in awake individuals. The major hazards of inserting a nasopharyngeal airway are bleeding or fracture of a turbinate. In nonemergent situations, prior application of a topical vasoconstrictor will ease insertion and prevent bleeding. Thrombocytopenia or a coagulation disorder are relative contraindications to insertion of a nasal airway. Proper sizing and careful placement of all pharyngeal airways is important. Improperly placed oropharyngeal airways can push the base of the tongue down into the hypopharynx, while both oropharyngeal and nasopharyngeal airways that are too large for the patient's airway have the potential to displace the epiglottis caudad toward the vocal cord inlet, causing worsened upper airway obstruction.

OPTIMIZING FACE-MASK VENTILATION

If initial maneuvers prove unsuccessful in allowing adequate face-mask ventilation, additional techniques include placing the base of the face-mask just caudad to the lower lip rather than into the mandibular groove in edentulous patients; this decreases the leak around the mask and may substantially increase tidal volume (Fig. 38-6).[8] As Figure 38-7 shows, a two-handed face mask technique with one person securing the mask and a second operator (out of view in the figure) providing ventilation by squeezing the bag may also increase tidal volumes.[9] A solo operator can also utilize a two-handed mask technique by using an intensive care unit ventilator set to deliver pressure-control ventilation with a limit of 20 cm H_2O as the "second operator."[10] In patients with factors that predict difficult mask ventilation, it may be advisable to employ all available maneuvers initially to provide for an optimal first attempt at face-mask ventilation.

TRACHEAL INTUBATION: INDICATIONS, PREPARATION, AND STANDARD TECHNIQUES

The indications for tracheal intubation are varied, but for the most part can be categorized into (a) the need for maintenance and protection of the airway, (b) the need for high

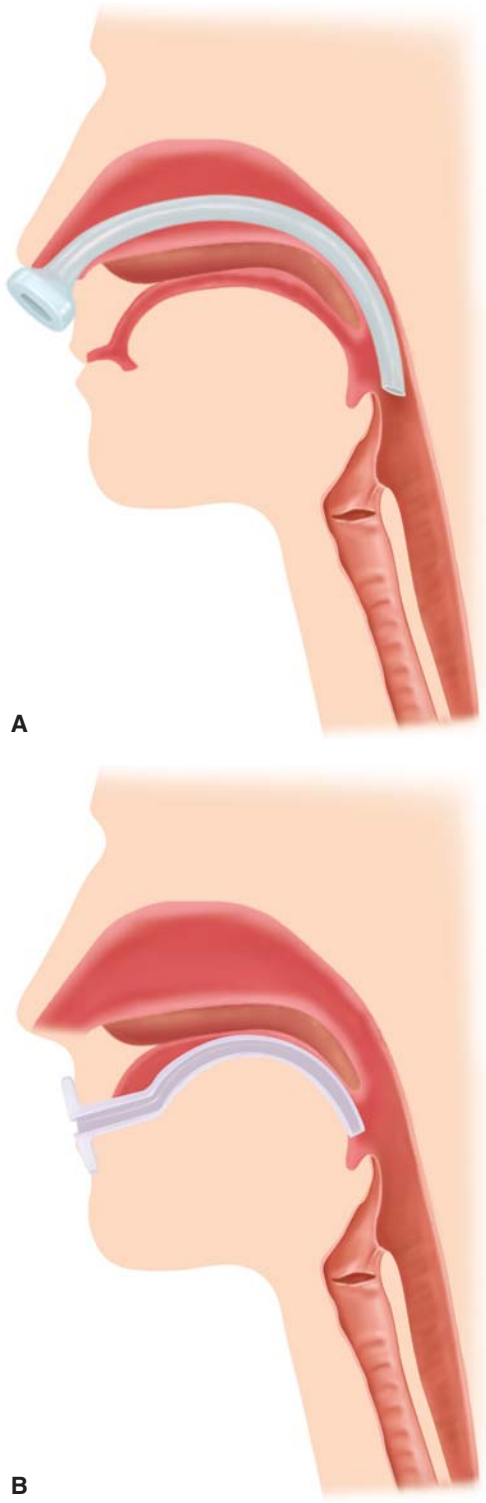

FIGURE 38-5 Nasal (**A**) and oral (**B**) airways in place. These improve the airway by separating the tongue and epiglottis from the posterior pharyngeal wall. (Used, with permission, from Pierson DJ, Kacmarek R, eds. *Foundations of Respiratory Care.* New York, NY: Churchill Livingstone; 1992.)

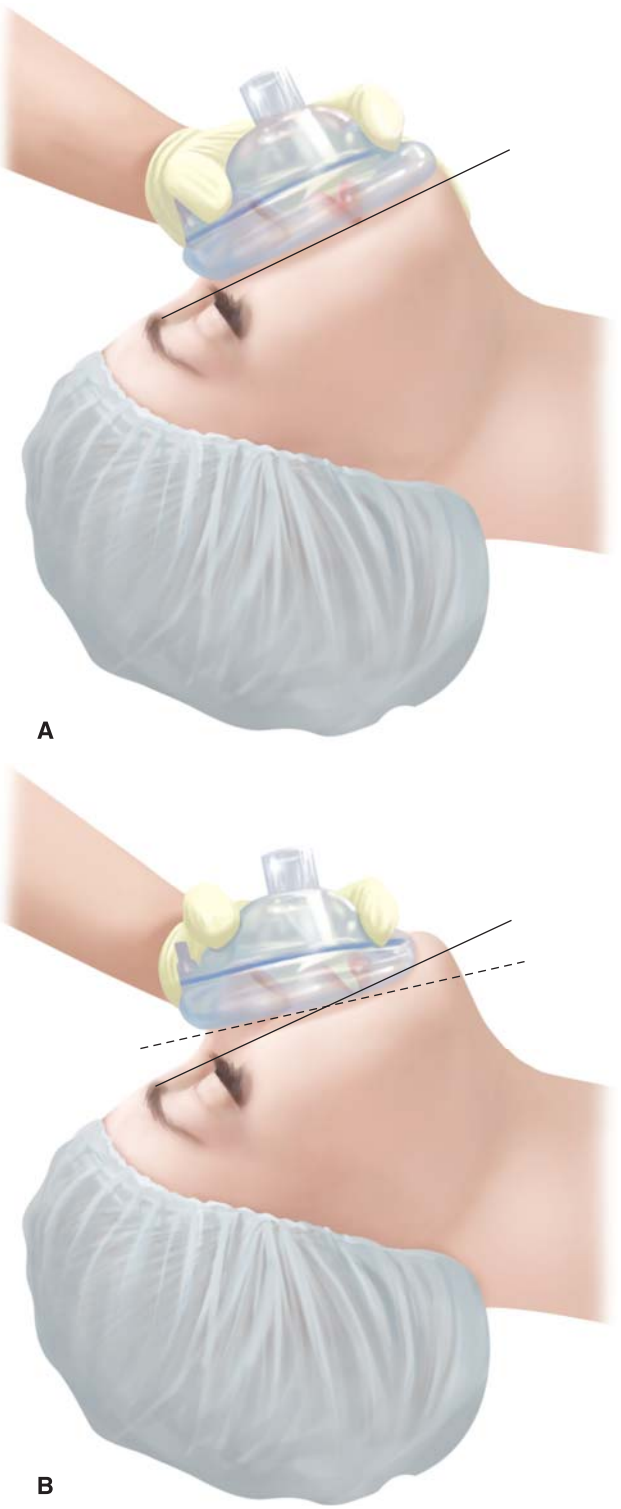

FIGURE 38-6 A comparison of the traditional location of the mask in relation to the patient's face (*top*) with the top of the mask over the bridge of the nose and the base of the mask over the mandibular groove. The *continuous line* represents the plane between the nose and the mandible. When the mask is moved caudally (*bottom*), the base of the mask becomes positioned above the lower lip. The *dashed line* represents the contact between the mask and the face. This "lower lip" placement is particularly advantageous in edentulous patients. (Images courtesy A. Joffe.)

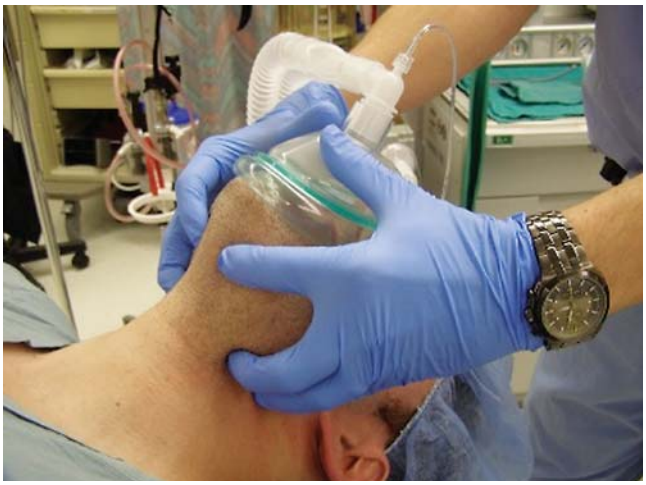

FIGURE 38-7 A two-handed jaw-thrust mask-hold technique. The key to the maneuver is providing sufficient anterior traction to effect maximal mandibular advancement such that the mandibular teeth are forward of the maxillary teeth. This pulls the tissues supported by the mandible—the tongue and epiglottis—away from the posterior pharynx, thereby increasing the airway caliber. In addition, traction may increase the patency of the glottic aperture. (Photograph courtesy A. Joffe.)

inspired oxygen concentrations, or (c) the need for application of positive pressure to the airway. Significant overlap may exist in individual patients. Specific etiologies of respiratory failure and the need for mechanical ventilation are covered in detail in Chapter 4.

Airway Evaluation

A substantial body of research has been directed toward identification of patients with "difficult airways"; unfortunately, anatomy-based predictors of the difficult airway are notoriously insensitive and have only moderate specificity.[11–13] Nonetheless, a basic history should be obtained and an airway examination performed to the extent possible in all patients to identify risk factors for difficult ventilation and/or intubation. Factors associated with difficult intubation include a previous history difficult intubation; morbid obesity;[14,15] obstructive sleep apnea;[16,17] and gross physical abnormalities, including marked prognathia or retrognathia, other congenital deformities, a marked overbite, facial swelling, postradiation fibrosis, and facial dressings. A basic examination includes a view of the patient's facial anatomy from the frontal and lateral perspectives, an oral examination with the mouth maximally open and tongue extended, an assessment of neck extension, and measurement of the distance from the tip of the mandible to the thyroid cartilage. Additional factors to consider in evaluating the airway are discussed below.

Based on oral examination, Mallampati devised a classification scheme to predict difficult intubation (Fig. 38-8).[18] In general, the likelihood of difficult intubation increases from Class 1 to Class 4, although the test has only approximately 50% sensitivity at identifying difficult airways, and is most useful as a positive predictor at the extreme (Class 4).[18,19] In addition, this test is often impractical in emergency settings, where patient cooperation with the examination is not possible.

The size of the mandible provides some measure of the space available to displace the tongue during laryngoscopy (Fig. 38-9). This can be assessed by measurement of the distance between the tip of the mandible and the thyroid cartilage (thyromental distance) using either a ruler or finger-breadths that have previously been calibrated against a ruler. A thyromental distance of less than 6 to 7 cm has a specificity of approximately 90% in identifying the difficult airway, but the test has very poor sensitivity (approximately 30%).[12] Complementary to the absolute distance between

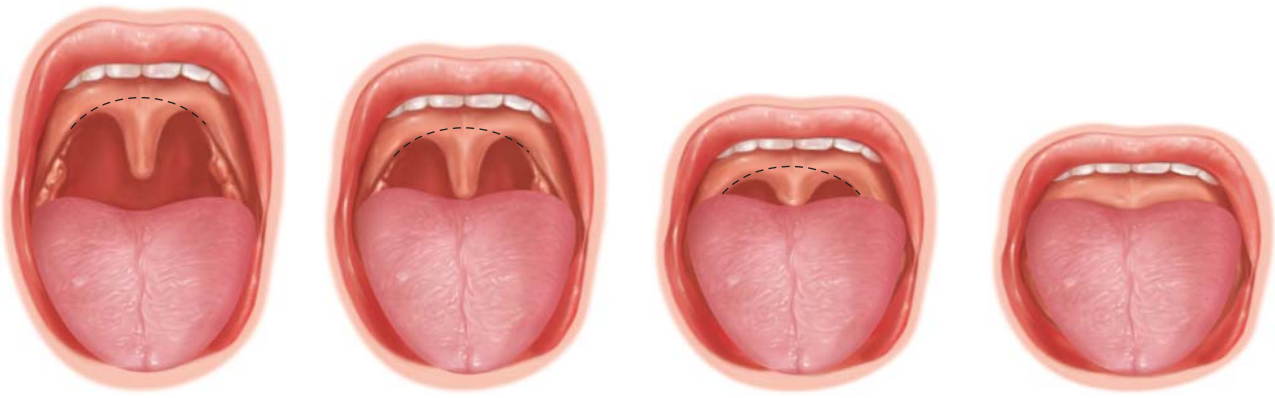

FIGURE 38-8 Mallampati Airway Classification. *From left to right:* Class 1: soft palate, fauces, uvula, and anterior and posterior tonsillar pillars visible; Class 2: soft palate, fauces, uvula visible; Class 3: soft palate, base of uvula visible; and Class 4: hard palate only.

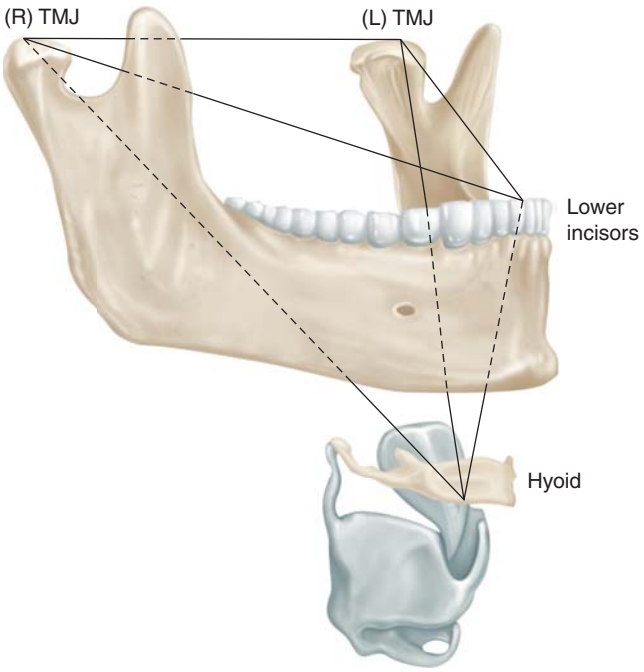

FIGURE 38-9 The submandibular space represented by an inverted pyramid bounded by the right and left temporomandibular joints (*TMJs*), lower incisors, and hyoid bone. This represents the potential space for tissues to be displaced anteriorly and away from the posterior pharynx and lines of sight during airway-management maneuvers. (Adapted, with permission, from Greenland KB. A proposed model for direct laryngoscopy and tracheal intubation. *Anaesthesia.* 2008;63:156–161.)

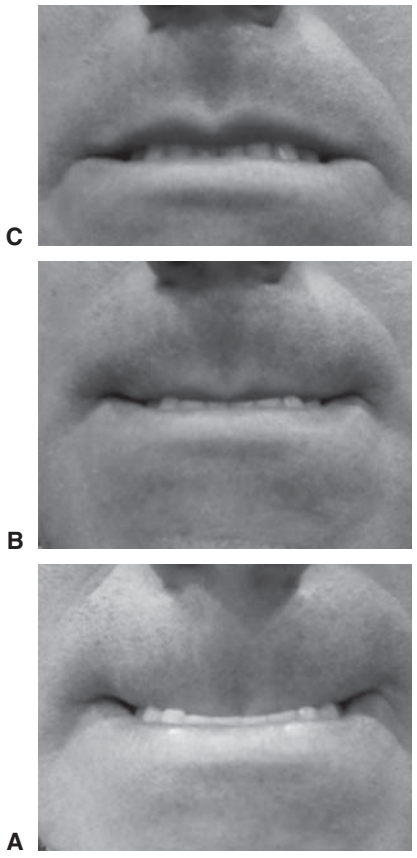

FIGURE 38-10 A frontal view of the upper-lip bite test. *From bottom to top (best to worst):* In Class 1, the lower incisors are able to bite the upper lip past the vermilion border, making the mucosa of the upper lip totally invisible **(A).** In Class 2, a portion of the lip below the vermilion border remains visible **(B).** In Class 3, the lower incisors fail to bite any portion of the upper lip **(C).** (Images courtesy A. Joffe.)

the mentum and thyroid cartilage is the potential distance as assessed by the upper-lip bite test. To perform the test, the patient is simply asked to bite his or her upper lip and is classified as follows: Class 1, lower incisors can bite the upper lip above the vermilion line; Class 2, lower incisors can bite the upper lip below the vermilion line; and Class 3, lower incisors cannot bite the upper lip (Fig. 38-10). Specificity and accuracy of the upper-lip bite test are significantly higher than that reported for thyromental distance alone.[20]

Extension of the head on the neck is necessary to bring the pharyngeal and laryngeal axes into alignment during direct laryngoscopy. Head and neck mobility can be assessed by simple examination, or quantitated by measuring the distance from the sternum to the tip of the mandible (sternomental distance) at maximum neck extension.[21] A sternomental distance of equal to or less than 13.5 cm has greater than 50% sensitivity and specificity at predicting difficult intubation, although this test has not been studied as extensively as either the Mallampati classification or the thyromental distance.[20]

Common sense dictates that a combination of the above tests may prove more useful at predicting the difficult airway than the individual tests. There is some literature to support this notion, although the predictive value of these tests remains modest even when used in combination.[22,23] When possible in the context of the critically ill patient, a minimal exam, which assesses mouth opening, the size of the tongue, cervical spine motion, and mandibular protrusion may be helpful to assess potential problems with laryngoscopy.

Other factors that may complicate emergency intubation and require special consideration include:

1. Risk factors for regurgitation and tracheal aspiration of gastric contents, including recent oral intake; gastroparesis because of drugs; intraabdominal infection, trauma, or diabetic neuropathy; increased intraabdominal pressure (pregnancy, ascites); and bowel obstruction. Most critically ill patients should be considered at risk for regurgitation and aspiration during intubation.
2. Hypovolemia and/or shock predisposes to severe hemodynamic depression during tracheal intubation because of sedative/hypnotic drugs and the initiation of positive pressure ventilation. Vascular access, drugs, fluids, and equipment for resuscitation should be present.

TABLE 38-2: SUPPLIES FOR ADULT TRACHEAL INTUBATION

Routine Supplies
Standard disposable inflatable-rimmed teardrop-shaped face mask in small, regular, and large adult sizes
Oropharyngeal (80 to 100 mm) and nasopharyngeal (28 to 32 Fr) airways
Self-inflating resuscitator circuit ("Ambu Bag" or modified Mapleson circuit)
Yankauer-type suction catheter
Standard and short laryngoscope handle
Blade of choice (curved or straight) in two sizes
Tracheal tube introducer (Eschmann, Frova, etc.)
Supraglottic airways to accommodate small to large adults (30 to 100 kg, laryngeal mask, laryngeal tube, other)
Tracheal tubes (size 7- to 8-mm internal diameter)
Resuscitation drugs and defibrillator immediately available
Device for tube placement confirmation (carbon dioxide detector, self-inflating bulb, other)
Medications
Sedative-hypnotics
Neuromuscular blocking drugs
Additional Difficult Airway Equipment
Indirect video laryngoscope (GlideScope, Airtraq, other)
Intubating laryngeal mask airway (LMA-Fastrach, Air-Q)
Fiber-optic bronchoscope
Aintree intubating catheter, Arndt wire-guided catheter exchange set
Prepackaged cricothyrotomy kit (Melker, Ardnt, other) *or* #11 or 20 scapel with 6.0 inner diameter tracheal tube for cricothyrotomy

3. Increased intracranial pressure, which can be exacerbated by direct laryngoscopy and tracheal intubation.
4. Acute trauma poses multiple problems during attempted intubation, including possible airway injury, head and brain injury, cervical spine injury, and hypovolemia. Intubation in the presence of known or possible cervical spine injury must proceed without movement of the spine (inline manual spine stabilization).
5. Severe hypoxemia reduces the time available for laryngoscopy and intubation before severe oxyhemoglobin desaturation occurs.

EQUIPMENT AND SETUP

Table 38-2 lists supplies that should be present at the site of tracheal intubation, some of which may be institution specific, particularly the equipment available for the anticipated or unanticipated difficult airway. In emergent situations, the endotracheal tube (ETT) should be prefitted with a stylet with a slight anterior bend on the tip ("hockey stick"), which may facilitate placement if the laryngeal view is suboptimal.

TABLE 38-3: INTUBATION CARE BUNDLE

Preintubation
1. Presence of two operators
2. Fluid loading (isotonic saline 500 mL or equivalent) in absence of cardiogenic pulmonary edema
3. Preparation of intensive care unit sedatives (bolus or infusions)
4. Preoxygenate (3 to 5 minutes with tight-fitting high-flow nonrebreather mask or noninvasive positive pressure ventilation in case of acute respiratory failure with FI_{O_2} 100%, pressure support 5 to 15 cm H_2O to obtain expiratory tidal volume of 6 to 8 mL/kg and PEEP of 5 cm H_2O)
Intubation
5. Rapid sequence induction, with or without application of cricoid pressure (see Table 38-4)
Postintubation
6. Immediate confirmation of tube placement
7. Vasopressor administration for postintubation hypotension
8. Initiate sedation
9. Initial ventilator settings to achieve lung protection

Abbreviations: FI_{O_2}, fractional inspired oxygen concentration; *PEEP*, positive end-expiratory pressure.

Adapted, with permission, from Jaber et al.[24]

Preparation for emergency tracheal intubation by following a checklist or bundle is recommended. Use of an intubation bundle incorporating preoxygenation, the presence of two operators, a rapid sequence induction, cricoid pressure, postintubation capnography, low-tidal volume lung-protective ventilation, fluid loading, and preparation and early administration of sedative and vasopressor infusions has been reported to significantly reduce the occurrences of cardiac arrest or death, severe cardiovascular collapse, and hypoxemia occurring within 60 minutes of emergency intubation in the intensive care unit (Table 38-3).[24]

Standard Intubation Techniques

ORAL VERSUS NASAL INTUBATION

The decision to place an oral or nasal tracheal tube is based on a variety of considerations. In general, the oral route is preferred. A larger tube can be placed orally than nasally, resulting in less airways resistance,[25] higher minute ventilation, easier passage of fiber-optic bronchoscopes, and more effective pulmonary toilet. Nasal tubes occlude the sinus ostia, potentially leading to a higher incidence of bacterial sinusitis compared to oral tubes.[1,26] Nasal intubation is contraindicated in the presence of coagulopathy or anticoagulation, basilar skull fracture, or significant nasal or sinus deformity.

PATIENT PREPARATION: RAPID SEQUENCE INDUCTION OF ANESTHESIA

In most cases, the most rapid way to secure the airway is to induce general anesthesia with a sedative and/or hypnotic, followed by administration of a neuromuscular blocking drug, followed by direct laryngoscopy with tracheal intubation. Table 38-4 describes a "rapid sequence induction." This approach, when combined with the application of cricoid pressure (Sellick maneuver) (Fig. 38-11), may minimize the chances of massive aspiration. Note that recent investigations have determined that the mechanism by which cricoid pressure may prevent regurgitation of gastric contents into the pharynx is related to occlusion of the hypopharynx (rather than the esophagus) by downward pressure on the cricoid cartilage.[27,28]

"Preoxygenation," or "denitrogenation," consists of allowing the patient to breathe 100% oxygen for 3 to 5 minutes before induction of anesthesia. Preoxygenation allows utilization of the functional residual capacity as an oxygen reservoir. When functional residual capacity and oxygen consumption are normal, preoxygenation allows 8 or more minutes of apnea before oxyhemoglobin desaturation, and greatly increases the margin of safety should there be difficulties in managing the airway.[29] Preoxygenation, however, is far less effective in patients with acute hypoxemic respiratory failure,[30] and increasing the duration of preoxygenation from 4 to 8 minutes is of only marginal benefit in these patients.[31] On the other hand, the use of noninvasive positive-pressure ventilation in critically ill, hypoxemic patients provides more thorough denitrogenation and longer apnea times than tidal breathing with a non–rebreather mask, and should be considered when staff and equipment are readily available.[32] At a minimum, if patients are already receiving noninvasive positive-pressure ventilation before intubation, it should be continued until laryngoscopy rather than switching to conventional face-mask preoxygenation.

TABLE 38-4: STEPS FOR RAPID-SEQUENCE INDUCTION AND TRACHEAL INTUBATION

1. Prepare equipment and position patient; use of styletted tubes is recommended
2. Preoxygenate patient (this may be occurring simultaneously or can precede #1 above)
3. Apply cricoid pressure (optional depending on circumstance)
4. Rapid administration of induction agent followed by a neuromuscular blocking drug
5. Wait for fasciculations (succinylcholine only) or a full 60 seconds (either succinylcholine or rocuronium), whichever comes first[a]
6. Direct laryngoscopy and tracheal intubation[b]
7. Verification of correct tube placement

[a]Depending on circumstances (suspected full stomach or not), mask ventilation may be briefly attempted before intubation attempts. The ability to provide mask ventilation assures the operator that if laryngoscopy is difficult or impossible, face-mask ventilation will suffice while other intubation pathways are pursued. If face-mask ventilation is unsuccessful in this circumstance, immediate placement of a supraglottic airway or performance of cricothyroidotomy may be necessary should initial intubation attempts fail.

[b]Initial attempts may be made by indirect video laryngoscopy via a supraglottic airway, or by fiber-optic bronchoscope, depending on the situation and the experience of the operator.

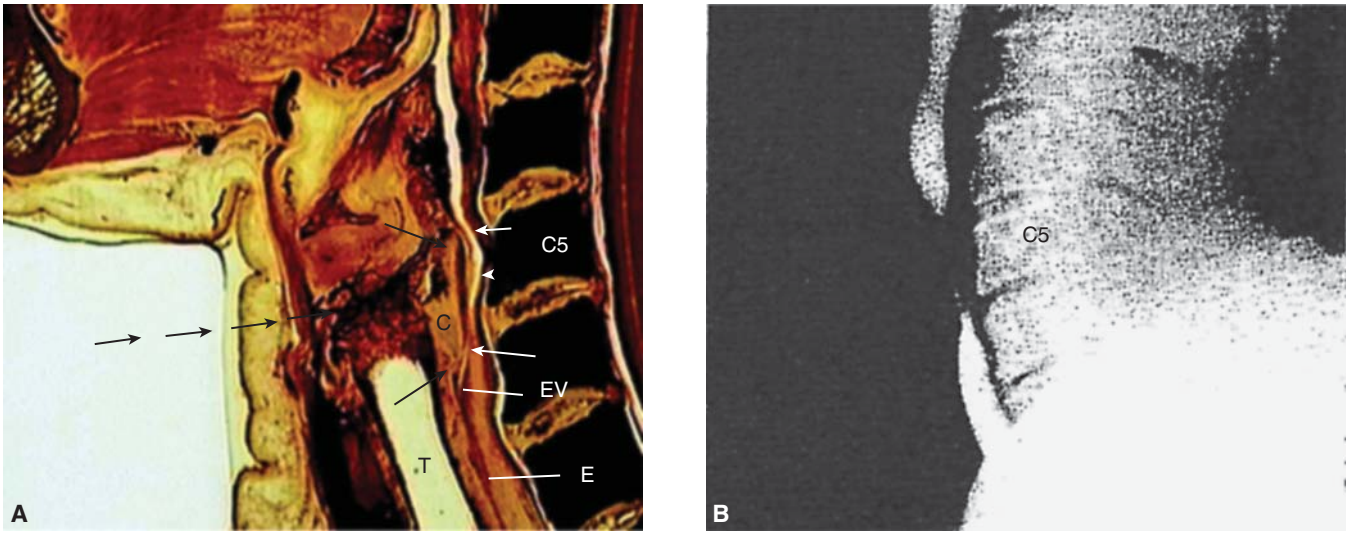

FIGURE 38-11 (**A**) A sagittal cadaver image of the cricoid pressure anatomic unit. The cricoid cartilage (*C*) is the foundation of the cricoid-pressure unit with its superior and inferior aspects indicated by *black arrows.* The postcricoid hypopharynx muscular wall and lumen (*white arrowhead*) and its superior and inferior limits (*white arrows*) have a constant and intimate relationship with the cricoid cartilage. As pressure is applied anteriorly (*serial black arrows*), the unit is compressed against the vertebral body (*C5*), sealing off the esophagus (*E*) at the esophageal verge (*EV*). Because the esophagus is well below the level of the seal, its position is irrelevant to the integrity of the seal produced by the pressure on the unit. (**B**) An image from Sellick's original report showing obliteration of the lumen by cricoid pressure at the fifth cervical vertebra. *T,* trachea. (Used, with permission, from Rice MJ, Mancuso AA, Gibbs C, et al. Cricoid pressure results in compression of the postcricoid hypopharynx: the esophageal position is irrelevant. *Anesth Analg.* 2009;109(5):1546–1552.)

If rapid sequence induction of anesthesia is not indicated, induction may proceed at a more measured pace, without application of cricoid pressure. On the other hand, preoxygenation should be attempted in all emergency intubations, recognizing that it may be neither possible nor effective in some circumstances.

DIRECT LARYNGOSCOPY

Intubation using direct laryngoscopy may be the fastest and surest way of securing an airway. This may be particularly true where use of video laryngoscopes or a fiber-optic bronchoscope may be hindered by airway soiling with secretions, blood, or vomitus. This important lifesaving skill, however, can result in great harm if performed incorrectly. The major, feared complications are failure to ventilate and intubate the trachea, and unrecognized esophageal intubation, both of which can lead to severe neurologic injury and death. The likelihood of successful intubation is increased with experience, in addition to the use of proper equipment and suitable pharmacologic adjuncts. Gaining expertise in manual face-mask ventilation and direct laryngoscopy in a controlled setting before attempting these maneuvers in an emergency cannot be overemphasized. The specifics and technical considerations of direct laryngoscopy are beyond the scope of this chapter. A brief description of the basic technique follows.

Numerous laryngoscope blades have been devised for various special situations but most intubations are performed using one of two categories of blades: (a) blades intended to be used to lift the epiglottis directly ("straight" blades); (b) blades designed to lift the epiglottis indirectly by placing anterior traction on the hyoepiglottic ligament in the vallecula ("curved" blades) (Fig. 38-12). In our experience, the curved laryngoscope blade is more easily mastered and more commonly used than the straight blade, although facility with both is ideal as each has distinct advantages. Laryngoscope blades are most commonly designed to be held by the left hand (for right-handed individuals), although right-handed blades are available.

Before starting, the patient's head should be positioned near the top of the bed so the laryngoscopist's arms are not fully extended. The force applied during the average intubation is 25 newtons (N),[33] the equivalent of lifting a mass of approximately 2.5 kg. This force is most easily applied when the elbow is flexed and relatively close to the laryngoscopist's body.

Classical teaching is that laryngoscopy is facilitated by flexion of the neck at the cervical–thoracic junction and extension of the neck at the atlantooccipital joint ("sniffing position"); this position brings the laryngeal and pharyngeal axes into alignment. The sniffing position is accomplished by raising the occiput with a firm pillow, folded towels, or other support. Recent studies, however, suggest that cervical extension is the most important component of this maneuver, and that the addition of neck flexion on the thorax improves the laryngoscopic view only in patients with limited neck extension and/or morbid obesity.[34,35]

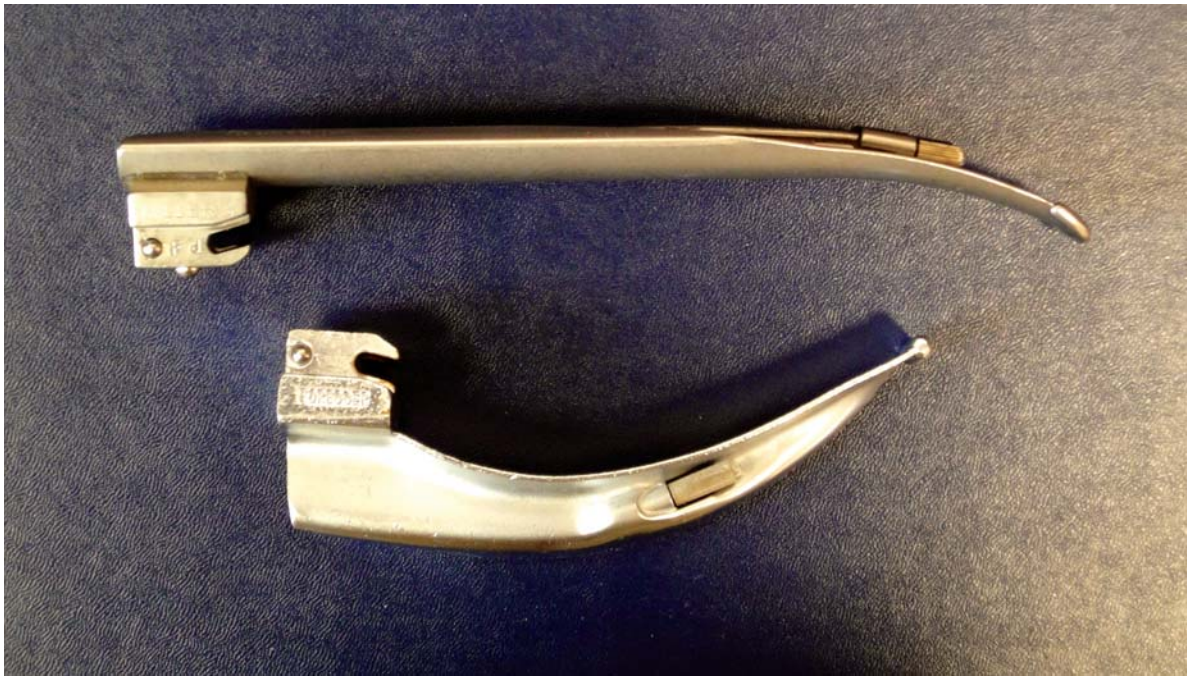

FIGURE 38-12 Typical straight ("Miller," *top*) and curved ("Macintosh," *below*) blades for direct laryngoscopy. Straight blades directly lift the epiglottis. Although this often provides a clear view of the glottis, the room available for inserting the endotracheal tube into the mouth is limited compared to curved blade. The curved blade, the most common variant of which is the Macintosh, is directed into the vallecula and then pulled forward. This lifts the epiglottis away from the glottis. (Photograph courtesy S. Deem.)

Laryngoscopy proper begins by positioning the blade in the right side of the patient's mouth; the mouth opening can be facilitated with the right hand. The right hand can then move to the occiput to extend or flex the neck into optimal position. The blade is then slowly advanced and the tongue swept to the left. The uvula and then the epiglottis should be identified, and are useful landmarks for maintaining a midline position. The blade should be advanced either into the vallecula (curved blade), or beyond the epiglottis toward the glottis (straight blade), and traction then applied at a 45-degree angle with floor. The wrist should remain firm, as flexing the wrist may cause pressure on the upper incisors and will push the epiglottis in front of the larynx. Traction at a 45-degree angle pulls the epiglottis forward to reveal the glottic opening. If the glottis is still not visible, external application of *b*ackward (toward the spine), *u*pward (toward the head), *r*ightward (toward the patient's right side) *p*ressure on the thyroid cartilage ("BURP" maneuver) may push the larynx into view; an assistant can then hold the larynx in this position.[36] Once the laryngeal aperture is visualized, the ETT can be advanced through the glottis, the stylet removed, and the cuff inflated; the correct position should be verified as described below.

If the nasal route is used, application of a topical vasoconstrictor before intubation is of critical importance in increasing the size of the nasal passage and minimizing bleeding. Topical 4% cocaine is effective, providing both vasoconstriction and anesthesia, but may be toxic at doses greater than 3 to 4 mg/kg. An effective alternative is to use a phenylephrine or oxymetazoline nasal spray several minutes before instrumenting the nose, particularly if topical anesthesia is not necessary. Both nostrils should be sprayed in case one side is partially obstructed. The nasal passage can be prelubricated by inserting a nasopharyngeal airway coated with either 2% lidocaine gel (for awake intubations) or water-soluble gel. In addition, briefly warming the ETT in 37°C (98.6°F) water will make it much more pliable and less likely to injure the mucosa. Nasal tubes (without a stylet) should be inserted with gentle pressure, directed posteriorly and advanced into the pharynx. Direct laryngoscopy is then performed, and the tube is guided into the larynx by manipulating the end extending out of the nose. Frequently, the tube tip must be guided with a Magill forceps while an assistant advances the tube.

THE DIFFICULT AIRWAY

The term *difficult airway* is best defined as the development of any airway management problem that requires an escalation of interventions to establish mask ventilation and/or tracheal intubation. For purposes of standardization in studies, difficult intubation is often defined as that requiring more than two attempts at laryngoscopy, or by a grade 3 or 4 laryngoscopic view as described by Cormack and Lehane (Fig. 38-13), although considerable subjectivity exists for all definitions.[37] "Failed" intubation implies that either attempts were aborted, or that the airway was secured surgically. The estimated incidence of difficult tracheal intubation in the operating room is approximately 5%, and failed intubation is less than 0.5%.[12] The reported incidence of difficult intubation in the emergency setting varies widely, but on the average is similar to that for the operating room. The reported incidence of failed intubation, however, is much higher (up to 5%), as is the incidence of other intubation-associated complications such as hypoxemia, aspiration, cardiac arrest, and death.[38–41]

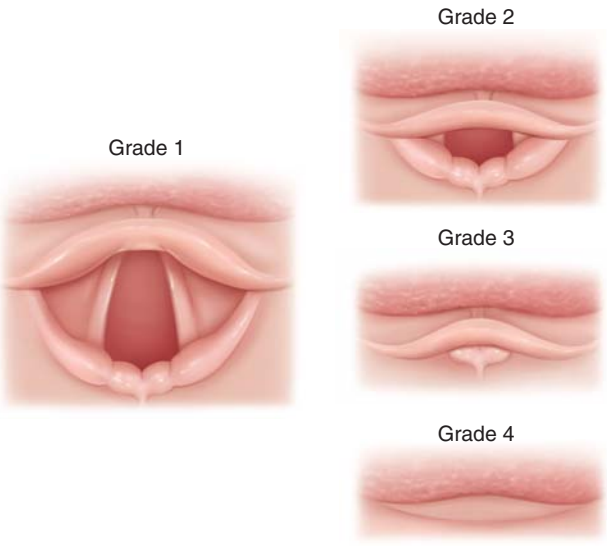

FIGURE 38-13 Laryngoscopy grading, usually referred to as Cormack-Lehane grade after the physicians who originally described them. *From left to right:* Grade 1: entire glottic opening can be visualized; Grade 2: only the posterior glottis or posterior arytenoids can be visualized; Grade 3: only the epiglottis is visible; Grade 4: no recognizable structures are visible.

It is not surprising that difficulties in managing the airway are more likely to occur during emergency intubation than during an elective situation given the comorbidities that may complicate emergency intubation. Emergency intubation also poses an additional problem in that the patient cannot be awakened and the intubation postponed, particularly as critically ill patients often require intubation because of inadequate oxygenation and/or ventilation.

Guidelines for management of the difficult airway based on available literature and expert opinion have been developed locally (at the hospital or practice level) and regionally or nationally.[12,42–45] The American Society of Anesthesiology was the first organization to publish such guidelines (including an accompanying algorithm), with the last update several years old at the time of this writing.[43] It is the general perception that difficult airway guidelines and algorithms have resulted in fewer airway mishaps. This appears to be true regarding airway management at the induction of anesthesia. The same conclusion, however, is not supported with respect to airway management during other phases of anesthesia or in locations outside of the operating room.[46] Thus, other groups have developed guidelines that are more prescriptive.[45]

Despite the lack of hard supporting evidence, common sense dictates that all airway providers should gain expertise in difficult airway management skills, and should have an algorithm for dealing with the difficult airway. Which published algorithm iteration is used is likely not as important as the act of learning and implementing it. Institutional specific algorithms based upon the types of patients to be cared for, the local experience, and available equipment may have a greater impact than broader, society-based difficult airway algorithms. Recent reports support this notion for elective surgical patients and in the prehospital setting.[47,48] Every institution should have an organized team for responding to critical airways, with minimal training standards for all designated responders, equipment standards, and a mechanism for providing the rare emergency surgical airway.

Predicted Difficult Airway: Awake Intubation

If the patient has a recognized difficult airway and is not combative or uncooperative, an awake intubation is generally preferable. This can be accomplished by one of several techniques, including blindly placing a nasotracheal tube, placing an oral or nasal tube using fiber-optic guidance, using awake direct laryngoscopy, or using a retrograde tube-over-guide technique. Alternatively, the airway may be surgically secured primarily by an awake tracheotomy or, in emergent situations, by an emergency cricothyrotomy. Preparation of the patient and some awake intubation techniques are outlined below.

PATIENT PREPARATION FOR AWAKE INTUBATION

Awake intubation can be performed with surprisingly little discomfort to the patient if topical anesthesia is first applied. Administration of an antisialagogue such as glycopyrrolate decreases secretions that impair visibility and enables better uptake of local anesthetics by the mucous membranes. If intubation is emergent or urgent, there may be insufficient time for the antisialagogue to become effective, however.

Topical anesthesia of the soft palate, pharynx, and larynx can be obtained by administration of atomized or nebulized lidocaine (2% to 4%) or benzocaine spray, and/or by asking the patient to gargle with viscous lidocaine solution. Caution is warranted regarding the use of benzocaine, as methemoglobinemia has been reported with this agent, and toxicity is not necessarily related to the administered dose.[49,50] Patients receiving benzocaine should be monitored for the development of cyanosis; the arterial saturation as estimated by pulse oximetry may fall, but this monitor underestimates the true oxyhemoglobin saturation.[51] A high level of suspicion is necessary, and methemoglobinemia can be confirmed by cooximetry. If lidocaine is used, the total administered dose should be limited to less than 300 mg as absorption via the mucosa is significant and can lead to central nervous system toxicity.

Anesthesia of the trachea can be achieved by nebulization of lidocaine, by spraying lidocaine through a fiber-optic bronchoscope, or via transtracheal injection of lidocaine, with the transtracheal approach providing the best anesthesia.[52] This can be accomplished by rapid injection of 2 to 3 mL of 4% lidocaine with a 22-gauge needle at end-exhalation; the subsequent cough helps distribute the anesthetic.

Direct or indirect video laryngoscopy can be performed in awake patients, provided that adequate topical anesthesia has been applied, although supplemental sedative may be required. Additional awake techniques are discussed below.

AWAKE BLIND NASAL

Blind nasal intubation has the advantage of not requiring a laryngoscope (or bronchoscope), can be performed even when blood or secretions are present in the airway, and can be performed on a patient in the sitting position. The technique is especially suited to dyspneic patients, as they breathe more comfortably when sitting, have easily heard breath sounds, and tend to maintain their glottis open. Once the tube is in the nasopharynx, it should be directed caudad, using breath sounds as a guide, and advanced through the glottis during inspiration. The course of the tube can sometimes be determined by external palpation of the neck. The larynx can often be pushed gently toward one side if the tube is slightly misaligned. Rotation of the tube and flexion or extension of the neck may also be useful if the tube does not initially enter the trachea. The overall success rate for blind nasal intubation is approximately 90% in experienced hands.[53]

FIBER-OPTIC TRACHEAL INTUBATION

Fiber-optic-aided intubation allows direct visual guidance, can be accomplished in the awake patient via either the nasal or oral route, and is less stimulating than direct laryngoscopy. In emergency situations, however, when blood, vomitus, or copious secretions are present, it may be quite difficult.

Preparation of the patient for awake fiber-optic intubation is described under Patient Preparation for Awake Intubation; the neck should be neutral or slightly extended. The scope and light source should be verified to be in working order, the bronchoscope lubricated, and the tube passed over it to ensure proper fit. Oxygen can be insufflated through the suction port of the scope, or direct through the patient's nose or mouth, depending on what intubation route is used. The nasal route may provide the best angle for viewing and entering the larynx. The ETT can be passed into the nose and advanced into the nasopharynx, and the bronchoscope then introduced. If the oral route is chosen, an oral intubating airway may facilitate passage of the scope

TABLE 38-5: A COMPARISON OF SOME COMMONLY USED VIDEO LARYNGOSCOPES

Device	Blade Shape	Monitor	Reusable/Disposable	Size Range
GlideScope	Angulated	Separate, 3.5-in. (ranger) or 7-in. LCD monitor	Reusable, single-use blades (cobalt, ranger)	Pediatric–large adult, depending on model
Storz C-Mac, D-Mac	Standard Macintosh blade, angulated	Separate, 7-in. TFT monitor	Reusable	Sizes 2 to 4
McGrath	Angulated	Integrated, 1.7-in. LCD monitor	Single-use blades	Three adult lengths
Pentax-AWS	Anatomically shaped with guide channel	Integrated, 2.4-in. LCD monitor	Single-use blades	One size only
Airtraq	Anatomically shaped with guide channel	None (with eyepiece) or external monitor	Single-use blades	Pediatric, small adult, regular adult, double-lumen

Abbreviations: LCD, liquid crystal display; *TFT,* thin-film transistor.

Data from Niforopoulou P, Pantazopoulos I, Demestiha T, et al. Video-laryngoscopes in the adult airway management: a topical review of the literature. *Acta Anaesthesiol Scand.* 2010;54(9):1050–1061.[128]

through the mouth and pharynx. Alternatively, an assistant can grasp and gently pull the patient's tongue with a gauze pad. This opens the pharynx and facilitates visualization of the larynx. If the patient is sedated or uncooperative, a bite block should be inserted to prevent biting of the scope. After the scope enters the trachea, the ETT can be advanced, and its position relative to the carina confirmed before withdrawing the scope. If the tube does not easily pass through the glottis, a 90-degree clockwise rotation may allow passage beyond the right vocal cord.

VIDEO (INDIRECT) LARYNGOSCOPY

A number of indirect laryngoscopes with video capability are commercially available and are generally classified into steering and nonsteering devices, although it is also useful to differentiate them by whether or not the device incorporates an integrated channel for delivery of the tracheal tube. Five devices, two of which are channeled, are currently available or soon will be. Table 38-5 compares the features unique or shared amongst the devices.

The most important feature shared amongst videolaryngoscopes is their ability to "look around the corner" enabling an almost universally improved view of the glottic structures compared to those obtained with direct laryngoscopy; the technique has recently been reviewed in detail.[54] Videolaryngoscopes can be used preferentially as an "optimal" first attempt at intubation, for rescue after failed direct laryngoscopy, after topicalization of the airway for awake intubation, or to inspect the airway and rule out airway edema or obstructing masses before extubation of the difficult airway.

THE UNRECOGNIZED DIFFICULT AIRWAY

The term *unrecognized* implies that the initial attempt by any method of airway instrumentation, but chiefly direct laryngoscopy, was not straightforward as expected. As mentioned previously, prediction of difficult intubation is an inexact science, and it is not uncommon to have unexpected difficulties with tracheal intubation after induction of anesthesia and paralysis. Furthermore, in the critically ill patient, awake intubation or postponement of intubation are frequently not options either because of patient combativeness or the immediate need for control of the airway or severe hypoxemia. Thus, perhaps the most essential component of airway management skills is the ability to rapidly and systematically respond to difficulties with intubation and/or face-mask ventilation. At the first sign of airway difficulties, help should be summoned, difficult airway equipment obtained if not already present, and a difficult airway algorithm followed.

The first laryngoscopy attempt should be the optimal attempt and thus particular attention must be paid to equipment setup, patient positioning, ergonomics of the operator, and the surrounding conditions such as support staff, lighting, and ambient noise. Potential technique modifications occurring at the time of laryngoscopy include adjustment of head and neck position, and external laryngeal manipulation/ bimanual laryngoscopy ("BURP" maneuver). Based upon the best laryngoscopic view obtained, intubation can be attempted by direct placement of the tracheal tube, use of an Eschmann introducer or bougie, or immediate switch to an alternate laryngoscope blade or device for a second attempt. For example, in large patients where the blade is not long enough to reach the vallecula, a longer blade (i.e., Macintosh #4 instead of Macintosh #3 blade) may be useful; in patients with a long, floppy epiglottis, switching from a curved to a straight blade may be helpful. If initial intubation attempts fail but mask ventilation is adequate, the situation remains controlled. In general, however, no more than two attempts at direct laryngoscopy should be made before choosing an alternate technique, as multiple laryngoscopies are associated with increased morbidity.

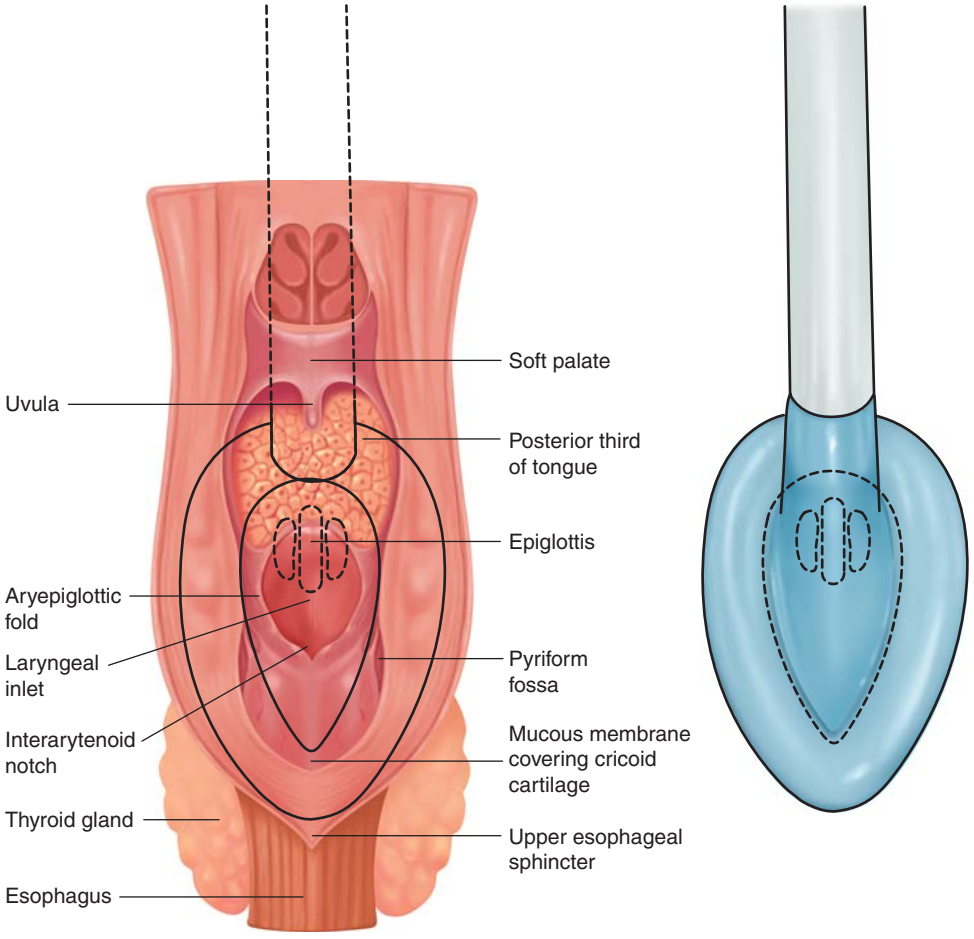

FIGURE 38-14 Dorsal view of the laryngeal mask airway (LMA) showing position relative to pharyngeal anatomy. (Image courtesy LMA North America, Inc.)

If mask ventilation remains effective, other alternate techniques to consider are video laryngoscopy, fiber-optic intubation, or laryngeal mask-facilitated intubation. If these techniques are not practical for any reason, remaining options are limited, and include a surgical airway and awakening the patient. Awakening the patient, however, is infrequently an option in the emergency setting, as discussed above.

DIFFICULT INTUBATION AND DIFFICULT FACE-MASK VENTILATION

If initial intubation attempts fail and face-mask ventilation becomes inadequate, a supraglottic airway should be used. In addition, a supraglottic airway may be placed preferentially in lieu of face-mask ventilation after initial intubation attempts in any patient exhibiting predictors of difficult mask ventilation. Several supraglottic airways are commercially available. The decision to use one or the other of these devices depends on clinical experience and availability of the devices, but at least one type of supraglottic airway should be included in difficult airway storage units. The devices have been described as either periglottic or retroglottic. Periglottic airways consist of a tube connected to an oval, somewhat pear-shaped mask with an inflatable or hydrocolloid gel-filled rim that fits into the periglottic area. The tip of the bowl of the mask, when correctly positioned, sits within the proximal end of the esophagus while the heel of the mask abuts the base of the tongue or within the vallecula (Fig. 38-14). Retroglottic airways have two inflatable cuffs: one distal designed to occlude the esophagus, and a more proximal cuff intended to seal the retropharynx. Between these two cuffs lies an opening through which air can flow (Fig. 38-15). Such devices have been used quite successfully to provide rescue ventilation in patients in whom face-mask ventilation has failed.[55] Although practice with supraglottic airways is recommended before use in an emergency, the insertion and ventilation success rate are high even in unskilled hands.[56–58]

The airway seal, that is to say, the airway pressure at which gas escapes around the cuff has a wide range depending on the device. The LMA-Classic and other similarly designed airways typically seal the airway up to pressures of 15 to 20 cm H_2O.[59] Devices such as the air-Q (Mercury

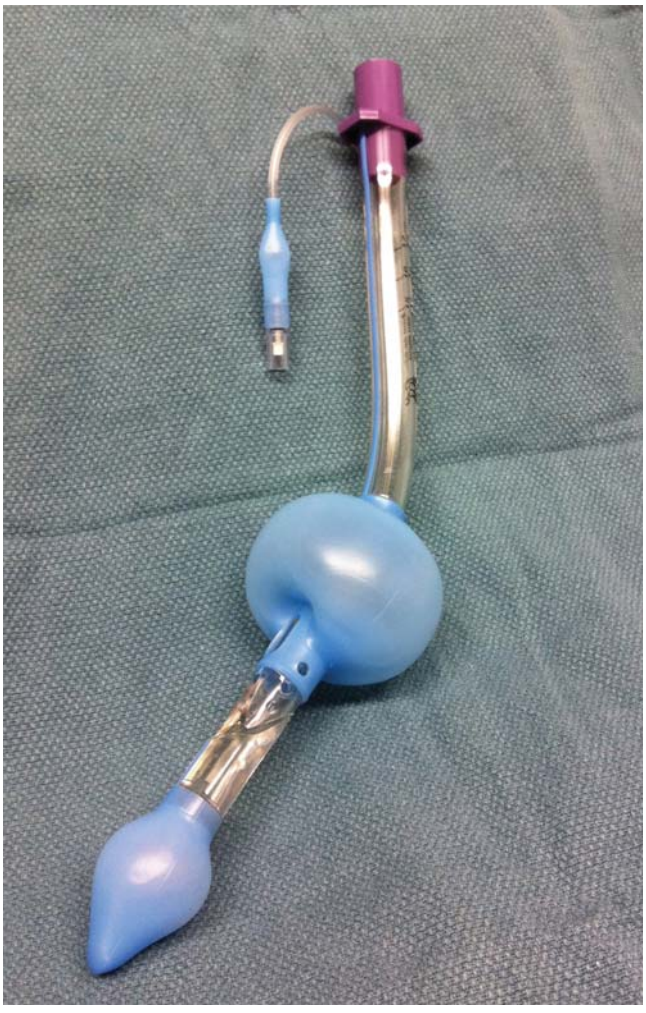

FIGURE 38-15 A retroglottic airway, the laryngeal tube. A single port inflates both the distal esophageal and more proximal pharyngeal balloons. The airway tube terminates in an opening just distal to the pharyngeal balloon. (Photograph courtesy A Joffe.)

Medical, Clearwater, FL) and the i-Gel (Intersurgical, Ltd., Berkshire, UK) supply a seal of approximately 25 cm H_2O and have the advantage of shorter, larger diameter airway tubes that allow direct passage of usual adult size tracheal tubes through them (7 to 8 mm inner diameter).[60,61] The LMA-Proseal is the most extensively studied device with the most reliable airway seal, up to pressures of 40 cm H_2O, although the reported average is approximately 30 cm H_2O.[62] It should be noted that the LMA-Classic and similar devices will not necessarily prevent aspiration of gastric contents, although this has not been a commonly reported problem during either elective use,[63] or during emergency ventilation. A number of supraglottic airways (LMA-Proseal, LMA-Supreme, i-Gel) have incorporated an esophageal vent to minimize the aspiration risk, although the benefit in this regard is contentious and there is a dearth of data supporting this claim.

Besides their simplicity, ease of insertion, and effectiveness, a major advantage of supraglottic airways is that they can provide a direct route to the larynx and trachea. When correctly seated in the supraglottis, the termination of the airway tube of the device sits directly opposite the glottic aperture. Intubation of the trachea through these devices has been described using several techniques. The most successful, however, involve the blind passage of an ETT through the device or fiber-optic bronchoscope aided techniques.[64,65] The clear advantage of the latter technique is that it allows direct visual guidance and confirmation of intratracheal placement, and reported success rates are higher for fiber-optic versus blind intubation.[45,66] The lumen of the originally designed, or "classic" size 3 LMA is only large enough to accept a 6-mm ETT, whereas the size 5 LMA will accept a 7-mm ETT. For this reason, difficult airways supplies for use in the intensive care unit may include newer supraglottic airways as detailed above so as to avoid this limitation.

An LMA specifically designed for intubation, the LMA-Fastrack, is modified to include a lumen large enough to accept an 8-mm ETT, a rigid structure to allow easier tube placement, and a bar to lift the epiglottis away from the laryngeal aperture. Like the classic LMA, placement and ventilation success rates are high with the intubating LMA, even for novice users.[67,68] Intubation can be done blindly or using fiber-optic guidance; although blind intubation is usually successful, multiple attempts may be necessary.[68] Fiber-optic guidance results in a higher success rate on the first attempt.

FAILED INTUBATION AND VENTILATION: CRICOTHYROTOMY

If intubation has been unsuccessful and ventilation via face mask and supraglottic airway is compromised, particularly if hypoxemia is present, more invasive airway management techniques must be employed. An important skill in airway management is the ability to recognize the need for a surgical airway *before* the development of injury-inducing, severe hypoxemia. The trachea can be accessed either percutaneously or surgically via the cricothyroid membrane; the approach used depends on the skill of the airway practitioner, and surgeon and equipment availability. Percutaneous placement of a large bore needle or catheter (13 to 16 gauge) permits transtracheal jet ventilation, which generally will provide adequate oxygenation and ventilation before a definitive surgical tracheotomy.[69] In order to carry out transtracheal jet ventilation, however, a high-pressure oxygen source and an adjustable, high-pressure device (jet injector) must be available; attempted manual ventilation through a catheter is largely ineffective. In addition, the potential complications associated with transtracheal jet ventilation are severe, particularly if the catheter is inadvertently positioned outside the trachea, and include barotrauma, arterial perforation, and gas trapping because of airway obstruction or insufficient expiratory time.[70]

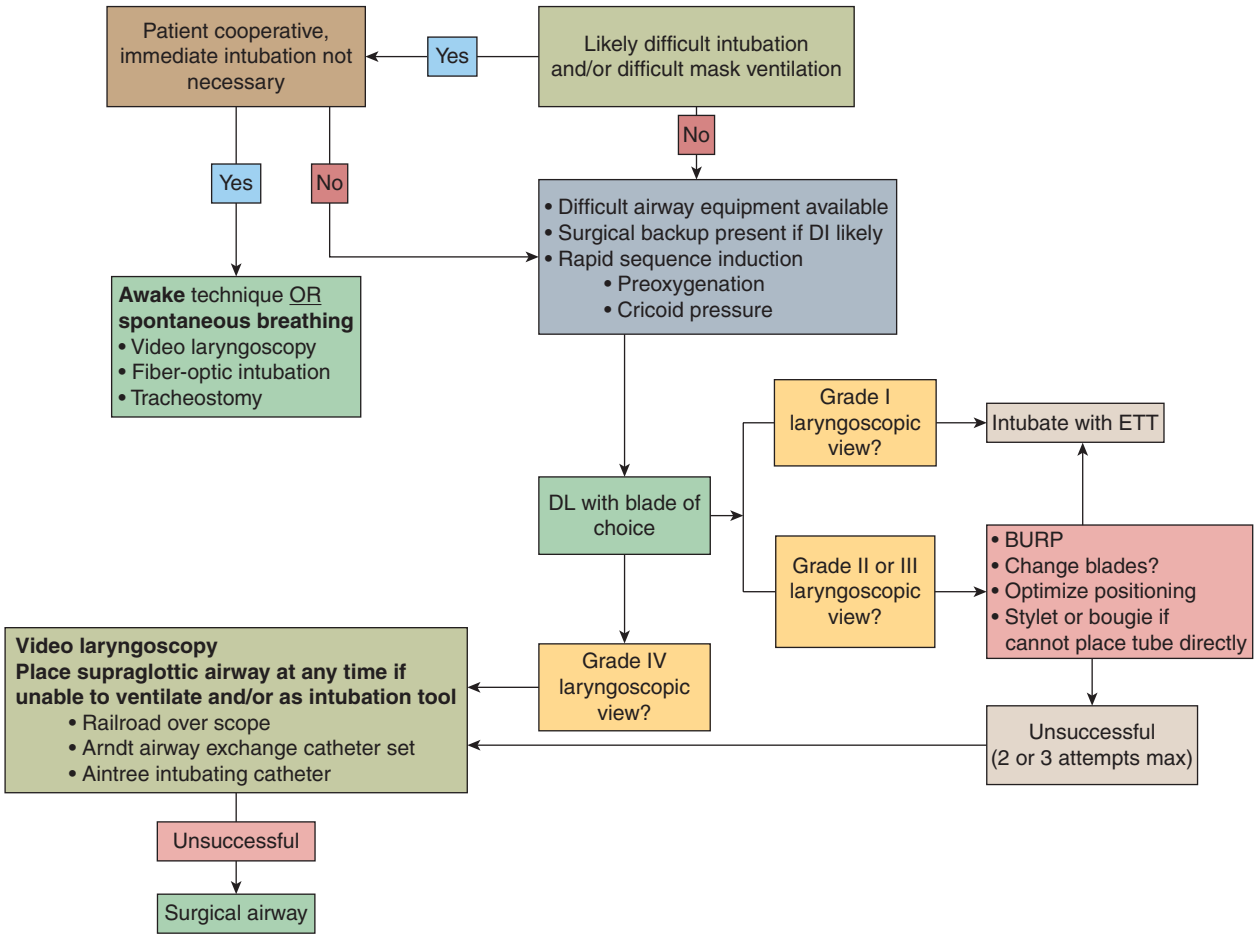

FIGURE 38-16 Airway management algorithm for emergent tracheal intubations. Additional help should be sought at the first indication of a difficult airway situation. It is critical that movement to the next step in the algorithm not be prolonged by repeated attempts at direct laryngoscopy that may traumatize the airway and lead to failed ventilation and oxygenation. Confirmation of intratracheal placement should always use CO_2 detection combined with clinical findings. *DI,* difficult intubation; *ETT,* endotracheal tube.

The correct position of the cannula should be verified by syringe aspiration of air before initiating ventilation, and care must be taken to avoid kinking of the catheter at the insertion site. For these reasons, transtracheal jet ventilation is becoming an increasingly uncommon recommendation in these situations and the necessary equipment has largely been relegated to the operating room.

Surgical cricothyrotomy is an effective and relatively safe and rapid way to secure the airway in experienced hands.[71,72] The standard surgical cricothyrotomy technique utilizes a #11 scalpel to penetrate the skin, subcutaneous tissue, and cricothyroid membrane, followed by hemostat-aided dilation of the cricothyroid space before tube insertion. The "rapid four-step technique" uses a #20 scalpel to penetrate the cricothyroid membrane in one move, followed by caudal retraction of the cricoid cartilage and introduction of the tracheal tube.[73] The latter technique appears to be faster with a comparable complication rate. Ideally, these techniques should be reviewed and practiced on a model before use in the emergency setting.

Figure 38-16 is a difficult airway algorithm for emergency intubation situations.

Verification of Intratracheal Tube Placement and Position

A disastrous complication of endotracheal intubation is the unrecognized placement of the ETT in the esophagus.[74] Placement of the tube into a main stem bronchus is less likely to result in death or severe neurologic injury, but is still a risk for significant morbidity. Although misplacement might seem simple to avoid or to detect, even experienced clinicians are sometime fooled, especially following a difficult intubation (Fig. 38-17). At one time, airway management failures including unrecognized esophageal intubation were a small but significant cause of intraoperative mortality, morbidity, and liability claims. Minimum standards for monitoring established by the American Society of Anesthesiologists in 1986 included a directive that all

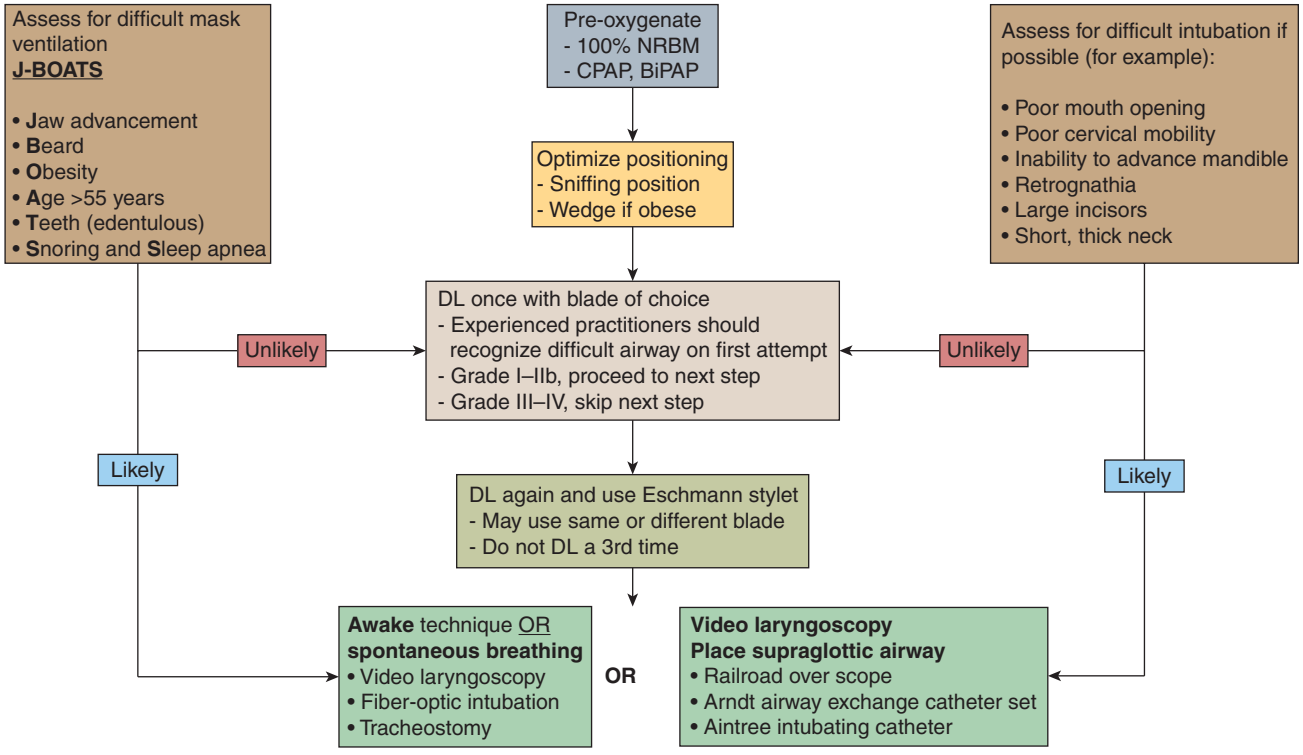

FIGURE 38-17 Incorporation of considerations for difficult ventilation and intubation. Help and airway equipment should be summoned early. When a "cannot intubate, cannot ventilate" situation occurs, or there is an inability to intubate by the means listed, the algorithm culminates in a surgical airway.

tracheal intubations be confirmed by the measurement of carbon dioxide in the exhaled gas (capnometry). This standard, likely complemented by the additional standard that ventilation be continuously monitored by capnometry during general anesthesia, has been associated with a reduction in the incidence of respiratory-related anesthesiology legal claims, and a greater than 50% relative reduction in claims related to esophageal intubation.[75] It is assumed that the incidence of esophageal intubation has also decreased, although this is not directly proven.

CONFIRMATION OF INTRATRACHEAL PLACEMENT

Clinical signs of intratracheal placement include direct observation of the tube entering the glottis, condensation in the ETT with exhalation, and observation and auscultation of the chest. Unfortunately, all clinical methods can and have failed. Inflation of the stomach results in some movement of the chest wall, creating sounds of air movement and some return of gas during the expiratory phase. Experimentally, placing a tube in the esophagus and attempting positive pressure ventilation actually results in some gas exchange because of diaphragmatic movement with consequent lung ventilation. This mechanism is thought to account for cases in which a patient survives for many minutes following an intubation that eventually proves to be esophageal. This is clearly the exception, however, and esophageal intubation that is unrecognized for more than a few minutes generally leads to adverse consequences.

Although observation of the tube entering the glottis would seem a fail-safe test, there are numerous reported cases of esophageal intubation in which the clinician stated that the cords were seen. This may occur because the tube itself obscures the view during placement and the tube may then enter the esophagus.

Multiple methods should be used to confirm intratracheal tube placement for each intubation attempt. These methods should include capnometry, which is now considered the "gold standard" for confirmation of intratracheal placement. Capnometry may fail to detect esophageal intubation if intubation follows a period of mask ventilation because of exhaled gas that has entered the stomach,[76–78] or if carbonated beverages are ingested shortly before intubation.[79] In these instances, however, the "exhaled" CO_2 levels will decrease to near zero as the gastric gas becomes diluted, whereas CO_2 will persist if the ETT is in the trachea. False negatives can occur if there is no CO_2 production or pulmonary blood flow, for example during cardiac arrest or after massive pulmonary embolism,[80] or after marked hyperventilation.[81]

Capnography, which refers to the graphical description of the exhaled CO_2 waveform, has become standard in operating rooms in the United States and much of the rest of the world. Portability and cost has limited the use of capnography in

areas where tracheal intubation is performed less frequently. Alternatives to capnography include portable capnometry using hand-held devices, or colorimetric CO_2 detectors. The latter contain an indicator (metacresol purple) that changes color from purple to yellow when it is exposed to CO_2. Colorimetric capnometry is comparable to capnography in differentiating tracheal from esophageal intubation.[82,83]

An alternative to exhaled CO_2 detection is to apply gentle suction to the in situ tube; if the tube is in the esophagus, the suction causes the pliable esophageal tissue to occlude the tube and no air can be aspirated. If the tube is in trachea, however, the semirigid walls prevent tube occlusion when suction is applied, and air can be obtained. Suction can be applied manually with a syringe, or more commonly with a self-inflating bulb ("bulb syringe"). This technique has good sensitivity for detection of esophageal intubation in elective and emergency settings,[84–88] but failures have been reported, particularly in pregnant subjects.[89] In addition, this technique has a relatively low specificity in detecting esophageal intubation compared to CO_2 detection, and incorrect identification of correct tube placement (bulb does not reinflate or air cannot be aspirated) has been reported in patients with morbid obesity, obstructive lung disease, copious secretions, and endobronchial intubation.[86,90,91] Thus, this technique cannot be advocated as a replacement for CO_2 detection, although it appears to have particular value in patients where CO_2 detection may fail, particularly during cardiac arrest.[86]

ASSESSING DEPTH OF INTRATRACHEAL PLACEMENT

The ETT tube can move as much as 5 cm during maximal cervical range of motion from flexion through extension; the tube moves cephalad as the neck extends.[92] The average distance from larynx to tracheal carina is 12 to 14 cm, and the top of the cuff of tracheal tubes in common use begins approximately 6 cm above the tip of the tube. Thus, the ETT should ideally be placed 5 ± 2 cm above the carina to ensure that the tip does not migrate endobronchially during neck flexion, or that the cuff does not herniate through the glottis with cervical extension.[92]

Endobronchial placement can result in atelectasis and hypoxemia,[93] and inadequate depth of placement has several possible adverse consequences. If the cuff is between the cords the seal will be inadequate risking both aspiration and inadequate ventilation. Adding more air to the cuff usually will not improve the seal as the cuff has a circular profile and the pentagonal shape of the glottic opening leaves the corners open. Inadequate depth of placement also may lead to serious long-term problems with subglottic stenosis. If the cuff is overinflated in the immediate subglottic region, mucosal ischemia may result. As this heals, scarring will lead to narrowing in the region of the cricoid. This problem is extremely difficult and is not readily surgically correctible.

Although auscultation of breath sounds is a reasonable adjunctive test for confirmation of ETT depth, the incidence of missed endobronchial intubation using auscultation alone may approach 10%.[93] In addition, auscultation does not detect ETTs that are either dangerously close to the carina, or positioned too high in the trachea.

The risk of endobronchial intubation can be minimized by: (a) observation of the ETT as it passes through the glottis; insertion of the tube no more than 3 to 4 cm after the upper end of the ETT cuff passes the glottis; (b) insertion of the tube no deeper than 20 cm at the teeth in adult females and 22 cm in adult males;[94] (c) palpation of the ETT cuff in the sternal notch.[95] These benchmarks will result in good placement in a high proportion of adults, but may fail at the extremes of stature, and are more likely to fail in women.[96]

Other methods for detecting endobronchial placement include chest radiography and fiber-optic bronchoscopy. Chest radiography confirms the position of the tube relative to the carina. Even if the carina is not visible, a tube tip overlying the third or fourth thoracic vertebral body with the head in the neutral position means the tube is in good position.[92] Fiber-optic bronchoscopy is as reliable as chest radiography and may be less expensive, but is not readily available at all intubation sites. Chest radiography has the added advantage of providing information about the lung fields as well.

PHARMACOLOGIC ADJUNCTS TO TRACHEAL INTUBATION

Except in cases of cardiac arrest, coma, or extreme neuromuscular weakness, tracheal intubation is facilitated by administration of pharmacologic agents, particularly if direct laryngoscopy is used. The goals of the administered drugs are threefold: (a) to provide optimal intubating conditions by minimizing muscular tone; (b) to ensure patient comfort during the procedure; and (c) to minimize physiologic responses to intubation, as follows.

The upper airway is richly innervated, resulting in a series of physiologic responses during intubation, including activation of both the sympathetic and parasympathetic nervous systems.[97] Bradycardia occasionally results, most commonly in children. In unanesthetized adults, blood pressure following intubation may reach levels as high as 250/150 mm Hg and the pulse will frequently rise to near maximal heart rates. Appropriate anesthesia will generally prevent these responses.

Direct laryngoscopy in the unanesthetized patient stimulates a strong gag reflex, and likewise insertion of a tube in the trachea will stimulate coughing. These reflexes are not only noxious for the patient, but can make tracheal intubation more challenging. Normal subjects develop a mild, clinically insignificant increase in lower-airway resistance following tracheal intubation,[98] and patients with reactive airways may develop marked bronchoconstriction. Bronchospasm following induction of general anesthesia accounts for a small but significant proportion of perioperative morbidity; notably, many cases of severe intraoperative

bronchospasm occur in patients without previously diagnosed reactive airways disease.[74,99–101] Ideally, tracheal intubation of patients with known asthma or other reactive airways disease should be preceded by administration of inhaled bronchodilators, in addition to anesthetic drugs with bronchodilating properties (e.g., propofol or ketamine, as discussed below).

Direct laryngoscopy causes mechanical obstruction of cerebral venous flow, and increases cerebral blood flow related to increased cerebral metabolic rate and transient increases in P_{CO_2}.[102,103] In the presence of preexisting intracranial pathology, these factors can lead to a rapid rise in intracranial pressure and carry a risk of herniation of brain contents. The increase in intracranial pressure can be blunted by the prior administration of anesthetic agents.

In addition to topical anesthetics (discussed earlier), the typical drugs administered to facilitate tracheal intubation are sedative-hypnotics, intravenous lidocaine, and neuromuscular blocking drugs ("muscle relaxants").

Sedative-Hypnotics

The most common sedative/hypnotics used as adjuncts to tracheal intubation are the short-acting barbiturates, propofol, etomidate, ketamine, and the benzodiazepines. With the exception of ketamine, these drugs are all γ-amino butyrate receptor agonists. They all have dose-dependent cardiovascular and/or respiratory depressant effects of varying degrees, and will result in loss of airway control at higher doses. Barbiturates, propofol, and etomidate are all very effective at reducing intracranial pressure; benzodiazepines are less potent in this regard, and ketamine can increase intracranial pressure.

SHORT-ACTING BARBITURATES

Sodium thiopental, the prototypical intravenous induction agent, is highly lipid soluble and thus rapidly enters the brain to produce unconsciousness. The return of consciousness is also rapid because of rapid redistribution of the drug. There is marked respiratory depression following injection with transient apnea the rule. Barbiturates cause vasodilation and myocardial depression, making them a poor choice for the hypovolemic patient. The typical induction dose of sodium thiopental is 3 to 5 mg/kg intravenously, with reduced doses given in the presence of cardiovascular instability, hypovolemia, and advanced age. Higher doses may be necessary if there is a history of heavy alcohol or tranquilizer use.

PROPOFOL

Propofol produces rapid loss of consciousness after bolus intravenous administration, with recovery beginning within 1 to 2 minutes. Propofol has cardiovascular depressant effects that are similar in magnitude to those seen with barbiturates, and its potency appears to be increased during hemorrhagic shock.[104] Thus, large doses of propofol should be avoided in patients with hypovolemia or significant cardiovascular depression for any reason. Propofol profoundly suppresses respiratory drive and airway reflexes, and has bronchodilating properties; thus, it is a useful agent for intubation of patients without concomitant administration of a neuromuscular blocking drug, or for intubation of patients with bronchospasm or reactive airways.[105] Propofol rarely causes myoclonus after bolus administration. Propofol is mixed in a lipid-based solution that supports bacterial growth; thus, propofol-containing syringes must be handled carefully and administered within a few hours of opening. Typical induction doses of propofol are 1 to 2.5 mg/kg intravenously, depending on age and cardiovascular stability.

ETOMIDATE

Etomidate has a rapid onset of action and a rapid recovery, has little effect on myocardial function, and has mild respiratory depressant effects. In addition, it has mild α_{2b}-adrenergic receptor agonist activity, which contributes to its lack of hypotensive effects compared to other induction agents.[106] Because of these favorable properties, etomidate has long been favored as an adjunct to tracheal intubation. Etomidate, however, can transiently suppress adrenal function by reversibly inhibiting 11β-hydroxylase, and prolonged infusions of etomidate in critically ill patients have been associated with severe suppression of adrenal cortical function and increased mortality.[107] Moreover, recent data suggest that even single doses of etomidate can result in prolonged adrenal suppression in critically ill patients, particularly those with sepsis.[108–110] This observation has generated considerable concern and debate about the advisability of using etomidate as an adjunct to tracheal intubation in critically ill patients, with some experts calling for caution if not complete abandonment of the use of etomidate in this patient population.[111,112] It remains unclear, however, if etomidate exerts an independent effect on mortality,[113] and a randomized, controlled trial comparing etomidate to ketamine for rapid sequence induction in acutely ill patients revealed no mortality difference between the two groups.[114] Further study of this issue will be necessary to definitively determine if etomidate should continue to be used as an intubation adjunct in critically ill patients; in the interim, it is reasonable to consider the use of alternative agents where feasible.

Etomidate also causes self-limited myoclonus relatively frequently. The latter may not be seen if etomidate is given in conjunction with a neuromuscular blocking drug. In addition, etomidate has proemetic effects and can causing a burning sensation when injected through a peripheral venous catheter, and these latter effects limit its use as an elective induction agent. The typical induction dose is 0.1 to 0.3 mg/kg intravenously; doses of 4 to 8 mg in an adult patient will typically produce deep sedation with maintenance of spontaneous ventilation.

KETAMINE

Ketamine is an *N*-methyl-D-aspartate-receptor antagonist, which gives it a different sedation and side effect profile in comparison with the other agents discussed here. Ketamine produces rapid loss of consciousness, although patients often appear awake because their eyes often remain open. Recovery from an intravenous dose of 2 mg/kg may take 10 to 15 minutes. Ketamine is a direct myocardial depressant[115,116] but clinically produces cardiovascular stimulation via release of catecholamines.[117] This sympathomimetic effect also gives ketamine bronchodilating properties.[118,119] Ketamine's major adverse effects include the potential for myocardial ischemia resulting from cardiovascular stimulation, increased intracranial pressure, and unpleasant dreams or hallucinations during the recovery phase. As noted above, ketamine appears to be equivalent if not superior to etomidate in safety when used for rapid sequence induction in acutely ill patients.[114] The typical induction dose of ketamine is 0.5 to 1 mg/kg, intravenously.

BENZODIAZEPINES

Midazolam is the benzodiazepine most widely used for hypnosis during intubation because of its rapid onset and short duration of action. It and the other benzodiazepines are more suited as sedative agents rather than for full induction of anesthesia, as the large doses of these drugs necessary to produce loss of consciousness result in prolonged sedation. In critically ill patients, however, smaller doses can result in loss of the airway, respiratory depression, and apnea; thus, titrated and closely monitored administration is recommended. Typical doses of midazolam for sedation during awake intubation are 0.5 to 2 mg intravenously.

Intravenous Lidocaine

High-dose intravenous lidocaine has general anesthetic effects, including a reduction of cerebral metabolic rate and a blunting of the hemodynamic response to intubation. Lidocaine 1.5 mg/kg given intravenously (before laryngoscopy) blunts the increase in intracranial pressure typically seen during intubation of patients with intracranial pathology.[120] Intravenous lidocaine also suppresses cough and bronchoconstriction during laryngoscopy, but only when given at doses of 1.5 mg/kg or greater and approximately 3 minutes before intubation.[121]

Neuromuscular Blocking Drugs

Although there are a wide variety of neuromuscular blocking drugs available, only two, succinylcholine and rocuronium, are sufficiently rapid in onset to be of value for emergency tracheal intubation. Succinylcholine's pharmacokinetic profile makes it the ideal drug for emergency tracheal intubation. Succinylcholine binds to the nicotinic receptor at the neuromuscular junction to cause depolarization of the end plate and, eventually, of surrounding fibers. This effect persists for several minutes, thus causing the muscle membrane to remain depolarized and refractory to further impulses. The diffuse depolarization of the muscles can be seen as generalized fasciculations. The usual intubating dose of 1 mg/kg of succinylcholine results in adequate intubating conditions in 90% of patients at 1 minute. The termination of drug action results from the metabolism of circulating succinylcholine by pseudocholinesterase with return of muscle strength in 3 to 5 minutes in most patients. Pseudocholinesterase deficiency occurs rarely, and results in prolonged action of succinylcholine.

Succinylcholine has a number of side effects, some of which are potentially lethal. Succinylcholine is a trigger agent for malignant hyperthermia, and should not be administered to malignant hyperthermia-susceptible patients. Administration of succinylcholine results in an efflux of intracellular potassium resulting in a clinically insignificant transient rise in serum potassium in most patients. In patients with central neurologic deficits, however, such as stroke, traumatic brain injury, encephalopathy, or spinal cord injury, or after peripheral denervation, succinylcholine can lead to massive potassium release and potassium levels over 10 mEq/L.[122,123] Similar responses are seen in burn patients beginning several days after the burn, in patients with myopathies, rhabdomyolysis, and after crush injuries.[122] The mechanism of hyperkalemia is in part related to extrajunctional proliferation of nicotinic receptors, but may also be related to direct muscle membrane damage during critical illness. The reported mortality with succinylcholine-induced hyperkalemia is more than 10%.[122] Succinylcholine is thus absolutely contraindicated more than several days to a week following a burn or new neurologic deficit. In addition, given the high incidence of critical illness-induced myopathy and neuropathy, succinylcholine should be avoided in patients who have been critically ill for a week or more.[124] Given the potential lethality of the hyperkalemic response after succinylcholine, an alternate agent should be used if there is any potential contraindication to succinylcholine.

Succinylcholine may also result in a transient increase in intracranial pressure, although this is probably not clinically significant and should not countermand the use of succinylcholine if rapid control of the airway is necessary.[125]

Rocuronium is a competitive antagonist of acetylcholine at the neuromuscular junction. Rocuronium is "nondepolarizing," does not result in muscle fasciculation or potassium release, and does not act as a trigger for malignant hyperthermia. Rocuronium at an intubating dose of approximately 1 mg/kg results in acceptable intubating conditions at 1 minute after administration, although intubation conditions are generally inferior to those achieved after succinylcholine.[126] Because rocuronium does not cause muscle fasciculation, which, in turn, can increase oxygen consumption, it may allow a longer apneic period before oxyhemoglobin desaturation compared

to succinylcholine.[127] Rocuronium's major drawback is that its duration of action is determined by hepatic and renal clearance, and has a variable range of 30 to 90 minutes. This makes rocuronium less than ideal for patients with difficult airways, as the option of allowing return of spontaneous ventilation should intubation and face-mask ventilation fail is not available, as it is for succinylcholine. Nonetheless, rocuronium is a reasonable alternative to succinylcholine for rapid sequence induction, particularly in patients who are at risk for complications from the latter agent.

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39

COMPLICATIONS OF TRANSLARYNGEAL INTUBATION

John L. Stauffer

The term *endotracheal intubation,* or *tracheal intubation,* broadly refers to the insertion of a definitive artificial airway into the trachea by either the translaryngeal or transtracheal route. *Translaryngeal intubation* (TLI), a more specific term, is transoral or transnasal intubation of the airway through the larynx. The term *endotracheal tube* (ETT), as opposed to *tracheostomy tube,* refers to a tube passed via the mouth or nose into the trachea.

Macewen is usually given credit for the first successful translaryngeal intubation. In a landmark paper in 1880, he described TLI in four patients for as long as 35 hours and reported complications, including cough, discomfort, tracheal mucosal congestion, and thickening of the vocal cords and posterior rim of the glottis.[1] The modern era of TLI began in the 1950s when it was used to manage respiratory failure from drug overdose[2,3] and polio,[4] and to provide an alternative to immediate tracheotomy when patients required prolonged ventilator support. As experience with TLI grew, so did knowledge of its complications and limitations. Comprehensive reviews of this subject appeared first in 1950[5] and frequently thereafter.[6–14]

TABLE 39-1: CLASSIFICATION OF COMPLICATIONS OF TRANSLARYNGEAL INTUBATION

- Temporal classification
  - Complications during endotracheal tube (ETT) placement
  - Complications while the ETT is in place
  - Complications during and after extubation
- Anatomic-physiologic classification
  - Nasal and paranasal
  - Oral
  - Pharyngeal
  - Laryngeal
  - Tracheal
  - Bronchial
  - Pulmonary
  - Miscellaneous
    - General
    - Esophageal
    - Gastric
    - Musculoskeletal
    - Neurologic
    - Physiologic
    - Other

TABLE 39-2: EARLY COMPLICATIONS OF TRANSLARYNGEAL INTUBATION AFTER 226 INTUBATIONS IN 143 ADULTS

Clinical Problem	No.	Percentage
Excessive cuff pressure to achieve seal by minimal occluding pressure technique[a]	42	19
Self-extubation	29	13
Inability to seal airway[b]	24	11
Right main-stem bronchus intubation	21	9
Aspiration[c]	17	8
Lip ulceration or cellulitis	16	7
Pharyngeal injury or bleeding	15	7
Mechanical problems with the ETT[d]	14	6
Difficulty suctioning via the ETT	12	5
Pain in nose, mouth, pharynx, or chest related to the ETT	8	4
Glottic edema	5	2
Oral mucous membrane injury	5	2
Tooth avulsion	4	2
Laryngospasm at the time of extubation	3	1
Pneumothorax	2	1
Esophageal intubation	2	1
Miscellaneous[e]	49	22
Total number of complications observed: 268		

[a]Defined arbitrarily as >25 mm Hg.

[b]Defined as leakage of air around the cuff because of a defect in the cuff or inadequate seal with cuff pressure <60 mm Hg.

[c]Defined as aspiration apparent clinically as an immediate result of the intubation attempt or after successful intubation.

[d]Includes partial dislodgment of the tube, length too short or too long, cuff laceration, and biting and occluding the tube.

[e]Includes nasal bleeding, which was recorded twenty-two times.

Source: Reprinted from *Am J Med*, Vol. 70, Stauffer JL, Olson DE, Petty TL. Complications and consequences of endotracheal intubation and tracheotomy: a prospective study of 150 critically ill adults, pages 65–76. Copyright © 1981, with permission from Elsevier.

This chapter provides a practical review of complications of TLI in critically ill adult patients, helps the reader understand the mechanisms underlying these adverse events, and illustrates how awareness of these complications may lead to their prevention, earlier recognition, and successful management. The chapter reviews important complications and consequences of TLI with standard ETTs that are encountered in the practice of adult critical care medicine. They are arranged according to the outline in Table 39-1. Complications of anesthetic intubations are occasionally cited to add awareness of complications that may also be seen in the critical care setting.

FREQUENCY OF COMPLICATIONS

The complication rate of TLI varies with the setting, the urgency of the procedure, the skill of the intubator, patient anatomy, and other factors. In the prehospital setting, the rate of complications of TLI ranges from 9.5[15] to 22.7%.[16] In the emergency department, 8%[17] to 38%[18] of patients undergoing TLI experience one or more complications.

In a prospective study in the adult critical care setting, Stauffer et al observed that 62% of all TLIs had one or more associated adverse events either during intubation or while the ETT was in place.[19] The mean number of complications per patient was 1.2. The most common early clinical problems were, in descending order of frequency, excessive cuff pressure required to seal the airway, self-extubation, inability to seal the airway, right main-stem bronchus intubation, and aspiration (Table 39-2). Other prospective studies have reported that 28% [20] to 39%[21] of TLIs in the intensive care units (ICUs) of academic centers were associated with one or more complications, many of which were life-threatening. The complication rate of emergency TLI by anesthesia residents in ICUs and wards of large tertiary academic health centers ranges from 4.2%[22] to 16.1%,[23] with endobronchial intubation, airway trauma, aspiration, and esophageal intubation leading the list of observed complications.

Little is known about the impact of TLI complications on utilization of health care resources. One report found a significant increase in health care costs and hospital length of stay resulting from tracheal injury from ETTs.[24]

COMPLICATIONS DURING ENDOTRACHEAL TUBE PLACEMENT

Nasal and Paranasal

Nasal intubation may inflict trauma to the nose, especially when it is performed urgently or without adequate premedication. A retrospective study of 105 nasotracheal intubations in the emergency department revealed a 26% rate of immediate complications, including epistaxis, emesis, and main-stem

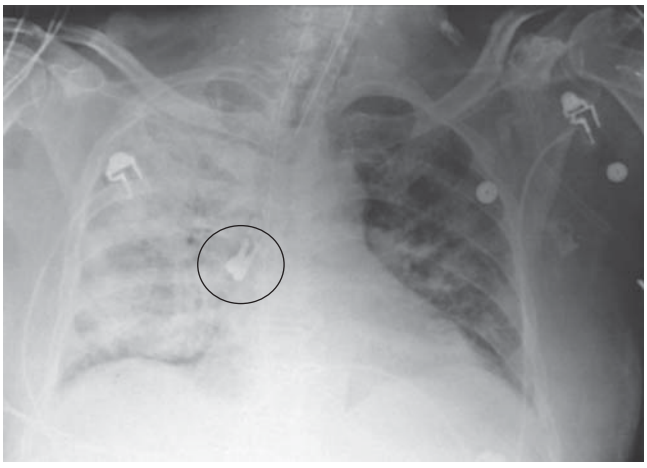

FIGURE 39-1 Chest radiograph showing an aspirated molar tooth in the right main bronchus of an intubated patient. Pneumonia in the right lung was also observed. (Reproduced, with permission, from Ostrinsky Y, Cohen Z. Tooth aspiration. *N Engl J Med.* 2006;354:e25. Copyright © Massachusetts Medical Society.)

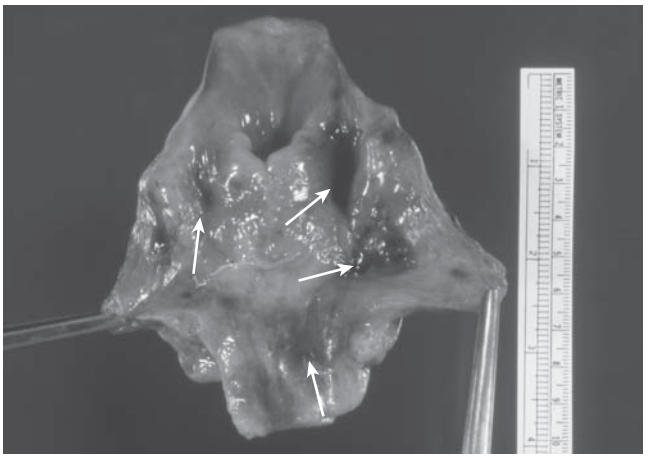

FIGURE 39-2 Autopsy specimen of larynx, hypopharynx, and upper esophagus opened posteriorly. The patient was an older man with chronic obstructive pulmonary disease (COPD) and acute respiratory failure in whom repeated forceful attempts at oral intubation by an inexperienced physician were not successful. The tip of the ETT traumatized the airway. Multiple areas of submucosal hemorrhage in the piriform sinuses and hypopharynx are evident (*arrows*).

bronchus intubation, and a 23% rate of late complications such as pneumonia, sinusitis, and sepsis.[25] Nasal bleeding complicated 54% of attempts at nasal intubation in an adult ICU.[19] Dislodgment of nasal turbinates[26] and nasal polyps[27] is rare. Intracranial placement of nasotracheal tubes, particularly in the setting of facial trauma, has also been reported.[28]

Oral

Overall, dental injury from TLI is uncommon, occurring in approximately 0.9% of prehospital TLIs,[29] 0.04%[30] to 0.13%[31] of anesthesia TLIs, and 0.2% of emergent nonoperating room TLIs.[22] In anesthetic intubations, loosening, luxation, or avulsion of teeth, damage to crowns and bridges, and crown or root fracture were the most commonly observed dental injuries in two large series.[30,31] Dental injury is the most common reason for anesthesia-related malpractice claims.[31] Avulsed teeth and dental appliances may be aspirated into the trachea or bronchi.[32] Figure 39-1 illustrates aspiration of a tooth in the setting of endotracheal intubation.[32] Difficult intubation, poor dentition, and inexperience of the intubator predispose to dental injury.[30] Oral mucous membrane injury has been observed in 1% to 2% of attempts at oral intubation.[19] Lip injury occasionally occurs from pressure exerted by the laryngoscope blade. Temporomandibular joint dislocation is a very rare complication of anesthetic orotracheal intubation.[33]

Pharyngeal

Lacerations, bleeding, contusions, excoriations, submucosal hemorrhage, and edema may result from intubation trauma to the nasopharynx, oropharynx, or hypopharynx. Oropharyngeal and hypopharyngeal injuries occur from trauma by the laryngoscope blade, ETT, stylet, or dislodged dental appliances.

Perforation of the posterior pharyngeal wall or hypopharynx is a particularly serious complication. It may result in mediastinal and subcutaneous emphysema, hematoma, upper airway obstruction, abscess formation,[34,35] mediastinitis, pneumothorax, pneumomediastinum,[36] pneumoperitoneum,[37] and even cardiac arrest.[8,38,39]

Hypopharyngeal injury from TLI has been the subject of a number of reports in both adults[8,37–42] and children.[43] Like oral injury, pharyngeal trauma from TLI occurs mainly in emergency settings and in the hands of inexperienced intubators, but it may occur in the anesthetic setting as well.[44] Piriform sinus laceration by forceful blind intubation may result in severe barotrauma with bilateral pneumothorax, pneumomediastinum, mediastinal abscess, and cardiac arrest.[40] Figure 39-2 illustrates hypopharyngeal contusions from repeated unsuccessful attempts at oral intubation by an inexperienced intubator.

Laryngeal

Reports of laryngeal complications that occur during ETT placement come mainly from the anesthesia literature. The larynx is the most common site of airway injury in anesthesia claims analysis.[45] Laryngeal injuries during ETT placement include glottic contusion, vocal cord hematoma and laceration, vocal process avulsion,[46] and arytenoid cartilage dislocation.[46,47] Vocal cord hematomas are reported to be more common on the left true vocal cord,[48] a finding that has been attributed to the fact that most intubators are right-handed.[10] Epiglottic hematoma from TLI is considered very rare.[49,50] Arytenoid dislocation from traumatic intubation occurs in up to 1.7%[47] of anesthetic intubations, leading to complications such as hoarseness and aspiration[47] and acute

respiratory failure.[51] Colice et al observed no cases of this complication in critical care intubations.[52]

Tracheal

Tracheal tears, reported variously as perforation,[53] laceration,[54] and rupture,[55–59] are rare complications of TLI. The large majority of cases occur in women and in patients older than 50 years of age,[60] and involve the posterior membranous portion of the trachea at or near the carina.[61] Causes of tracheal tears include emergency intubation, damage to the posterior membranous trachea by a stylet,[56] overinflation of the cuff,[43,56] excessive coughing or movement during intubation, and preexisting abnormalities of the trachea such as tracheomalacia.[55,60,61] Subcutaneous emphysema, pneumomediastinum, and respiratory distress are commonly seen after this type of tracheal injury.[55,56]

Malpositioning of the ETT in the trachea is a frequent consequence of emergency TLI in both the prehospital and the intensive care settings. In one report of prehospital airway management in a large urban region, malposition of the ETT was detected in 5.2% of 846 patients with attempted TLI in the field who were transported to a hospital.[62] In a prospective series of 271 emergency TLIs in critically ill adults, Schwartz et al observed nine (3.3%) cases in which the ETT tip was too high (>6 cm above the carina) and twenty-three (8.5%) cases in which it was too low (<2 cm from the carina), in addition to ten cases (3.7%) of right main-stem bronchus intubation.[63] Malpositioning of the ETT was significantly more common in women than in men.

Bronchial

Intubation of a main-stem bronchus is a potentially serious complication of intubation.[19,64,65] Right main-stem bronchus intubation has been reported in 10.7%[66] and 15.2%[67] of prehospital TLIs and in 3.7%[63] and 9.6%[64] of cases in prospective series of critical care intubations. In contrast, only 1.6% of anesthetic TLIs are complicated by endobronchial intubation.[68] Left main-stem bronchus intubation is very rare.[69] Potential complications of right main-stem bronchus intubation include hyperinflation of the right lung, right pneumothorax, atelectasis of part or the entire left lung, and impaired gas exchange. Figure 39-3 illustrates right main-stem bronchus intubation with the complication of atelectasis of the left lung.

Pulmonary

Pulmonary aspiration, which is usually defined as the appearance of new infiltrates on the chest radiograph immediately after intubation, has been observed in 2% to approximately 6% of emergent intubation procedures.[20–22,29,70] The prospective investigation of 297 TLIs in critically ill adults reported by Schwartz et al revealed twelve cases (4%) of new unexplained lung infiltrates attributed to aspiration and two cases

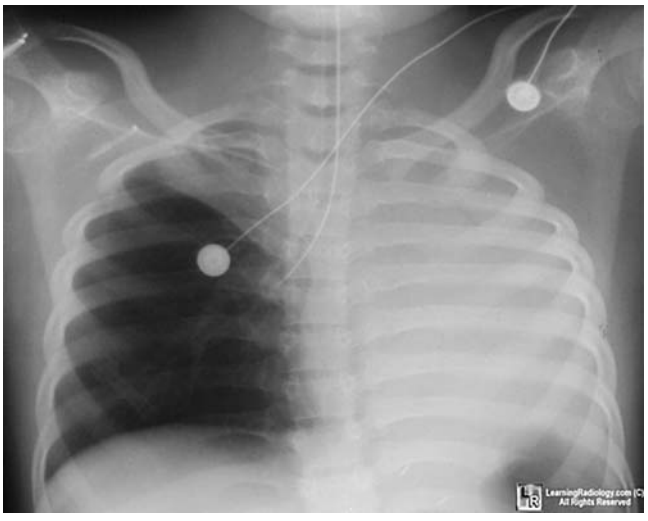

FIGURE 39-3 Chest radiograph showing the tip of the endotracheal tube in the right main-stem bronchus. This case of right endobronchial intubation is complicated by left lung atelectasis. (Reproduced, with permission, from William Herring MD, www.learningradiology.com. Published with permission from LearningRadiology.com.)

of pneumothorax (1%).[70] Aspiration of gastric contents was second only to failed intubation among all major complications of anesthetic airway management in a recent national survey in the United Kingdom.[71] Besides pneumothorax, other types of barotrauma may occasionally be seen. Failed intubation attempts may lead to worsening gas exchange, including severe hypoxemia.[72] Hypoxemia (oxyhemoglobin saturation <90%) has been reported in 18%[72] to 21%[73] of emergency TLIs. Hypoxemia was observed in 10.5% of TLIs when two or fewer intubation attempts were made, compared with 70% of TLIs requiring three or more attempts.[72] Bronchospasm was reported in three (0.8%) of 358 prehospital TLIs.[29] The bronchospasm response to TLI is rarely severe. Patients with asthma are at the highest risk.

Miscellaneous

GENERAL

Without adequate premedication, critically ill patients may experience pain in the upper airway, generalized discomfort, and anxiety during intubation. These important complications are difficult to assess objectively and are usually overlooked in large case reviews in the literature.

Bacteremia is an overlooked but potentially important consequence of both orotracheal and nasotracheal intubation.[74,75] Staphylococci and streptococci are the most common bacterial isolates.[75] The frequency of transient bacteremia following orotracheal intubation ranged from 3.2%[74] in elective TLI for anesthesia to 9% in urgent TLI performed in ICU patients.[76] In the latter series, only *Streptococcus* species were isolated immediately after TLI, and no patient had streptococcal bacteremia before or 1 hour after TLI. Bacteremia has been detected following 5.5%[77] to 16%[78] of nasotracheal intubations.

ESOPHAGEAL

An analysis of claims for airway injury from anesthesia showed that the esophagus was the third most common site of injury, and esophageal injuries were more severe than all other types of airway injury combined.[45] Inadvertent perforation of the posterior wall of the esophagus or pharynx by the ETT tip or rigid stylet is a rare but serious complication of TLI. Risk factors for this injury include inexperience of the operator, anatomic abnormalities, and difficult intubation, especially in the setting of cardiopulmonary resuscitation. The literature describing this complication is limited to single case reports[79,80] and small series. O'Neill et al described two cases of esophageal and pharyngeal perforation from elective anesthetic intubation, noting that this severe complication is not always limited to emergency or difficult intubations.[41] The potential consequences of esophageal perforation include subcutaneous emphysema, pneumomediastinum, pneumothorax, mediastinitis, and mediastinal abscess. Anterior esophageal perforation from TLI has not been reported.

Esophageal intubation is a common complication of TLI, particularly in emergency settings, and it has potentially severe consequences, including hypoxemia, regurgitation and aspiration of gastric contents, cardiac arrest, and irreversible hypoxic brain injury.[81–83] Esophageal intubation occurred in ten (6.7%) of 149 patients intubated in the prehospital setting in Germany [66] and in thirty-seven (5.4%) of 691 patients intubated in the prehospital setting in France.[29] It was reported in thirty-three (5.5%) of 603 patients intubated in an emergency department.[17] In tertiary care centers the frequency of esophageal intubation complicating emergency TLI ranges from 1.3% to 9.7%.[22,67,70,72]

GASTRIC

Gastric distension may result from esophageal intubation. Swallowing of foreign objects such as teeth and dental fixtures may also occur.[84] TLI may stimulate the gag reflex, leading to vomiting.

MUSCULOSKELETAL

Musculoskeletal complications during intubation are uncommon. Injuries to the cervical spine and cervical spinal cord during orotracheal intubation have been reported.[85]

NEUROLOGIC

Hypoxic brain injury may result from ineffective ventilation, oxygenation, or circulation as a result of failed intubation or mishaps such as esophageal intubation. Cervical spinal cord injury is reportedly a rare complication of anesthetic TLI.[86] Neck hyperextension during direct laryngoscopy to facilitate TLI in patients with restricted neck mobility or preexisting cervical spine instability has been proposed as a risk factor for cord injury,[87] but proof of this relationship has been difficult to establish.[88] Transient increases in intracranial pressure occur with TLI, particularly with endotracheal suctioning,[89] putting patients with head injury at risk for secondary brain injury.[90]

PHYSIOLOGIC

Cardiovascular. The cardiovascular pressor response to laryngoscopy and TLI includes transient and variable increases in heart rate and both systolic and diastolic blood pressure as a result of pharyngeal stimulation. The magnitude of these responses varies with the route and ease of TLI,[91] the use of anesthetic agents, concurrent medications, underlying cardiovascular status, and many other factors. In healthy individuals these cardiovascular responses are usually inconsequential, but complications may result when they are exaggerated[92] or occur in patients with hypertension, cardiac disease, or cerebrovascular disease.[93] Some, but not all, studies document a rise in plasma epinephrine and norepinephrine levels with TLI.[94–97]

The hypertensive response to nasotracheal intubation is greater than that to orotracheal intubation.[96] The hemodynamic response to orotracheal intubation is greater than that to insertion of the laryngeal-mask airway (LMA North America, San Diego, CA),[94] but less than that to insertion of the esophageal-tracheal Combitube™ (Covidien, Mansfield, MA).[94]

Hypotension may also occur during TLI. In the setting of rapid sequence intubation for general anesthesia, Istvan observed hypotension in 27% of 248 patients undergoing appendectomy.[98] Franklin et al observed that twenty-four (29%) of eighty-four patients requiring TLI in an emergency department developed life-threatening hypotension, which was significantly associated with the presence of chronic obstructive pulmonary disease, hypercapnia, and hypoxemic respiratory failure, but not with the administration of sedatives or paralyzing medications.[99] Griesdale et al observed severe hypotension in thirteen (9.6%) of 136 patients requiring TLI in an academic ICU.[21]

MacKenzie et al reported cardiac arrhythmias in 58% and 32% of nasal and oral anesthetic intubations, respectively.[100] Bradycardia was observed in 1.6% of emergency intubations in a large tertiary hospital when two or fewer intubation attempts were required versus 18.5% of intubations requiring three or more attempts.[72] Most cases with bradycardia were associated with severe hypoxemia (arterial oxyhemoglobin saturation [SpO_2] <70%) and half culminated in cardiac arrest.[72]

Other. TLI causes transient but significant increases in intraocular pressure.[101,102]

Cardiac Arrest and Mortality Rate of Translaryngeal Intubation

Cardiac arrest from emergency TLI is common. Mort reported cardiac arrest in sixty (2%) of 3035 critical care patients during emergency TLI in a tertiary care institution. Inadvertent esophageal intubation with profound

hypoxemia, regurgitation, aspiration, and bradycardia were highly associated risk factors for cardiac arrest.[103] Adnet described cardiac arrest as a complication of TLI in four (1.1%) of 358 patients with initial conditions other than cardiac arrest who required intubation in the prehospital setting.[29]

Schwartz et al reported a mortality rate of 0.85% during or within 30 minutes of emergency TLI in critical care patients without preexisting hypotension.[70] Biboulet et al prospectively recorded eleven anesthesia-related cardiac arrests in a series of 101,769 anesthetics performed from 1989 to 1995 (frequency: 1.1 per 10,000), and the mortality rate was 0.6 per 10,000.[104] All the cardiac arrests were considered avoidable.

COMPLICATIONS WHILE THE ENDOTRACHEAL TUBE IS IN PLACE

Nasal and Paranasal

NASAL COMPLICATIONS

In a prospective series of 379 patients with nasotracheal intubation, Holdgaard et al found inflammation and ulceration of the nostrils or nasal septum in 110 patients (29%) within 5 days of extubation.[105] Nasal bleeding occurred in 19% of patients and conchae fractures in 11%. Necrosis of the nasal alae may occur at the site of constant pressure on the nose by an upturned nasotracheal tube (Fig. 39-4).[106] This injury was seen in 4% of nasotracheal intubations,[107] and it may be accompanied by bacterial invasion with cellulitis.[108] Nasal septal ulceration is uncommonly seen.[19]

PARANASAL COMPLICATIONS

Sinus Effusions. Nasotracheal intubation for more than a few days commonly results in accumulation of fluid in the paranasal sinuses.[108–110] Fassoulaki and Pamouktsoglou found computed tomographic (CT) scan evidence of paranasal sinus fluid accumulation, opacification, or mucosal thickening in all of sixteen adult patients studied prospectively by the eighth day of nasotracheal intubation.[109] The maxillary and sphenoid sinuses each were affected in 87% of cases, followed by the ethmoid (50%) and frontal (12.5%) sinuses. Sinus effusions were unilateral and on the same side as the nasotracheal tube. Involvement of more than one sinus at a time was common.[109] Ultrasound evaluation has demonstrated sinus effusions in 30% of patients with nasotracheal intubation[108] and 63% of patients with orotracheal intubation.[110]

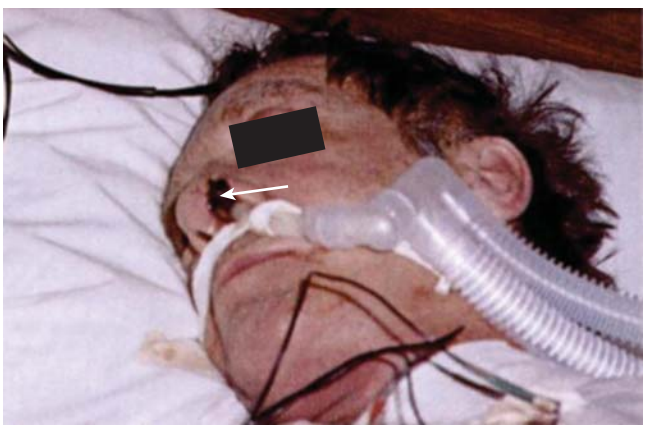

FIGURE 39-4 Hemorrhagic ulceration of the left ala nasi (*arrow*) as a result of pressure exerted by a previously upturned nasotracheal tube. This type of injury can be prevented by positioning the endotracheal tube so that its proximal end points straight down from the anterior naris. (Modified, with permission, from Zwillich and Pierson.[106])

Sinusitis. In 1982, Knodel and Beekman called attention to nasotracheal intubation as a cause of maxillary sinusitis with fever in mechanically ventilated patients.[111] Sinusitis has subsequently been recognized as a common and potentially serious complication of TLI, particularly nasotracheal intubation (see Chapter 47).[109,110,112–114] Sinusitis may also complicate orotracheal intubation[115] and the use of nasogastric tubes.

Severe complications of TLI-associated sinusitis include fever, bacteremia, pneumonia, sepsis, and meningitis. Van Zanten et al reported that sinusitis was discovered as the sole cause of fever in fifty-seven (16.2%) of 351 critically ill patients with orotracheal intubation who were evaluated for fever of unknown origin.[115] Gram-negative bacteria such as *Klebsiella* and *Enterobacter* species are commonly isolated from sinus aspirates in patients with sinusitis complicating nasotracheal intubation. Gram-positive bacteria, particularly *Staphylococcus aureus,* and fungi are also frequently isolated. Anaerobic infection, particularly with *Bacteroides* species, also occurs. Polymicrobial infections are common.

Middle Ear Effusions and Otitis. Middle ear effusion is an underrecognized but common complication of prolonged TLI, occurring in as many as half of patients.[116,117] Cavaliere et al observed that twenty-eight (80%) of thirty-five unconscious ICU patients had middle ear effusion, and there was a significant association with TLI and mechanical ventilation.[118] Lucks et al found middle ear effusions in twenty-three (29%) of seventy-eight adults with prolonged TLI, most of whom were intubated orally.[119] Tympanocentesis revealed organisms in 22% of patients with middle ear effusion, particularly *Pseudomonas aeruginosa, Klebsiella oxytoca,* and *Enterobacter cloacae,* typical of the gram-negative organisms colonizing the airway in patients with TLI.[118]

Oral

Ulceration or cellulitis of the lips was noted in 7% of TLIs in critically ill adults.[19] Lip edema, bleeding, and hemorrhagic crusts are very common during TLI as a result of pressure injury and abrasion by the orotracheal tube, oropharyngeal airway, tape, orogastric tube, or ETT holder.[19,120] Figure 39-5 illustrates lip injury from prolonged orotracheal intubation.[120]

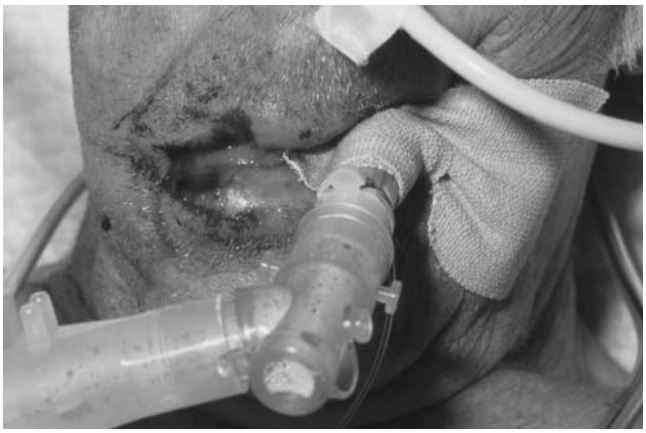

FIGURE 39-5 Ulceration of the right side of the upper and lower lip in a patient with prolonged orotracheal intubation. This type of injury can be prevented by proper securing of the endotracheal tube (ETT), minimizing the direct pressure transmitted to the mouth from the ETT and ventilator tubing, and regular oral examination during the period of translaryngeal intubation. (Modified, with permission, from Stauffer.[120])

Hanley et al reported reactivation of herpes simplex virus infections in 53% of patients with oral TLI longer than 48 hours, but clinical findings were noted in only half of these cases.[121] Figure 39-6 demonstrates herpes simplex virus type 1 complicating orotracheal intubation.[122] Dental injury, stomatitis, erosion of the hard palate, and soft-tissue injury to the tongue and oral mucosa may develop during TLI, and in some cases these complications are severe (Fig. 39-7).[19,123] They are reported to be more likely to occur in patients with concurrent use of oropharyngeal airways or those with rigid contracture of the jaw or propulsive movements of the tongue.[123]

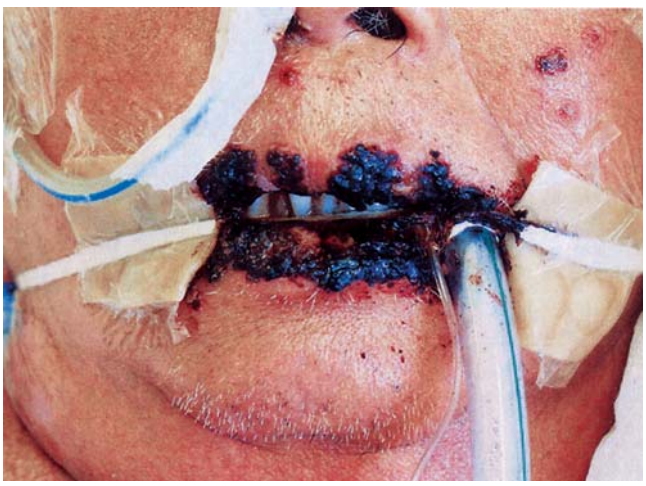

FIGURE 39-6 Severe hemorrhagic lesions on the lips of a patient with an oral endotracheal tube (ETT) in place. Herpes simplex virus type 1 (HSV-1) was identified by culture and polymerase chain reaction assay. Reactivation of HSV-1 was considered to be related to immunosuppression of critical illness and friction trauma of the lips by the ETT. (Reproduced, with permission, from Tang JW, Chan PKS. Herpes labialis. *N Engl J Med.* 2007;357:1855. Copyright © Massachusetts Medical Society.)

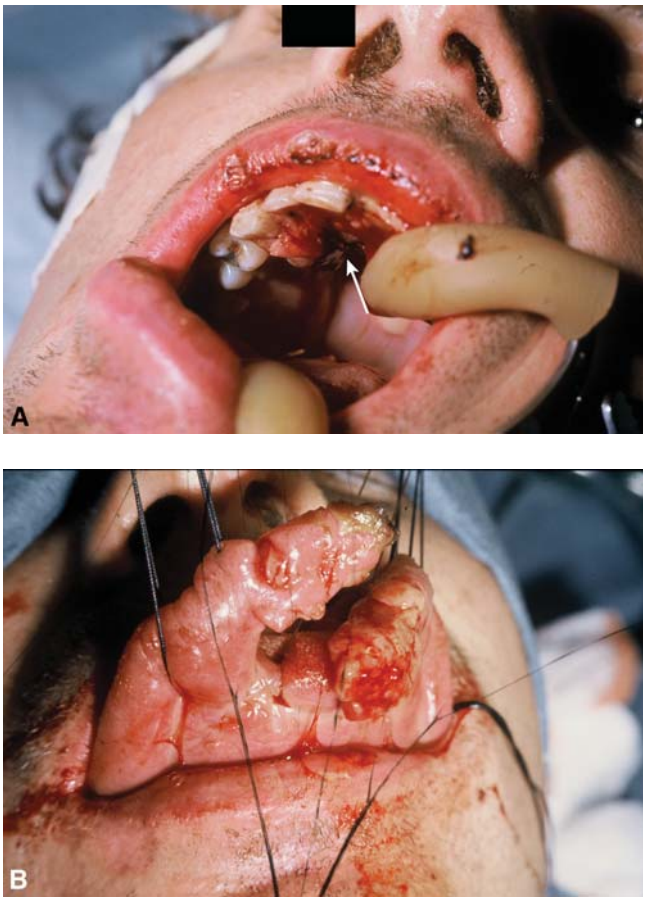

FIGURE 39-7 Severe injury to the mouth may occur during translaryngeal intubation because of pressure-induced necrosis. This patient was a young man who was intubated because of status epilepticus and need to control the airway. Rigid contracture of the jaw occurred repeatedly while an oral pharyngeal airway was in place to prevent occlusion of the endotracheal tube by biting. Evidence of oral injury included erosion of the hard palate (*arrow*) by the oropharyngeal airway (**A**), and complete transection of the tongue, photographed at the time of surgical repair (**B**). (Modified, with permission, from Stauffer and Petty.[123])

Pharyngeal

Pharyngeal complications while an ETT is in place are uncommon.

Laryngeal

Laryngeal injury is the most common and potentially the most severe complication of TLI,[52,124–134] and fear of late laryngeal complications of TLI is cited as the primary reason for performing tracheotomy for long-term airway maintenance. The most common postmortem findings in the larynx after prolonged TLI are mucosal ulceration, edema, and submucosal hemorrhage (Table 39-3).[19,135] Figure 39-8 presents a schematic and illustrations of common TLI-induced laryngotracheal lesions. Figure 39-9 presents endoscopic views of

TABLE 39-3: COMMON AUTOPSY FINDINGS AFTER PROLONGED TRANSLARYNGEAL INTUBATION IN FORTY-ONE PATIENTS

	Mucosal					
	Mucosal Ulceration		Inflammation and/or Edema		Submucosal Hemorrhage	
Site	**No.**	**%**	**No.**	**%**	**No.**	**%**
Epiglottis	5	12	3	7	2	5
Glottis	21	51	12	29	5	12
Subglottis	5	12	1	2	3	7
Trachea, cuff site	6	15	16	39	3	7
Trachea, other site	2	5	20	49	3	7
Total	39	–	52	–	16	–

Source: Reprinted from *Am J Med*, Vol. 70, Stauffer JL, Olson DE, Petty TL. Complications and consequences of endotracheal intubation and tracheotomy: a prospective study of 150 critically ill adults, pages 65–76. Copyright © 1981, with permission from Elsevier.

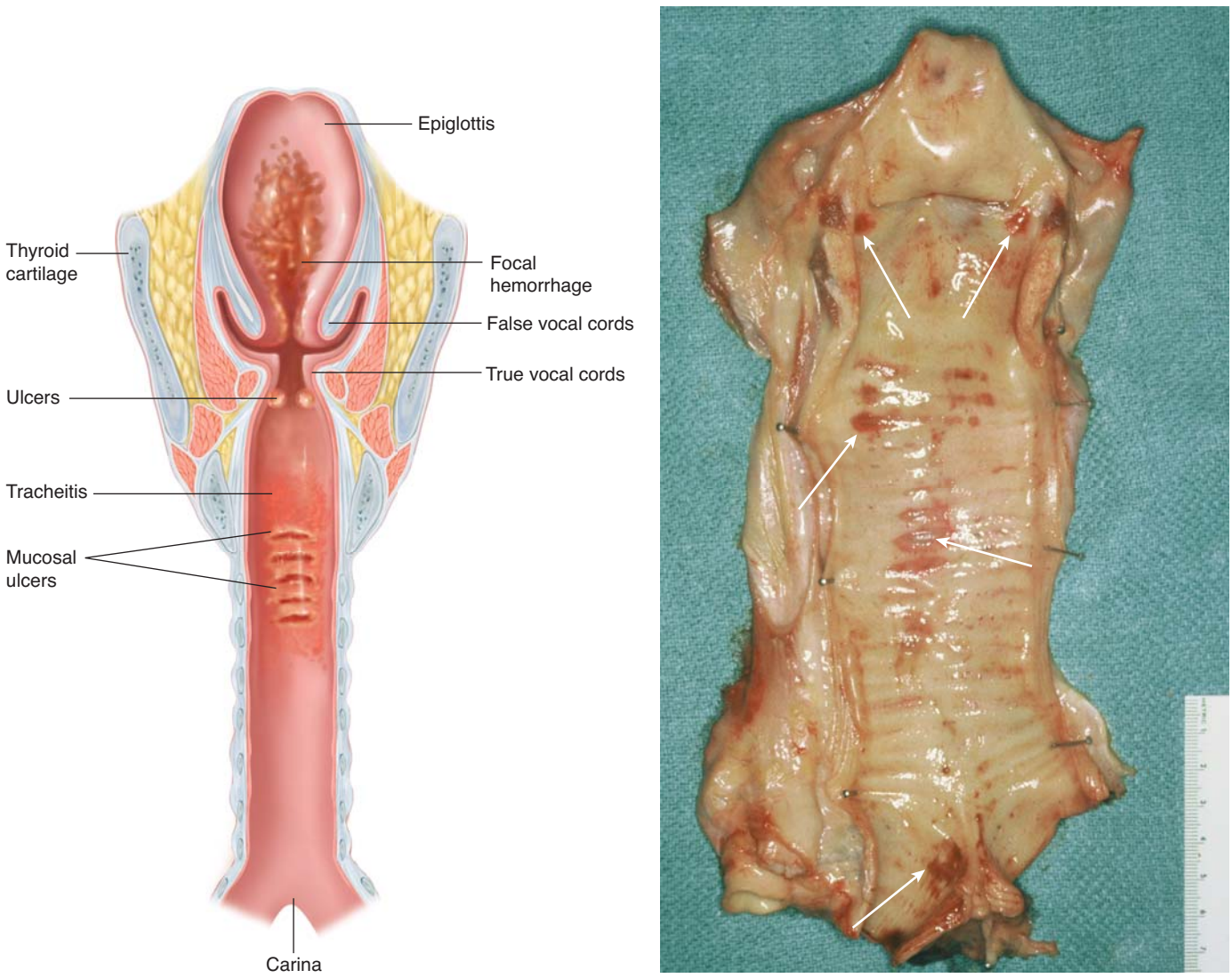

FIGURE 39-8 Schematic of the larynx and trachea opened posteriorly, illustrating common laryngotracheal lesions following translaryngeal intubation in the critical care setting (*left*). Autopsy specimen of larynx and trachea from an orally intubated patient showing hemorrhagic ulcers on the posterior aspect of the true vocal cords (*arrows*), patchy areas of mucosal hemorrhage on the anterior wall of the trachea from the subglottis to the carina (*arrows*), and a superficial mucosal ulcer at the site of the endotracheal tube cuff (*arrows*) (*right*). (Left panel modified, with permission, from Stauffer.[135])

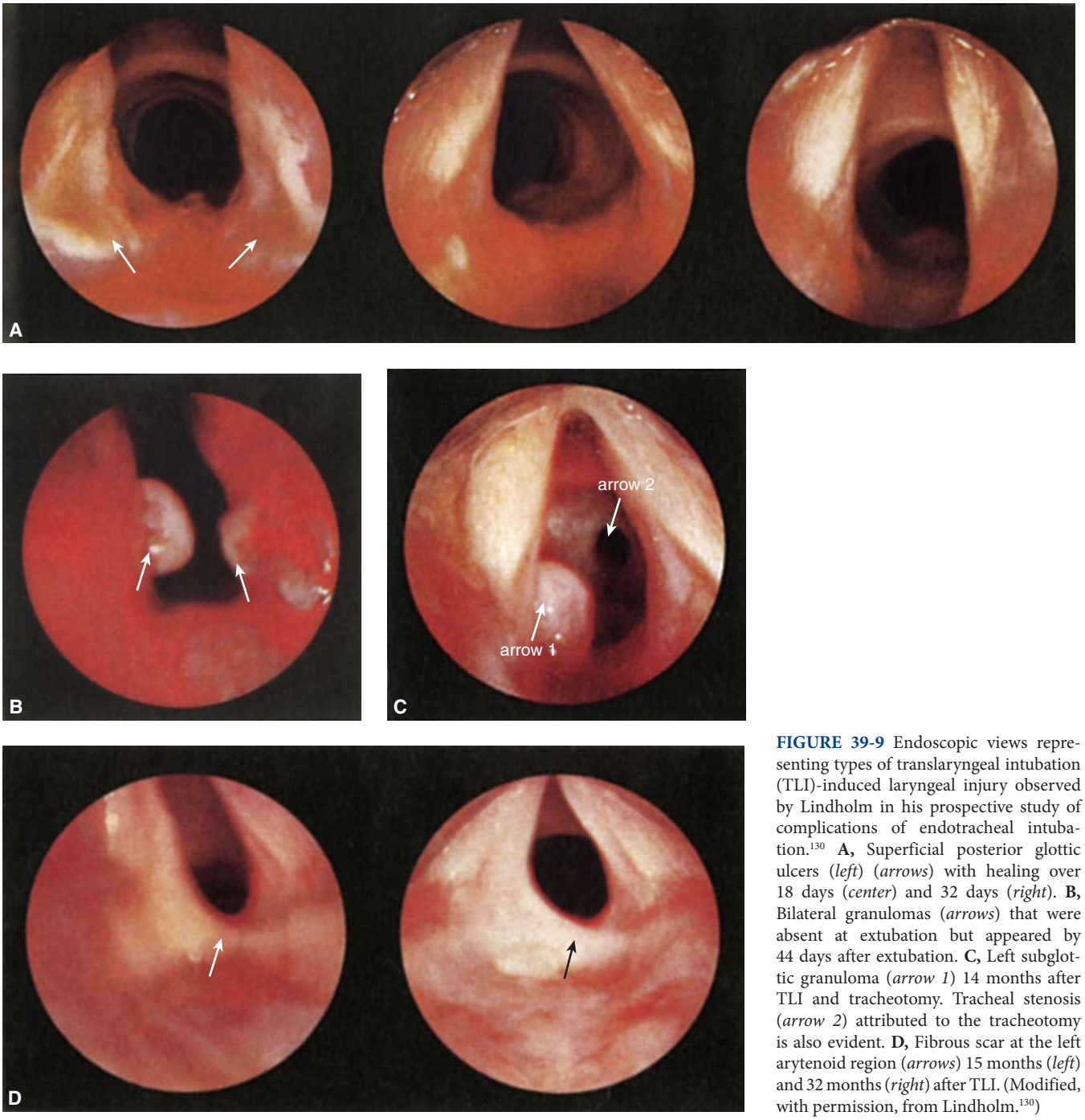

FIGURE 39-9 Endoscopic views representing types of translaryngeal intubation (TLI)-induced laryngeal injury observed by Lindholm in his prospective study of complications of endotracheal intubation.[130] **A,** Superficial posterior glottic ulcers (*left*) (*arrows*) with healing over 18 days (*center*) and 32 days (*right*). **B,** Bilateral granulomas (*arrows*) that were absent at extubation but appeared by 44 days after extubation. **C,** Left subglottic granuloma (*arrow 1*) 14 months after TLI and tracheotomy. Tracheal stenosis (*arrow 2*) attributed to the tracheotomy is also evident. **D,** Fibrous scar at the left arytenoid region (*arrows*) 15 months (*left*) and 32 months (*right*) after TLI. (Modified, with permission, from Lindholm.[130])

selected cases of glottic injury from TLI in Lindholm's comprehensive study.[130]

Experience with prolonged TLI in the 1970s showed moderate to severe laryngeal injury in 4.2%[136] to 7.2%[137] of cases. Kambic and Radsel found severe laryngeal injury in sixty-two (6.2%) of 1000 patients after anesthetic intubations, indicating that TLI for short periods and in a controlled setting was not without risk.[124] Most prospective studies reveal that serious permanent laryngeal injury from TLI is very uncommon.[19,129,138] All but a few TLI-induced laryngeal injuries tend to heal within 6 to 8 weeks and leave no permanent sequelae.[52,128,138,139]

SUPRAGLOTTIC INJURY

Mucosal ulceration, significant inflammation or edema, and submucosal hemorrhage at autopsy have been noted in 12%, 7%, and 5%, respectively, of patients with prolonged TLI (see Table 39-3).[19] Astrachan et al found severe supraglottic edema in 1% of TLIs.[107]

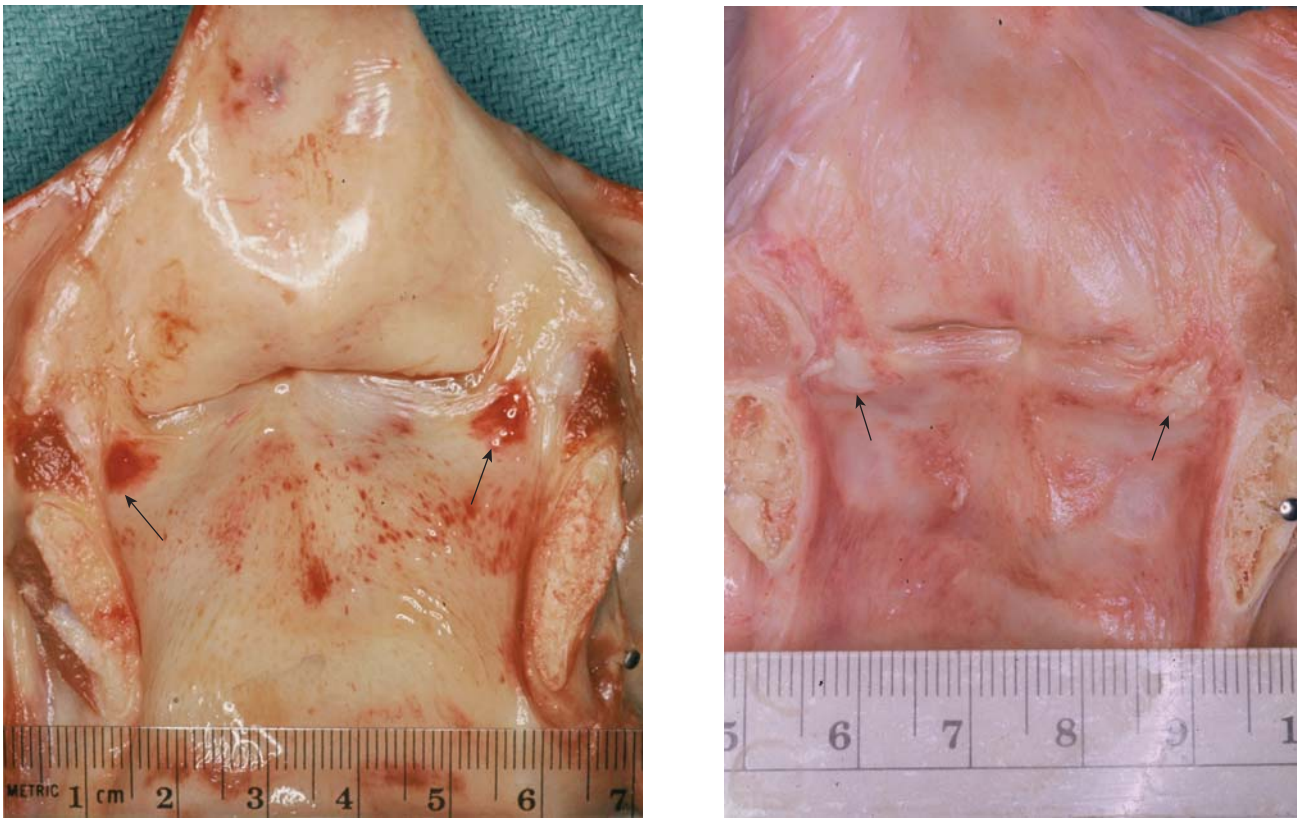

FIGURE 39-10 Autopsy specimens of larynx from two patients showing typical translaryngeal intubation-induced ulcers on the posterior true vocal cords. *Left:* Superficial hemorrhagic ulcers (*arrows*). Focal mucosal hemorrhage is also seen. *Right:* Deeper ulcers to the level of cartilage (*arrows*).

GLOTTIC INJURY

Laryngeal Ulceration. Ulceration of the posterior aspect of the true vocal cords and arytenoids has been reported in 51%[19] to 79%[130] of TLIs. This injury represents the most common significant complication of TLI.[47,108,131–134,136,139,140] Investigators first reported posterior laryngeal ulcers from TLI in the early 1950s.[141,142] Lindholm observed postmortem macroscopic ulceration or necrosis in the interarytenoid area, the medial side of the arytenoids, and the inner posterolateral area of the cricoid cartilage in 9%, 79%, and 68% of adults, respectively.[130] Laryngeal ulcers from TLI are symmetrical, triangular-shaped erosions of the posterior and medial aspects of the vocal processes (Fig. 39-10) and arytenoids and the posterolateral area of the cricoid cartilages.[47] They are typically 4 to 12 mm in diameter and 1 to 5 mm in depth, and they may penetrate into the cartilage[131] and the cricoarytenoid joints. The areas most vulnerable to ulceration by pressure from the shaft of the ETT are the posterior endolarynx, the arytenoids, the cricoarytenoid joints, and the interarytenoid space.[126] Using telelaryngoscopy, Deeb et al examined 142 adults who required tracheotomy because of failed extubation.[143] They observed that mucosal erosions and ulcerations, often with exposed cartilage, were common, and the most severe ulcers affected the intercartilaginous glottis and posterior subglottis, often with extensive granulation tissue. In some cases, the paired posterior ulcers may be large enough to join each other, producing a "horseshoe lesion."[108]

Glottic Edema and Inflammation. Varying degrees of hyperemia, edema, and inflammation of the glottic mucosa occur in practically all patients during TLI.[19,52,125,130,139,140] Stauffer et al found severe edema and inflammation at autopsy in 29% of patients following TLI, particularly in the posterior commissure area.[19] Figure 39-11 illustrates an example of intubation-related laryngeal edema.[144]

Vocal Cord Paresis and Paralysis. This complication during TLI presents after extubation and is discussed (see the section Early Complications After Extubation/Laryngeal/Vocal Cord Paresis and Paralysis).

Glottic Hemorrhage. The incidence of glottic hemorrhage developing after intubation is not known. Stauffer et al found evidence of submucosal hemorrhage in the glottis in 12% of TLI cases at autopsy (see Table 39-3).[19]

Granuloma Formation. The term *vocal fold granuloma* refers to growths of granulation tissue at the site of mucosal injury as a result of abnormal tissue healing. These lesions typically appear at the site of laryngeal ulceration and vary in size from 2 to 3 mm to more than 1 cm in diameter. They may be unilateral or bilateral.[130] Figures 39-9B and C and 39-12

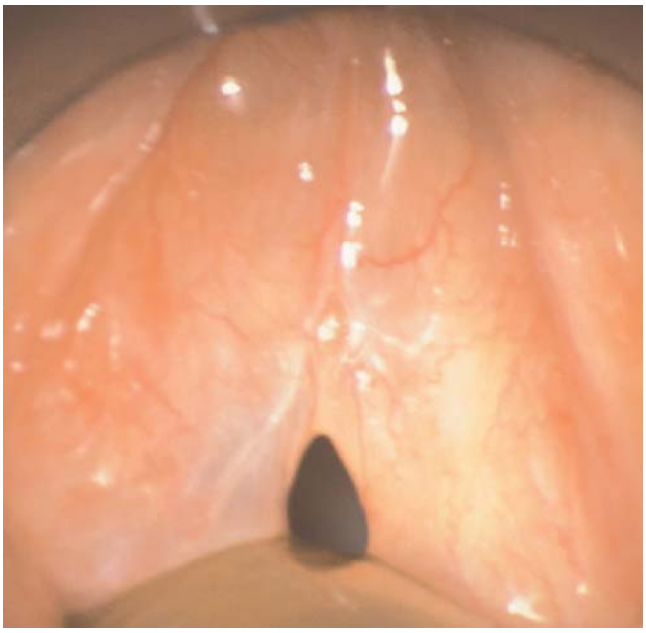

FIGURE 39-11 Laryngoscopic view of edema of the vocal folds following translaryngeal intubation. Some patients with this complication, which presents as postextubation stridor, may require reintubation. (Used, with permission, fromWittekamp.[144])

TABLE 39-4: TRACHEAL COMPLICATIONS WHILE THE ENDOTRACHEAL TUBE IS IN PLACE

Edema and inflammation
Ulceration of the mucosa and tracheal wall
Granuloma formation
Submucosal hemorrhage
Necrosis
Destruction of cartilage
Tracheal rupture and tracheal laceration
Tracheal dilation
Tracheomalacia
Tracheoesophageal fistula
Tracheoarterial fistula
Epithelial damage
Squamous metaplasia of tracheal epithelium
Reduction in mucociliary clearance
Airway colonization with bacteria
Pseudomembranous tracheitis
Miscellaneous
Too high or too low endotracheal tube position
Tracheobronchitis
Carina irritation, leading to cough and bucking
Suctioning complications

from the series of Lindholm et al,[130] present endoscopic views of small and large laryngeal granulomas following extubation. Laryngeal granulomas during TLI have been observed in up to 16%[128] of patients during TLI. Although usually associated with prolonged TLI, laryngeal granulomas may also occur after short-term intubation.[145,146] This topic is discussed below in "Late Complications After Extubation."

SUBGLOTTIC INJURY

Cricoid cartilage abscess results from bacterial invasion of the cricoid cartilage after pressure ulceration by the ETT.[10,108] Cricoid cartilage abscess may appear as long as 8 weeks after extubation and predispose to posterior glottic stenosis.[10]

Tracheal

Tracheal injury during TLI (Table 39-4) may occur at the site of the inflated cuff, at the level of the tip of the tracheal tube, and at the site of injury by suction catheters. Cuff-site injuries are the most common.[19]

EDEMA AND INFLAMMATION

Fiberoptic bronchoscopy during TLI often reveals varying degrees of tracheal inflammation and edema below the tip of the ETT. Mucosal edema or inflammation is found at autopsy in 39% of TLI patients at the cuff site and in 49% at other levels of the trachea (see Table 39-3).[19] Infiltrates of neutrophils and mononuclear cells are found in the mucosa and submucosa at the cuff site.[147]

TRACHEAL ULCERATION

The use of high-volume, low-pressure cuffs on ETTs has greatly reduced the frequency of cuff-site ulceration. Figure 39-8 (*right panel*) illustrates a small cuff-site ulcer with exposed cartilage on the anterior tracheal wall. Severe cuff-site ulcers that were common in the era of hard-cuff ETTs[148,149] are now rarely seen. Modern soft-cuff ETTs, however, do not completely protect the mucosa from injury. Stauffer et al reported tracheal mucosal ulceration at autopsy in 15% of patients with prolonged TLI with soft-cuff ETTs at the cuff site and in 5% at other tracheal sites (see Table 39-3).[19] Soft cuffs apply lateral pressure over a longer segment than hard cuffs, and pressure from overlapping folds of the fabric of soft cuffs may create channels in the tracheal mucosa.[150]

GRANULOMA FORMATION

Granulomas in the trachea are much less common than in the larynx following prolonged TLI, because tracheal ulceration is now much less common than laryngeal ulceration. All of the laryngotracheal granulomas observed by Lindholm were in the larynx.[130] Astrachan et al found tracheal granulomas in only 1% of patients.[107]

SUBMUCOSAL HEMORRHAGE

Submucosal hemorrhage was found at autopsy in 7% of patients at both the cuff and other tracheal sites (see Table 39-3).[19]

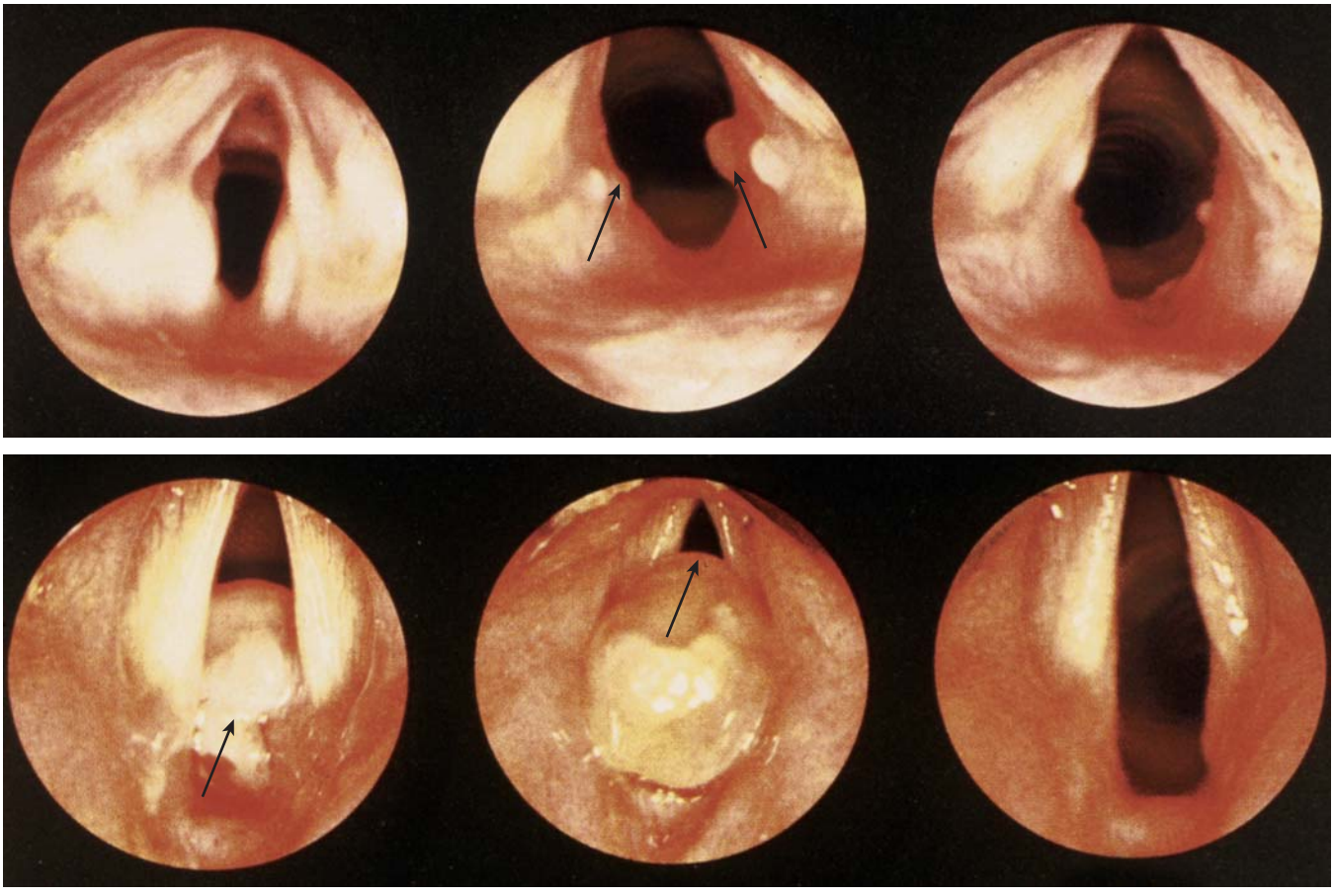

FIGURE 39-12 Laryngeal granulomas are growths of granulation tissue that may result from abnormal wound healing at the site of laryngeal ulcers. The *top panel* shows endoscopic views of the larynx 24 hours after extubation (*left view*), 20 days after extubation (*middle view*), and 34 days after extubation (*right view*). Small laryngeal granulomas (one on the left vocal fold and two on the right vocal fold) are evident in the middle view, and marked spontaneous improvement is observed 14 days later (*right view*). The *bottom panel* shows a very large polypoid laryngeal granuloma 5 months following short-term intubation (*left* and *middle views*) that caused respiratory difficulty and required surgical removal. Healing was achieved following surgery (*right view*). (Used, with permission, from Lindholm.[130])

TRACHEAL NECROSIS

Abbey et al reported a case of massive tracheal necrosis and suppuration after 10 days of TLI.[151] Possible risk factors include sepsis, hypotension, and elevated cuff pressures.

DESTRUCTION OF TRACHEAL CARTILAGE

Ulceration and eventual destruction of the C-shaped cartilaginous tracheal rings may occur as a result of sustained elevation of cuff pressure,[152] resulting in tracheal dilation, tracheomalacia, and injury to the adjacent great vessels and esophagus.

TRACHEAL RUPTURE AND TRACHEAL LACERATION

Tracheal laceration and tracheal rupture are rare complications of TLI during the period when the ETT is in place.

TRACHEAL DILATION

Dilation of the trachea, a sign of severe tracheal wall damage,[152] may appear even with soft-cuff ETTs during TLI or after extubation (See the section Late Complications After Extubation/Tracheal/Tracheal Dilation),[153] although this complication is mainly related to tracheotomy.[154] When tracheotomy is performed following long-term TLI, it may be difficult to determine whether the cuffed ETT or the cuffed tracheostomy tube was primarily responsible for the injury.[155]

TRACHEOMALACIA

Although tracheomalacia has been reported in patients with tracheotomy following TLI,[156] tracheomalacia after TLI alone is very rare when ETTs with high-volume, low-pressure cuffs are used.

TRACHEOESOPHAGEAL FISTULA

Cuff pressure–induced necrosis and erosion of the posterior membranous portion of the trachea and anterior wall of the

esophagus may result in tracheoesophageal fistula.[132,157,158] This rare complication of artificial airways has been mainly associated with tracheotomy,[132,159,160] but TLI, even with soft-cuff ETTs, is also a risk factor.[161] The concurrent use of a nasogastric tube could conceivably enhance the risk. Tracheoesophageal fistula may be silent or present with the appearance of gastric contents in tracheal secretions or with massive gastric distension.[162] After cuff deflation or extubation, it may present with cough following ingestion of food.[161]

TRACHEOARTERIAL FISTULA

Tracheoarterial fistula is a very rare complication associated with long-term tracheotomy. This usually fatal event has been attributed to high cuff inflation pressure leading to tracheal necrosis and erosion of the wall of the innominate artery. Only a few cases of tracheoarterial fistula during prolonged TLI have been reported.[163–165] In one of these cases, erosion into the innominate artery occurred at the level of the tip of the ETT, leading to fatal exsanguination on the fortieth day of TLI.[165] There is one report of tracheoinnominate artery fistula complicating short-term anesthetic orotracheal intubation.[166]

EPITHELIAL DAMAGE

Contact of the tracheal surface with an inflated cuff, ETT tip, or suction catheter results in loss of columnar tracheal epithelium cells and distortion of their cilia.[167–169] Regeneration of the ciliated surface and restoration of ciliary structure and function occurs within 2 weeks after extubation[167,168]

SQUAMOUS METAPLASIA OF THE TRACHEAL EPITHELIUM

Squamous metaplasia of the tracheal mucosa has been observed in dog models of intubation and in humans[147,170,171] and is attributed to abrasion of the mucosa by the inflated cuff or suction catheter. It may involve both surface and glandular epithelium adjacent to necrotic tracheal ulcers following prolonged TLI.[172]

REDUCTION IN MUCOCILIARY CLEARANCE

Tracheal injury at the cuff site depresses mucociliary clearance in both experimental animals and humans. Cuff inflation,[168] squamous metaplasia,[173] and loss of cilia[169] all contribute to impaired mucociliary transport during TLI.

AIRWAY COLONIZATION WITH BACTERIA

Colonization of the trachea with bacteria occurs in nearly all patients during TLI,[174–176] mainly from aspiration of secretions above the inflated ETT cuff and from infected ETT biofilm.[177] Gram-negative bacteria, particularly *Pseudomonas* species, have a particular tropism for the tracheobronchial mucosa. Bacterial colonization of the trachea during TLI is a risk factor for ventilator-associated pneumonia (VAP; see Chapter 46).[177,178] Ventilator-associated tracheobronchitis in intubated patients (fever, purulent lower airway secretions, positive sputum cultures, and absence of new or progressive lung infiltrates) is also increasingly recognized as an important clinical infection in the ICU.[179,180]

PSEUDOMEMBRANOUS TRACHEITIS

Pseudomembranous tracheitis, a rare and little known complication of TLI that has been attributed to ischemic cuff-site injury, was first reported in 1969.[131] Lins et al reported five cases and reviewed a total of twenty-four cases.[181] Tracheal epithelial injury from aspiration of gastric contents during TLI has been also cited as a cause of tracheal pseudomembrane formation.[182] Harbison et al reported a patient who presented with acute stridor from a fibrinous tracheal membrane 3 days after TLI lasting 48 hours.[183] Removal of the membrane by rigid bronchoscopy was curative. Deslee et al described one fatal case of fibrinous tracheal pseudomembrane from TLI.[184]

MISCELLANEOUS

Tracheobronchitis, protracted coughing, and consequences of ETT suctioning,[89,185] such as chest pain, hypoxemia, and cardiac arrhythmias, are sometimes observed.

Bronchial

Main-stem bronchus intubation (see Fig. 39-3) is mainly a complication during ETT placement, but it may also occur after intubation. In a retrospective series of 278 adult ICU patients with TLI, Kollef et al found that seven (2.5%) had inadvertent endobronchial ETT placement.[186]

Pulmonary

Pulmonary complications during TLI include aspiration, pneumonia, retained secretions, and atelectasis.

ASPIRATION

Aspiration of oropharyngeal secretions or gastric contents can be a serious complication while the ETT is in place.[35,177,187–189] Leakage of contaminated subglottic secretions around the ETT cuff into the lower airway increases the risk of VAP.[177] Estimates of the frequency of clinically significant aspiration during TLI range as high as 20%.[188] Aspiration of gastric contents during TLI may be less common than aspiration of oral and pharyngeal secretions, but data are sparse.

PNEUMONIA

VAP (see Chapter 46) is a common and serious threat to patients with artificial airways who require mechanical ventilation.[35,177,178,190] VAP occurs in as many as 28% of patients during the course of mechanical ventilation.[190] A large, retrospective, matched cohort study showed that VAP

developed in 9.3% of adult patients receiving mechanical ventilation for more than 24 hours.[191] The mortality rate of VAP ranges from 24% to 50%.[190] Mechanisms of pneumonia related to TLI are discussed (see the section Pathogenesis of Complications of Translaryngeal Intubation/Complications While the Endotracheal Tube Is in Place/Clinical Influences in Pulmonary Complications/Pneumonia and Tracheobronchitis).

RETAINED SECRETIONS

TLI may promote retention of bronchopulmonary secretions in the lung because of impaired cough performance.[192]

ATELECTASIS

Atelectasis may complicate TLI as a result of retained bronchopulmonary secretions, migration of the ETT into a main-stem bronchus, and other factors operative during mechanical ventilation.

Miscellaneous

GENERAL

Pain, Discomfort, and Psychological Impact. Certainly all who have cared for intubated patients recognize that anxiety, depression, feelings of isolation and withdrawal, and frustration with impaired communication are major psychological detriments related to TLI. The immediate and long-term psychological impact of TLI, however, has been the subject of only a few investigations. The psychological health of intubated patients is influenced not only by TLI, but also by noise, light, sleep deprivation, stresses of underlying illness, and other adverse influences in the ICU.[193] In a study that was not entirely limited to TLI patients, Swaiss and Badran recorded the following distressing complaints in interviews of adult patients 1 day after discharge from the ICU: anxiety (68%), discomfort from the ETT (60%), fear (54%), pain (52%), discomfort from the nasogastric tube (48%), difficulty in communicating (33%), dreams and hallucinations (31%), discomfort from physiotherapy (24%), noise (15%), insomnia (13%), and thirst (10%).[194]

Unplanned Extubation. "Unplanned extubation" is a broad categorical term that includes self-extubations and other extubations that are variously called "accidental," "deliberate," and "inadvertent" in the literature.[19,64,107,195–197] The overall frequency of unplanned extubations in critically ill adults is 8.6%.[197] In a prospective epidemiologic study of more than 5000 critically ill adults with TLI, self-extubation was the most common accident related to TLI.[198] Unplanned extubation is more likely to occur with oral than with nasal TLI.[199,200] In a large case series, Chevron et al reported that unplanned extubation was usually deliberate (87% of patients) and associated with insufficient sedation.[200] Unplanned extubation may occur from forces applied to the ETT by ventilator tubing, bedrails, patient motion, bucking, coughing, and forcing the tube forward with the tongue.

Coppolo and May reported a 12-month experience with self-extubation in adult ICU patients and noted self-extubation in 11%, cardiorespiratory sequelae of self-extubation in 31%, and need for reintubation in 31% of cases.[195] Others have documented reintubation rates following self-extubation as high as 74%.[201] Not surprisingly, the need for reintubation is much lower when self-extubation occurs during weaning from mechanical ventilation than during the period of full ventilator support.[202] Besides the need for reintubation, sequelae of unplanned extubation include longer ICU and hospital stays,[199,203,204] prolongation of mechanical ventilation,[203] and complications of TLI.[204]

Mechanical Complications. Various mechanical problems with ETTs occur in approximately 6% of intubations (Table 39-5),[19] and they may place patients at risk for serious complications and need for reintubation. Beckmann and Gillies examined a large database of voluntary incident reports from ICUs in Australia and New Zealand to determine the frequency of reintubations not related to accidental or self-extubation.[205] Among 143 such incidents, the reasons for reintubation included the following mechanical complications: tube malposition (twenty-five [17%]), tube securing or taping problems (twenty-four [16%]), pilot tube or cuff problem (twenty-three [16%]), and blocked or kinked

TABLE 39-5: MECHANICAL COMPLICATIONS WHILE THE ENDOTRACHEAL TUBE IS IN PLACE

- Tube dislocation
  - Endobronchial intubation
  - Self-extubation
- Tube obstruction
  - From tube and cuff problems
    - Kinking of nasotracheal tube
    - Overinflation of the cuff
    - Herniation of the cuff over the distal end of the tube
  - From external compression
    - Biting
    - Cuff overinflation
  - From impaction of the tip of the tube on the tracheal wall
  - From internal obstruction
    - Retained secretions
    - Blood and blood clots
    - Foreign body
    - Tumor
    - Anesthetic jelly
    - Nasal turbinate
    - Nasal polyp
- Disconnection from the ventilator
- Difficulty passing suction catheters
- Cuff problems
  - Leak
  - Rupture
  - Inability to seal the airway in spite of high cuff inflation pressures
- Malfunction of the one-way inflation valve
- Severance of the inflation tube or pilot balloon

airway (twenty [14%]), in addition to failed extubation (nineteen [14%]), inadequate preparation for extubation (eight [6%]), and other events (twenty-four [17%]).[205]

Dislocation or misplacement of an ETT may result in endobronchial intubation (see Fig. 39-3), carinal irritation by the ETT tip, high placement at the level of the upper trachea or hypopharynx, and self-extubation. Potential complications of high tube placement include injury to the larynx and adjacent structures including the recurrent laryngeal nerves, inability to seal the airway, leading to aspiration and inadequate ventilation, and subglottic stenosis. Kollef et al reported that twenty-two (8%) of 278 adult ICU patients had at least one significant ETT dislocation, with complications such as anoxic encephalopathy, hypoxemia, gastric aspiration, atelectasis, and pneumothorax.[186] An earlier prospective study revealed ETT malposition in five (8.2%) of sixty-one patients with prolonged TLI.[35]

If an ETT is positioned too low in the trachea, flexion of the neck may allow it to migrate into a main-stem bronchus, and conversely, if an ETT is positioned too high in the trachea, extension of the neck may allow it to migrate into the pharynx, potentially leading to unplanned extubation.[206] Conrardy et al showed that flexion of the neck moved the tip of the ETT an average of 1.9 cm toward the carina (range: 0 to 3.1 cm), and extension of the neck moved the ETT a similar distance away from the carina (range: 0.2 to 5.2 cm).[206] The route of intubation (nasal vs. oral) and cuff inflation or deflation did not affect tube movement.

The ETT may become partially or completely obstructed during placement or while it is in place by patient biting, retained secretions, blood or blood clots, foreign bodies, tumor, or other material. Obstruction from tube kinking or external compression by cuff overinflation is very rare. The tip of the ETT may impact on the tracheal mucosa leading to tube obstruction if the tube lacks a Murphy eye.[207]

ETT cuff problems during TLI include leak, rupture, and inability to seal the airway. Rashkin and Davis noted leaky cuffs during TLI in fifteen (25%) of their sixty-one patients.[35] Cuff rupture is now rarely observed. Inability to seal the airway by inflating or overinflating the cuff was the most common early clinical problem following TLI in one series.[19] Vyas et al checked cuff pressures in thirty-two patients intubated with ETTs with high-volume, low-pressure cuffs and found that 62% had elevated cuff pressures, some as high as 100 cm H_2O.[208] They performed a telephone survey that revealed that cuff pressure was checked regularly in only 17% of ICUs.

A wide variety of other mechanical problems have been encountered while the ETT is in place, including malfunction of the one-way inflation valve, inadvertent severance of the inflation tube or pilot balloon, disconnection from the ventilator, and difficulty passing a suction catheter through the ETT.

Malnutrition. TLI precludes effective swallowing and necessitates feeding by way of enteric tubes or intravenous lines. Chapter 41 discusses malnutrition in patients with TLI.

ESOPHAGEAL

Tracheoesophageal fistula may develop during TLI (see the section Complications While the Endotracheal Tube Is in Place/Tracheal/Tracheoesophageal Fistula).

GASTRIC

Gastric distension may occur if a tracheoesophageal fistula develops during TLI.[162]

MUSCULOSKELETAL AND NEUROLOGIC

Musculoskeletal and neurologic complications directly related to TLI while the ETT is in place have not been reported.

PHYSIOLOGIC

Compared with a normal upper airway, an ETT increases the resistance to airflow. Gal and Suratt demonstrated that TLI in healthy men increased total airways resistance from 0.99 cm H_2O/L/s to 2.25 cm H_2O/L/s, an increase of 178%.[209,210] Approximately half of this increase was attributed to the ETT itself, and the remainder to reflex bronchoconstriction.[209,210] TLI increases lower airway resistance slightly in normals without reactive airways disease by stimulation of irritant receptors, provoking bronchoconstriction,[211] and prophylactic treatment with bronchodilators has a protective effect.[212]

Airflow resistance during TLI increases as the length of the ETT increases or its diameter decreases.[213] Because they increase airflow resistance, ETTs increase the patient's work of breathing.[214] The work of breathing increases as the patient's minute ventilation increases and as the diameter of the ETT decreases.[214–216] At minute ventilation rates at or below 8 L/min, an ETT has little impact on the work of breathing.[215] Although the extra work of breathing imposed by an ETT is not clinically important in most patients, it may be clinically significant in patients with poor ventilatory function.

COMPLICATIONS DURING AND AFTER EXTUBATION

Complications During Extubation

Oral, nasal, pharyngeal, and laryngeal complications that developed while the ETT was in place may, of course, first be detected at extubation. Table 39-6 lists complications of TLI that Stauffer et al observed immediately after extubation in the ICU.[19] Hoarseness and sore throat are the most common symptoms at extubation. New complications occurring in the brief period of extubation are transient and uncommonly reported. They include discomfort, pain, and anxiety.[193] Significant increases in heart rate, blood pressure, and plasma catecholamine levels occur at extubation.[94] Nasal

TABLE 39-6: CLINICAL FINDINGS AT EXTUBATION IN A SERIES OF 81 PATIENTS

	No.	Percent (%)
History (obtained in sixty-nine patients)		
Symptoms related to TLI	59	86
No symptoms related to TLI	10	14
Specific symptoms		
Hoarseness	49	71
Sore throat	29	42
New cough	18	26
New sputum production	15	22
Hemoptysis	7	10
Other upper airway complaints	9	13
Physical examination (obtained in seventy-eight patients)		
Abnormal, related to TLI	42	54
Normal	36	46
Specific abnormalities		
Auscultatory abnormalities over the trachea	20	26
Lip ulcer or cellulitis	12	15
Pharyngeal bleeding or ulceration	7	9
Ulceration of the palate	6	8
Nasal bleeding	6	8
Oral mucous membrane bleeding, ulceration, or inflammation	5	6
Stridor	4	5
Nasal ulceration	2	3
Tooth avulsion	2	3
Tongue injury	2	3

Source: Reprinted from *Am J Med*, Vol. 70, Stauffer JL, Olson DE, Petty TL. Complications and consequences of endotracheal intubation and tracheotomy: a prospective study of 150 critically ill adults, pages 65–76. Copyright © 1981, with permission from Elsevier.

bleeding and dental injuries may occur during extubation, but such events are rarely reported.

Partial laryngeal obstruction at extubation is most often related to laryngeal edema (see the section Early Complications After Extubation/Laryngeal/Edema). Laryngeal injury and other complications during self-extubation of an ETT with an inflated cuff have not been adequately studied. Surprisingly, few patients appear to develop laryngeal complications following self-extubation. Pulmonary aspiration may occur if extubation and suctioning techniques are faulty. The requirement for reintubation soon after extubation is usually caused by laryngeal edema or respiratory failure. Difficult extubation should be anticipated in patients whose intubation was difficult.[217]

Early Complications After Extubation

This section discusses those complications of TLI that appear during roughly the first week after extubation. This period is dominated by symptoms of pharyngeal and laryngeal injury from TLI, including hoarseness, dysphonia, sore throat, cough, dysphagia, and odynophagia.

NASAL, PARANASAL, AND ORAL

There are no specific new complications that develop in this time interval, but complications that began earlier may of course be observed.

PHARYNGEAL

Postextubation sore throat has been reported in up to 42%[19] of ICU patients, similar to the frequency observed in patients who required TLI for general anesthesia.[218,219] Persistent and severe dysphagia after extubation following prolonged TLI should alert the clinician to the possibility of active infection in the posterior larynx.

There may be a temporary loss of the gag reflex after extubation. This was observed in 24% of patients who had direct laryngoscopy within 24 hours of extubation, supporting the notion that some patients have a sensory denervation of the pharynx and larynx from TLI.[52] Loss of upper airway reflexes increases the risk of aspiration.[52] We found pharyngeal bleeding or ulceration in 9% of patients at extubation (see Table 39-6),[19] although Colice et al did not report this complication after prolonged TLI.[52]

LARYNGEAL

Prospective studies using fiber-optic laryngoscopy within 24 hours of extubation in the ICU setting have revealed laryngeal injury in 73% to 94% of patients.[52,220,221] Colice et al performed direct fiber-optic laryngoscopy within 24 hours of extubation in eighty-two patients who had been intubated for 4 or more days (mean: 9.7 ± 0.6 days).[52] Seventy-seven (94%) of their patients had laryngeal injury (42% mild, 29% moderate, and 23% severe). Nearly all patients had posterior true vocal cord ulceration. Laryngeal edema was present in the patients with moderate to severe damage. Two patients had such large ulcers that the vocal cords could not be adducted, permitting free aspiration into the trachea.[52] Most patients who displayed initial laryngeal damage had complete resolution of laryngeal findings on laryngoscopy within 4 weeks after extubation.[52] Kastanos et al reported the following early laryngeal lesions in nineteen patients after extubation: true vocal cord granulomas in eight (42%), true vocal cord ulcerations in seven (37%), true vocal cord paresis in one (5%), and subglottic edema in one (5%).[128] Thomas et al performed fiber-optic endoscopy through the ETT just before extubation and found visible laryngeal pathology in 131 (88%) of 150 patients.[222] Table 39-7 summarizes the important laryngeal complications after TLI.

Hoarseness. In fifty-four adult male patients followed closely by Colice et al after TLI, thirty (56%) had significant hoarseness.[52] Holdgaard et al observed hoarseness in 42% of ICU patients following nasotracheal intubation.[105] Hoarseness following TLI usually resolves within a few days in most patients as laryngeal edema and inflammation subside and normal vocal cord adduction is restored.[125] In

TABLE 39-7: IMPORTANT EARLY AND LATE LARYNGEAL COMPLICATIONS AFTER EXTUBATION

Early
Hoarseness
Edema
Stridor
Muscle dysfunction
Vocal cord paresis and paralysis
Vocal cord hematoma
Posterior glottic infection and cricoid cartilage abscess
Late
Glottic and subglottic stenosis
Granulomas
Synechiae

some cases, transient postextubation hoarseness requires 7 to 10 days to resolve. Hoarseness persisting beyond 10 to 14 days suggests serious laryngeal injury such as granuloma formulation, vocal cord paresis or paralysis, or cricoarytenoid joint dysfunction, and requires the attention of an otolaryngologist–head and neck surgeon.

Edema. Postextubation laryngeal edema (see Fig. 39-11), an important complication of TLI, may occur at the supraglottic, glottic, or subglottic levels.[8] It presents with postextubation stridor and dyspnea and commonly precipitates the need for reintubation. Laryngeal edema is observed immediately after extubation in approximately 40% of patients after anesthetic intubation and in a roughly a third[223] to half of critical care patients.[52]

Laryngospasm. Postextubation laryngospasm in the recovery from general anesthesia is a well-known phenomenon. Although postextubation stridor in the ICU is sometimes attributed to laryngospasm, this complication after extubation of ICU patients is not well documented. Colice et al reported true laryngospasm in only one of eighty-two ICU patients within 24 hours of extubation.[52] True laryngospasm following extubation of the critically ill patient should be distinguished from laryngeal edema and other more common causes of postextubation stridor.

Stridor. A literature review by Wittekamp et al reported postextubation stridor in up to 30.2% of critically ill adults.[144] Many studies have investigated postextubation stridor.[19,52,224–226] Stridor occurring after extubation is usually inspiratory, indicating variable extrathoracic airway obstruction. Mackenzie et al observed severe stridor after prolonged TLI in 0.1% to 0.6% of patients.[224] This complication was found to be caused by vocal cord edema or subglottic stenosis, not laryngospasm. Symptoms of stridor appeared from 5 minutes to 4 hours after extubation.[224] Repeated intubations or tracheotomy were required in the majority of patients. Postextubation stridor should always indicate the possibility of subglottic stenosis at the level of the cricoid cartilage, a level that is particularly vulnerable to airway narrowing in children.

Muscle Dysfunction. Laryngeal incompetence is common after extubation and has been attributed to a sensory impairment or mechanical dysfunction of the larynx.[227] The frequency of aspiration secondary to laryngeal incompetence in postoperative patients ranges from 22% to 35%.[227,228] Inability of the vocal cords to adduct increases the risk of aspiration.[52,125]

Vocal Cord Paresis and Paralysis. Unilateral vocal cord paresis or paralysis is a serious but uncommon complication of TLI.[47,125,229,230] It presents in the early postextubation period as persistent hoarseness. Santos et al reported vocal cord immobility in sixteen (20%) of ninety-seven patients after extubation, and in half of these cases, a delayed presentation over a period of 1 to 10 weeks following extubation was observed.[139] Others have reported vocal cord paralysis in less than 1% of cases.[47] True bilateral vocal cord paralysis after TLI, which presents as severe stridor, is very rare.

Whited evaluated sixteen patients with vocal cord paresis or paralysis after TLI of 5 days or longer.[125] Common features in these patients were symmetry of vocal cord paresis or paralysis, edema and erythema of the arytenoids and posterior commissure, median or paramedian vocal cord positioning, late return of vocal cord abduction, a tendency for aspiration to occur, and spontaneous recovery in nearly all patients within 4 weeks.[125] Postextubation vocal cord paresis or paralysis may result from traumatic dislocation of the arytenoids,[231,232] cricoarytenoid joint arthritis, cuff inflation immediately below the vocal cords resulting in compression of the anterior branch of the recurrent laryngeal nerves,[233] or the mechanical effects of laryngeal edema and inflammation.[108] Bilateral vocal cord paralysis from intubation injury may present with hoarseness and recurrent aspiration[233] or with upper airway obstruction requiring immediate tracheotomy.

Vocal Cord Hematoma. Hematomas of the vocal cords that occur during placement of an ETT apparently resolve by the time of extubation. They were not seen after extubation in eighty-two patients studied by Colice et al.[52]

Posterior Glottic Infection and Cricoid Cartilage Abscess. Severe odynophagia or odynophonia after extubation should suggest the possibility of posterior glottic infection or cricoid cartilage abscess.[108] Posterior glottic infection may result in destruction of laryngeal cartilage and predispose to posterior glottic stenosis.[108]

TRACHEAL

In a prospective study of nineteen patients, Kastanos et al reported finding tracheal granulomas in six patients (31%) and cuff-site tracheitis in three (16%).[128] Tracheal

pseudomembranes leading to airway obstruction in the first few days after extubation have been the subject of individual case reports.[181,182]

BRONCHIAL

Specific bronchial complications of TLI in this time period have not been reported.

PULMONARY

Pulmonary aspiration may occur with laryngeal incompetence after extubation.[52,125,227] Pulmonary aspiration was observed after extubation in two (2.4%) of eighty-two patients after prolonged TLI in the series of Colice et al.[52] This finding was attributed to vocal cord dysfunction and temporary loss of sensorimotor function of the larynx and pharynx.[52] Burgess et al observed aspiration of swallowed contrast material in 33% of surgical patients immediately after extubation.[227] Endoscopic evaluation of swallowing after prolonged TLI has revealed aspiration in 14%[234] to 45%[235] of patients.

Postextubation negative pressure pulmonary edema secondary to laryngeal or tracheal obstruction following TLI and prolonged forceful inspiration has been described in small case series or individual case reports.[236,237]

MISCELLANEOUS

There are no significant miscellaneous complications of TLI in the early postextubation period.

Late Complications After Extubation

Late complications of TLI, those appearing in the weeks to months after extubation, are usually the result of abnormal airway mucosal healing with fibrosis or granuloma formation. Laryngeal stenosis is the most serious of these events (see discussion below).

NASAL AND PARANASAL

Nasal stricture and nasal septal perforation following prolonged nasotracheal intubation are rare.

ORAL

The only late oral complications of TLI are those related to initial dental or oral trauma.

PHARYNGEAL

In some patients, dysphagia may persist for several weeks. Residual problems related to pharyngeal perforation during ETT placement may persist late after extubation.

LARYNGEAL

Fortunately, late laryngeal complications of TLI (see Table 39-7) are uncommon because of the normal healing of laryngeal ulcers and other laryngeal injuries discussed above. Healing of laryngeal mucosal injury after extubation is usually complete within 8 to 12 weeks.[138] Nevertheless, abnormal healing may result in serious late laryngeal complications of TLI. Hoarseness that fails to improve for many weeks after extubation suggests abnormal healing with structural deformity of the larynx.[130]

Laryngeal Stenosis. Laryngeal stenosis following TLI may be supraglottic, glottic, or subglottic in location. Supraglottic stenosis is unusual. Glottic or subglottic stenosis is a serious but fortunately uncommon late complication of TLI. Although rarely severe, it represents the most notorious complication of TLI and has received extensive attention in the literature.[52,108,125–127,130,238–242] TLI is the most common cause of posterior glottic laryngeal stenosis.[242]

Most prospective studies of TLI document a very low rate of laryngeal stenosis.[19,128,130,138,243] The reported frequency of this complication ranges from 0% to 12%. When the results of seven prospective studies are combined, the overall incidence of laryngeal stenosis is 1.3% to 2.9% (Table 39-8), depending on whether the disproportionately higher number of cases in the Whited analysis is included. Colice found no cases of laryngeal stenosis in fifty-four prospectively studied survivors of prolonged TLI.[138] Elliott et al found that three (10%) of thirty survivors of the acute respiratory distress syndrome had laryngeal stenosis.[240] Laryngeal stenosis following TLI for general anesthesia is very rare.

Whited found posterior commissure fibrosis with stenosis in two (12.5%) of sixteen patients with TLI of 5 days or longer who were referred for evaluation of vocal cord paralysis or paresis.[125] Later, he reported frequencies of laryngeal stenosis of 6% in 200 patients with prolonged TLI[126] and 14% in fifty patients intubated for 11 days or longer.[127] This rate

TABLE 39-8: RATES OF LARYNGEAL STENOSIS AFTER PROLONGED TRANSLARYNGEAL INTUBATION IN PROSPECTIVE STUDIES

Year	Reference	Frequency of Laryngeal Stenosis
1969	Lindholm[130]	1/206 (0.5%)
1981	Stauffer et al[19]	2/27 (7.4%)
1982	Pecora and Seinige[243]	0/21 (0%)
1983	Kastanos et al[128]	2/19 (10.5%)
1983	Whited[126]	12/200 (6.0%)
1989	Colice[138]	0/54 (0%)
1994	Santos et al[139]	0/62 (0%)
	Total	17/589 (2.9%)[a]

[a]With the exception of the study by Whited, the rate of laryngeal stenosis is five of 389 (1.3%).

of laryngeal stenosis is higher than the rates in other prospective studies (see Table 39-8). In Whited's study, duration of TLI was the only independent variable assessed, and other potential risk factors for laryngeal stenosis were not evaluated.[126,127]

Lindholm noted only one case of laryngeal stenosis (subglottic) in 206 adult patients after TLI,[130] but patients in his series had a relatively short duration of intubation (mean: 32 hours). Stauffer et al found that two (7%) of twenty-seven patients evaluated for airway stenosis with tomograms after extubation had subglottic stenosis, defined as a 10% or greater reduction in transverse diameter of the trachea at the cricoid level.[19] Subglottic stenosis in adults following prolonged TLI appears to be much less common than in neonates and children, in whom this complication occurs with a frequency as high as 8%.[244]

Laryngeal Granuloma Formation. Granuloma formation is an important late complication of TLI, typically presenting as persistent hoarseness. Granulomas occur primarily in the larynx,[19,130,139,245] but rarely may occur in the trachea. Laryngeal granulomas (see Figs. 39-9 *B* and *C* and 39-12) are usually a few millimeters in diameter and rarely grow large enough to compromise the airway lumen. They may be sessile or pedunculated. As a manifestation of the healing process, albeit abnormal, granulomas may not appear until weeks after extubation. Laryngeal granulomas usually appear at the edges of posterior glottic ulcers, particularly those on the vocal processes and arytenoids. They usually resolve spontaneously, but surgical excision is sometimes required because of persistent hoarseness or airway compromise.[138]

The reported frequency of laryngeal granulomas after TLI is highly variable. After anesthetic intubation, they are extremely rare.[245] Colice et al found laryngeal granulomas in four (7%) of fifty-four patients carefully examined after TLI.[52] In that series, all patients with persistent hoarseness after TLI had laryngeal granulomas. Lindholm found postintubation granulomas in approximately one-third of adults after TLI, but not in any infants or children.[130] In the Lindholm series, only seven (2.6%) of 265 patients followed after extubation required surgical excision of laryngeal granulomas. The report of Santos et al of ninety-seven patients with prolonged TLI described laryngeal granulomas in 44%, and in 57% of these cases, the granulomas developed an average of 4 weeks after extubation.[139]

Synechia Formation. Synechia (membrane or web) formation at the glottis occurs in less than 1% of TLIs.[130,246] Synechia formation may "weld" the vocal cords together, leading to aphonia and airway obstruction.[8]

TRACHEAL

Tracheal Stenosis. Tracheal stenosis is an uncommon complication of TLI alone. Figure 39-13 illustrates endoscopic and clinical features of tracheal stenosis in a patient with dyspnea following TLI.[247] Stenosis of the trachea in adults surviving prolonged periods of mechanical ventilation is usually attributed to tracheotomy rather than TLI.[248] Severe tracheal stenosis following TLI alone is fortunately rare.[249] Santos et al prospectively observed no cases of tracheal stenosis in sixty-two adults surviving long-term TLI.[139] A retrospective review of laryngotracheal stenosis following TLI, tracheotomy, or both in 315 neurologic patients reported by Richard et al found tracheal stenosis in only one patient in the group of 172 patients (0.6%) with TLI only (mean duration: 17 days).[241] In contrast, twenty-five (19%) of 131 patients with TLI followed by tracheotomy had tracheal stenosis. Tracheal stenosis following tracheotomy usually occurs at the site of the tracheal stoma,[250] whereas this lesion is observed at the site of the inflated cuff when it follows TLI alone. Spiral computed tomography with multiplanar reconstruction and virtual bronchoscopy are highly accurate in diagnosing tracheal stenosis.[251]

Tracheal Dilation. Persistent tracheal dilation is caused by cartilaginous injury at the cuff site.[152–154] This complication was reported in 2% to 5% of patients following use of hard-cuff tracheostomy tubes,[153] and it is rarely seen following TLI with soft-cuff ETTs.

Tracheal Granuloma Formation. Tracheal granulomas occur mainly at the site of tracheal cuff-site ulcers. These are extremely rare in the era of soft-cuff ETTs.

BRONCHIAL

There are no late bronchial complications of TLI.

PULMONARY

There are no late primary pulmonary complications of TLI.

MISCELLANEOUS

There are no important late miscellaneous complications of TLI other than residual problems related to tracheoesophageal fistula.

PATHOGENESIS OF COMPLICATIONS OF TRANSLARYNGEAL INTUBATION

This section reviews the causes and mechanisms of selected complications of TLI. Most of the investigation of mechanisms of complications of TLI has focused on laryngeal injury and tracheal cuff-site injury.

Complications During Endotracheal Tube Placement

Complications during placement of an ETT often occur as a result of suboptimal technique stemming from poor judgment or inexperience. Failure to prepare the patient for

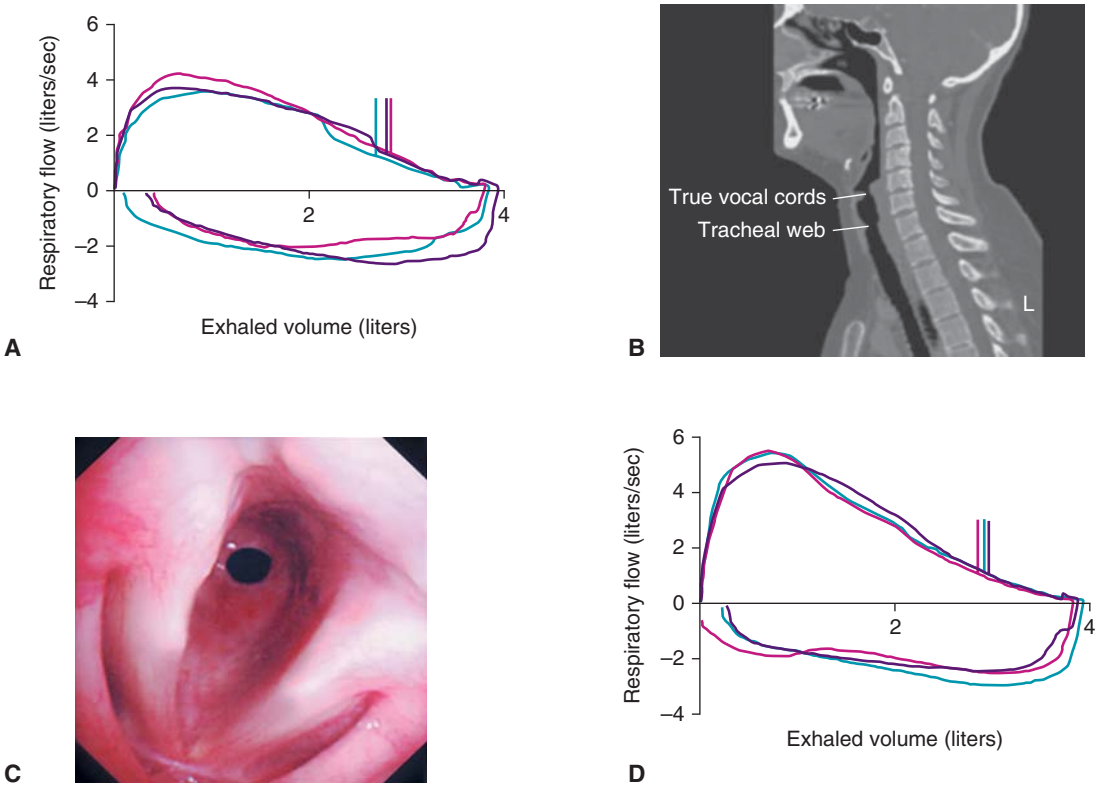

FIGURE 39-13 Tracheal stenosis is an important but uncommon complication of endotracheal intubation. Panel **C** illustrates subglottic tracheal stenosis in a 45-year-old woman with dyspnea who had required prolonged endotracheal intubation 8 years earlier. Computed tomography demonstrated tracheal narrowing 2.8 cm below the vocal cords (**B**), and a flow-volume loop revealed attenuated expiratory/inspiratory flow rates (**A**). Marked improvement in symptoms and stridor and improvement in flow rates (**D**) were reported after resection of the stenotic segment and tracheal dilation. (Reproduced, with permission, from Datta A, Cale A. Postoperative tracheal stenosis. *N Engl J Med.* 2010;362:e5, January 14, 2010. Copyright © Massachusetts Medical Society.)

intubation and equipment malfunction may also lead to complications. For example, during nasal intubation attempts, failure to prepare the nasal mucosa with a topical anesthetic or vasoconstrictor or failure to select the more patent side of the nose for intubation may result in nasal mucosal laceration or turbinate injury.

It is generally taught that complications of intubation are more likely to occur in emergency situations than in elective, controlled intubations, but there are few data to establish this with certainty. Wang et al found that failure of prehospital intubation attempts was significantly associated with a number of covariates by multivariate logistic regression, including the presence of clenched jaw/trismus, inability to pass the ETT past the vocal cords, intact gag reflex, and increased body weight.[252] Adnet et al found significant associations between the number of intubation attempts and the rate of mechanical and general complications of emergency prehospital TLI,[29] but Schwartz et al did not find this association in critical care intubation.[70] Supervision of TLI in teaching hospitals by senior physicians is associated with a lower rate of complications.[20]

Incorrect use of the laryngoscope may cause dental injury or pharyngeal laceration. Blind jamming of the ETT into the hypopharynx may cause serious soft-tissue injury. Failure to oxygenate and ventilate the patient before intubation may result in hypoxic brain injury. Deep insertion of the ETT far beyond the vocal cords may result in right main-stem bronchus intubation. These are only a few examples of how faulty intubation technique, inexperience, and poor judgment may lead to intubation complications.

Complications While the Endotracheal Tube Is in Place

Complications of TLI during this time interval depend upon anatomic, physiologic, ETT, and clinical influences.

ANATOMIC AND PHYSIOLOGIC INFLUENCES

Nasal and Paranasal Complications. Necrosis of the nasal alae and ulceration and perforation of the nasal septum result from ischemic necrosis secondary to pressure on these structures from the nasotracheal tube. Sinus effusions and sinusitis are caused by obstruction of the sinus ostia by the adjacent nasotracheal or nasogastric tube, edema, inflammation, or mucus plugging. Otitis and middle ear effusions are related to obstruction of the eustachian tube by the same influences.

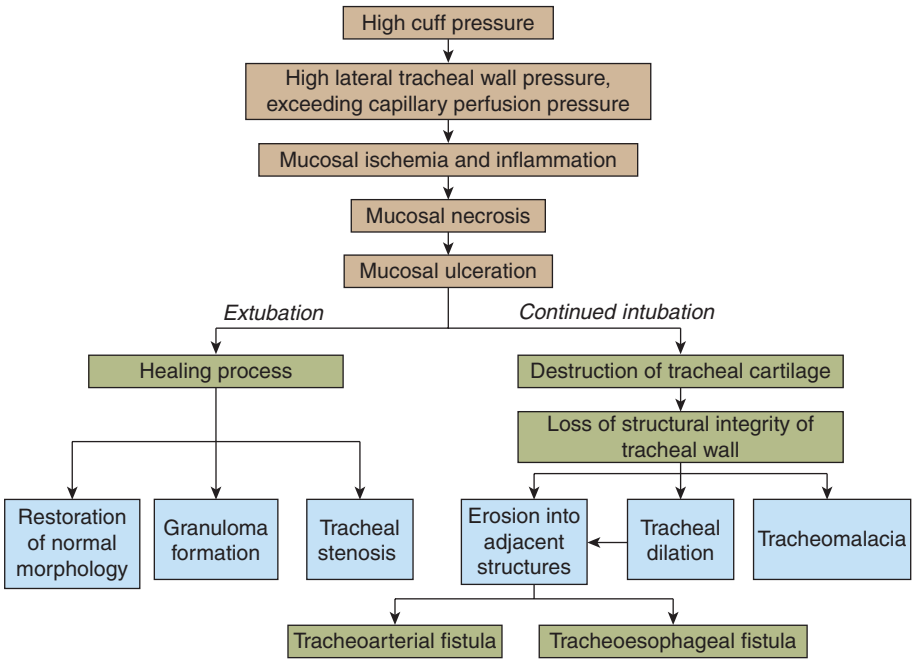

FIGURE 39-14 Outline of pathogenesis of tracheal injury at the site of the air-inflated cuff.

Laryngeal and Tracheal Complications. Serious laryngeal and tracheal injury during TLI is generally attributed to ischemic injury of the mucosal surface and deeper tissues by pressure exerted at vulnerable anatomic sites.[253] For example, ischemia occurs when the pressure exerted on the posterolateral wall of the larynx by the ETT or on the tracheal wall by the inflated cuff exceeds the capillary perfusion pressure in these areas. Necrosis, sloughing of the mucosa, and ulceration follow. Microscopically, inflammatory cell infiltrates and bacterial invasion are seen in the devitalized mucosal tissues. Eventually, destruction of soft tissues and cartilage in the wall of the larynx and trachea occur. In severe cases, there is loss of structural integrity of the tracheal wall, producing dilation or softening. If the patient survives, the healing process begins with one of three eventual outcomes: restoration of normal morphology, development of granulation tissue, or fibrosis. In the larynx, fibrosis results in glottic or subglottic stenosis, synechia formation, or cricoarytenoid joint fixation. In the trachea, fibrosis results in segmental stenosis.

The concept of tracheal mucosal injury by an air-filled cuff was established by studies performed in the 1960s and 1970s. It is outlined in Figure 39-14. Tracheal mucosal perfusion pressure is a critically important determinant of ischemic injury at the tracheal cuff site.[254–260] In humans, the tracheal capillary perfusion pressure is estimated to be 25 mm Hg (range: 22 to 32 mm Hg) or 34 cm H_2O (range: 30 to 44 cm H_2O).[258,259] The role of capillary perfusion pressure in the pathogenesis of tracheal cuff-site injury is discussed (see the section Clinical Influences in Tracheal Cuff-Site Injury).

Laryngeal and tracheal structures that are vulnerable to ETT pressure are the arytenoids, the posterior rim of the glottis, the subglottis, the cuff site, and the site of the tip of the ETT.[261] The posterior rim of the glottis is a contact point or fulcrum where the ETT abrades and applies constant pressure to the mucosa, leading to the risk of mucosal ischemia and ulceration.[47,239] Quartararo and Bishop have described the geometric shape of the glottis as a pentagon, which of course does not resemble the circular shape of the ETT.[48] This geometric mismatch creates several points of contact where ulceration is most likely to occur (Fig. 39-15).[48] An experimental ETT was once designed to fit the natural shape of the glottis.[262]

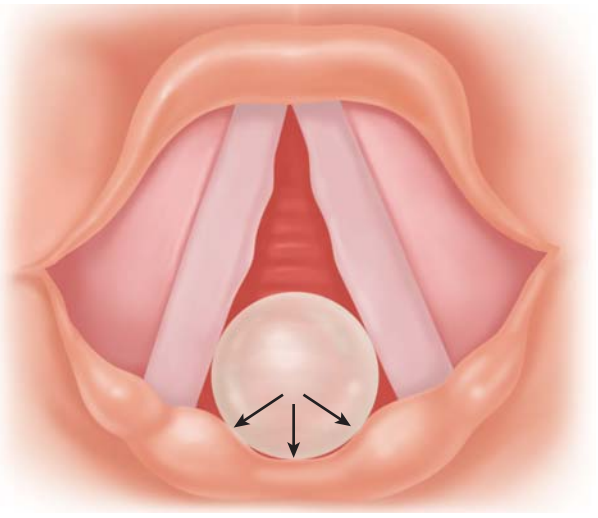

FIGURE 39-15 Schematic of an endotracheal tube (ETT) in the glottis, showing the circular shape of the ETT and the pentagonal shape of the glottis. The *arrows* indicate the points of maximum pressure on the posterior wall of the glottic opening. (This article was published in Semin Anesth, Vol. 9, Quartararo C, Bishop MJ. Complications of tracheal intubation: prevention and treatment, pages 19–27, Copyright © Elsevier.)

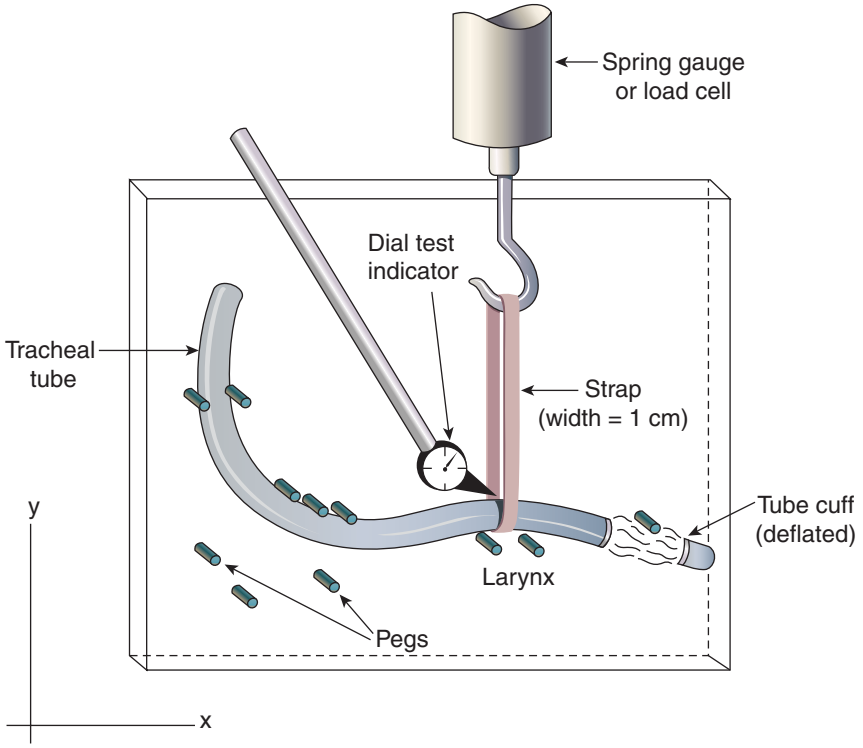

FIGURE 39-16 Method of estimating forces exerted on the posterior larynx by endotracheal tubes (ETTs). A pegboard is used to simulate the shape of the ETT in vivo. A gauge measures the force needed to barely lift the tube at the level of the larynx, thereby estimating pressure on the larynx. Modern polyvinyl chloride and silicone rubber tubes under simulated in vivo conditions exert forces on the larynx in the range of 162 to 265 g. (Modified, with permission, from Steen et al.[263])

The essential curvature of the ETT necessitates that force be directed posteriorly and laterally at the posterior glottic rim and cricoid ring.[253] Furthermore, the tongue muscles force the ETT posteriorly. Glottic pressure by the ETT has been estimated in both in vitro[263] (Fig. 39-16) and animal[264] studies to range as high as 200 to 400 mm Hg. In vitro studies of a variety of ETTs indicate that deforming forces from 230 to 1000 g are applied to the posterior laryngeal wall.[265] Pressure-induced ischemic injury of the posterior cricoid lamina and vocal processes of the arytenoids is accompanied by cricoid and arytenoid perichondritis and chondritis, which may heal with eventual fibrosis and scar contracture.[242]

Cricoarytenoid joint injury may occur while the ETT is in place but be recognized only after extubation. Postextubation symptoms of hoarseness and odynophagia along with the findings of malposition and no movement of the arytenoids suggest cricoarytenoid joint dysfunction. Paulsen et al reported that laxity of the cricoarytenoid joint capsule and large synovial folds are predisposing factors for cricoarytenoid joint trauma from TLI, including hemarthrosis.[266]

The cricoid ring, a completely circumferential ring that encircles the lower part of the larynx, is an important contact point with an ETT. Inflammation and edema of the laryngeal mucosa at the level of the cricoid ring narrow the airway lumen, making the subglottic area vulnerable to acute stenosis. Postextubation stridor is a manifestation of this phenomenon.[224] Experiments in dogs have demonstrated clearly that the posterior third of the cricoid cartilage is a major site of deep ulceration from pressure and abrasion by the ETT.[263] Ischemic necrosis in this area may be followed by bacterial invasion and abscess formation.[108] Simultaneous use of a nasogastric tube with an ETT could conceivably increase the risk of this complication.

Whited observed that the anterior wall of the trachea is a vulnerable site for tracheal injury from an ETT because of positioning of the cuff and tip of the tube.[261] Surprisingly few complications of TLI, however, are noted in the anterior wall of the trachea in these locations in the modern era of soft-cuff tubes.

ENDOTRACHEAL TUBE INFLUENCES

Physical Characteristics of an Endotracheal Tube. Technical standards for modern ETTs[267–269] establish the shape, size, and stiffness of an ETT, all of which influence TLI-induced airway injury. As previously discussed, the curved shape of an ETT invites pressure injury at the contact points with the airway, including the posterior larynx, cricoid cartilage, and tracheal cuff and tip sites.[130,270] The cross-sectional round shape of an ETT is also poorly suited for the shape of the glottis as noted above.[48,271] Large ETTs are more likely than small ones to cause pressure injury to the larynx[130,261,264] and the trachea. Large ETTs also cause more postextubation sore throat and hoarseness than do smaller tubes.[272] Modern

ETTs vary considerably in their stiffness and thermolability (ability to become less stiff at body temperature).[273]

Surface Characteristics. A slimy coating or *biofilm* may accumulate on the walls of the ETT during use, promoting the adherence of oral microorganisms and placing the patient at risk for VAP.[274,275] Use of silver-coated ETTs to suppress biofilm formation and bacterial colonization reduces the risk of VAP.[276]

Chemical Composition. The manufacture of modern ETTs follows strict guidelines set by Committee F29 on Anesthetic and Respiratory Equipment of the American Society for Testing and Materials.[267] Modern ETTs are composed of polyvinyl chloride, which is nontoxic, but chemical additives such as stabilizers, plasticizers, fillers, and pigments may incite inflammatory reactions in tissue.[268]

Cuff Characteristics. The value of cuffs on ETTs to seal the airway became apparent in the 1930s, but in the following decade investigators observed that high cuff inflation pressures could cause ischemia and sloughing of the tracheal mucosa.[277] Animal studies in the 1960s clarified the mechanisms of cuff-site tracheal injury,[148,278,279] and several groups of investigators described the critical role of high cuff inflation pressures in producing ischemic necrosis of the tracheal mucosa (see the section Clinical Influences in Tracheal Cuff-Site Injury/Cuff Pressure). Others later implicated high cuff inflation pressures in mucosal inflammation, tracheal dilation, destruction of tracheal cartilage leading to tracheal stenosis and tracheoesophageal fistula, and erosion of the tracheal mucosa and submucosa with loss of submucosal glands.[147] By the early 1970s, investigators established clearly that inflating the ETT cuff to pressures that exceeded tracheal capillary perfusion pressure could cause mucosal ischemia. Studies of the microcirculation of the rabbit trachea by Nordin et al revealed that the mucosa overlying the cartilaginous tracheal rings would become ischemic if hard cuffs were inflated to the point where lateral tracheal wall pressure exceeded 30 mm Hg.[257]

Besides intracuff pressures, other cuff characteristics may contribute to airway injury. Overlapping folds of cuff fabric may create channels that permit migration of fluid into the lung. This aspiration process is promoted by larger tubes, larger cuff diameters, stiffer cuff fabrics, and spontaneous breathing.[280] Bernhard et al demonstrated that modern ETTs display considerable variability in cuff characteristics such as diameter, thickness, compliance, shape, resting volume, and just-seal volume.[273,281] These various factors, as well as the size and shape of the trachea,[282] may affect the pressure–volume relationship of a given ETT cuff in vivo.[206,281]

CLINICAL INFLUENCES IN LARYNGEAL INJURY

Multiple factors may be important in the pathogenesis of laryngeal and tracheal cuff-site injury during TLI. Clinical investigation of the pathogenesis of airway injury from TLI has been complicated by difficulty in controlling these many factors while examining the effect of one variable on airway injury. Accordingly, the role of most of the specific clinical influences on laryngeal or tracheal injury discussed below remains unsettled.

Tube Size Relative to Laryngeal Size. The relationship of ETT size to laryngeal injury is controversial. Several prospective studies of critical care TLI have observed no relationship of laryngeal injury with ETT size.[19,52,283] Lindholm, however, concluded that large ETT size with respect to laryngeal size is an important determinant of laryngeal injury,[130] and Santos et al observed that laryngeal erythema, ulceration, and delayed true vocal cord immobility were related to ETT size.[139]

Laryngeal Abrasion. Abrasion of the laryngeal mucosa by movement at the interface between the ETT and the surface of the larynx would intuitively seem to be of great importance in the pathogenesis of laryngeal ulceration. This concept, however, has been difficult to prove. Some degree of abrasion of the laryngeal mucosa likely occurs whenever there is movement of the ETT or movement of the larynx. Breathing, swallowing, coughing, yawning, hiccupping, attempting phonation, and head and neck movements[206] are all plausible contributors to the abrasive action of the ETT on the laryngeal surface. ETT movement with cycling of the ventilator, suctioning the airway, and nursing care interventions may further contribute to mucosal abrasion.[126]

The role of laryngeal mucosal abrasion by movement of the ETT has been considered by a number of investigators.[19,52,126,129,130,283,284] The findings of El-Naggar et al suggested that friction between the ETT and laryngeal mucosa is an important factor in the pathogenesis of laryngeal injury.[129] Colice et al reported that the severity of laryngeal injury following extubation was significantly associated with neuromotor activity while the ETT was in place.[52] Patients with flaccid paralysis had milder degrees of injury.[52] Dunham and LaMonica found more laryngotracheal injury in patients with head and neck rigidity than in those with a nonrigid posture.[284]

Duration of Intubation. Since the early 1950s, clinicians and investigators have speculated, and often assumed, that duration of TLI is an important determinant of complications of TLI. This relationship obviously has an important influence on decisions about performing tracheotomy for long-term airway maintenance. It would seem obvious that a longer duration of TLI increases the risk of laryngeal (or tracheal) injury, but this relationship remains controversial because of conflicting data from a number of studies.

Early reports suggested that duration of TLI is important in the pathogenesis of laryngeal injury in critical care intubation.[131,285–287] Donnelly observed that the severity of histopathologic injury to the larynx at autopsy was related to the duration of TLI.[131] A retrospective study by Hedden et al came to the same conclusion.[285] Later observations by Whited[126,127] and by Supance et al[244] suggested that longer

periods of TLI increased the risk of laryngeal stenosis. Santos et al found significant relationships between duration of TLI and aspiration, laryngeal granulomas, and vocal cord immobility, but not laryngeal ulceration.[139] Two prospective studies reported a significant relationship between duration of TLI and postextubation stridor or requirement for reintubation.[225,288]

A number of prospective studies, however, have not been able to establish that duration of TLI is an important determinant of overall laryngeal injury.[19,35,52,128,138,283,284] Rashkin and Davis found no correlation between acute laryngotracheal injury and duration of TLI in sixty-one adult patients intubated for more than 3 days,[35] and Kastanos et al found no such relationship in nineteen patients intubated longer than 1 day.[128] In a prospective study of trauma patients, Dunham and LaMonica found no difference in laryngotracheal pathology between those patients undergoing early tracheotomy and those with 2 weeks of TLI.[284] Colice et al noted that serious laryngeal injuries could develop after only 1 to 3 days of TLI.[52] In fifty-four patients surviving after TLI, they found no relationship between the frequency of nonstenotic laryngeal complications and the duration of intubation.[52] Subsequently, Colice reported that prolonged TLI (>10 days) did not influence the rate of resolution of laryngeal injury.[138]

Some animal studies support the absence of a relationship between duration of TLI and laryngeal complications. Bishop et al[289] and Weymuller[290] reported that length of intubation was not related to the severity of laryngeal injury in dogs. In the dog model used by these investigators, TLI caused mucosal inflammation and erythema by 24 hours and loss of mucosal architecture within 1 week, but laryngeal damage remained relatively stable after 1 week.[289]

It can be concluded that studies in both animals and humans fail to provide convincing evidence of an association between duration of TLI and laryngeal complications. Most prospective clinical studies have not been able to prove that duration of TLI by itself is an important determinant of laryngeal injury.

Age. Clinical and autopsy findings in prospective studies suggest that age is not a significant determinant of overall laryngeal injury from TLI.[19,52,139]

Gender. The role of gender in laryngeal injury from TLI is unclear. Hedden et al reported in a retrospective study that laryngeal injury at autopsy following TLI was more severe in women than in men.[285] Postmortem observations in separate studies could not confirm this relationship.[19,131] Clinical studies have suggested that laryngeal stenosis following TLI is more common in women than in men.[242,270] Lindholm interpreted his observations to suggest that tube size relative to laryngeal size is an important determinant of laryngeal injury,[130] but Colice et al reported contrasting results.[52]

Hypotension. The pivotal role of laryngeal and tracheal capillary perfusion pressure in the pathogenesis of ETT-induced airway injury has led investigators to speculate that hypotension is an important risk factor for laryngeal injury during TLI. There are no convincing data, however, to support this concept.[52]

Route of Intubation. Two studies suggest that posterior laryngeal ulcers are more common with oral intubation than nasal intubation.[19,134] Possible reasons for this observation are that nasotracheal tubes are generally smaller than orotracheal tubes, they move less because they are stabilized by the walls of the nasal cavity, and they enter the glottis at a straighter angle of entry, thereby decreasing pressure on the posterior glottis. Another study, however, did not find less laryngeal injury with nasal intubation than oral intubation.[243]

Miscellaneous Factors. Underlying disease state, infection, corticosteroid therapy, head position, state of consciousness, gastric acid reflux, and many other factors have all been considered as possible determinants of laryngeal injury during TLI, but none of these factors have proven to have a contributing role. Several studies have suggested that laryngeal injury following TLI is more common in patients with diabetes mellitus.[143,270] Bacterial invasion of subglottic tissue injured by TLI may have a role in the pathogenesis of subglottic stenosis. In a rabbit model of subglottic ischemic injury from ETT cuff overinflation, Kil et al observed diffuse mucosal and submucosal inflammation, necrosis, and loss of surface epithelium.[291] Treatment with high-dose dexamethasone 1 hour before extubation and 6 hours after extubation had no effect on the histologic pattern of injury.

Posterior glottic stenosis may be more likely if TLI is followed by tracheotomy.[127,242] This association might occur because tracheotomy results in nonuse of the larynx, which might promote the formation of adhesions across ulcerated laryngeal surfaces.[242] Whited found a high statistical association between posterior laryngeal stenosis after TLI and subsequent tracheotomy, but cautioned that this might reflect selection bias rather than a true cause-and-effect relationship.[126,127] Colice et al also reported in their prospective study that the severity of laryngeal injury after TLI was associated with subsequent tracheotomy.[52]

In summary, it is likely that many factors contribute to laryngeal injury from TLI. Available data suggest that the mechanical force applied to the posterior larynx by the ETT is the most important risk factor for laryngeal injury. It is intuitive that abrasion of the laryngeal mucosa by movement at the interface with the ETT is an important risk factor, but supportive data are limited. Duration of TLI by itself has an uncertain role in the pathogenesis of laryngeal injury.

CLINICAL INFLUENCES IN LARYNGEAL GRANULOMA FORMATION

The prospective study of ninety-seven patients by Santos et al found significant associations between the early appearance of true vocal cord granulomas after extubation

and (a) duration of TLI, (b) subsequent tracheotomy, (c) use of a larger ETT in those patients who required tracheotomy, and (d) use of a nasogastric tube.[139] The delayed appearance of true vocal cord granulomas 2 to 10 weeks after extubation was significantly associated with subsequent tracheotomy and with use of a nasogastric tube. Lindholm also found a positive correlation between ETT diameter and the subsequent development of laryngeal granulomas.[130]

CLINICAL INFLUENCES IN TRACHEAL CUFF-SITE INJURY

Cuff Pressure. The important role of high cuff inflation pressures in the pathogenesis of tracheal cuff-site injury is now well established, based on studies of both TLI and tracheotomy.[148–150,254,256,258,260,278,279,292–296] The pioneering studies of Cooper and Grillo,[148,278,279] Grillo et al,[149] Ching and Nealon,[292] Ching et al,[293] and Nordin et al[257,259,294] established conclusively in both animal models and in humans that hard cuffs were more injurious to the tracheal mucosa than soft cuffs. These observations were confirmed by other investigators.[254,256,260] Figure 39-17 shows the critical role of cuff pressure in causing tracheal cuff-site injury in animal experiments performed by Cooper and Grillo.[148]

Intracuff pressure is transmitted laterally against the wall of the trachea (see Fig. 39-14). The intracuff pressure exceeds the pressure exerted against the tracheal wall (the lateral tracheal wall pressure) by a small amount in soft cuffs and by a greater amount in hard cuffs. Ischemia and eventual necrosis occur when the lateral tracheal wall pressure exceeds the capillary perfusion pressure of about 25 mm Hg,[258–260,294,295] as illustrated in Figure 39-18. Ischemia of the tracheal mucosa occurs in rabbits when the cuff inflation pressure exceeds 30 mm Hg.[257] Necrosis of the tracheal mucosa leads to sloughing and ulceration of the mucous membrane, exposing tracheal cartilage. Continued ischemia may be followed by partial or complete destruction of cartilaginous tracheal rings and loss of the structural integrity of the affected tracheal segment, leading to tracheal dilation (see Fig. 39-14).[153,154] Healing of the injured tracheal segment during any stage of this process may lead to a tight fibrous stricture (tracheal stenosis).

Modern soft-cuff ETTs transmit intracuff pressure to the tracheal wall, but not to the extent that hard-cuff ETTs do. Overinflation of soft cuffs, however, may cause high lateral tracheal wall pressures to develop, even to the point at which capillary perfusion pressure is exceeded.[258] In the clinical setting, it is important to note that variations in ETT cuff pressure are commonly observed after the ETT pressure is set to a safe level, so high pressures may develop periodically.[297] The amount of lateral tracheal wall pressure appears to be more important than the duration of intubation in producing tracheal damage.[259,296]

Cuff Design and Shape. The geometric shape of the cuff relative to the shape of the tracheal lumen has been implicated in tracheal cuff-site damage.[293,298] Asymmetric inflation of cuffs, leading to focal tracheal mucosal injury, was occasionally reported when hard-cuff ETTs were used, but with soft-cuff tubes that inflate evenly, this phenomenon is no longer observed. Because modern soft-cuff tubes do have quite variable physical characteristics, including inflation diameter, fabric thickness, compliance, and geometric shape,

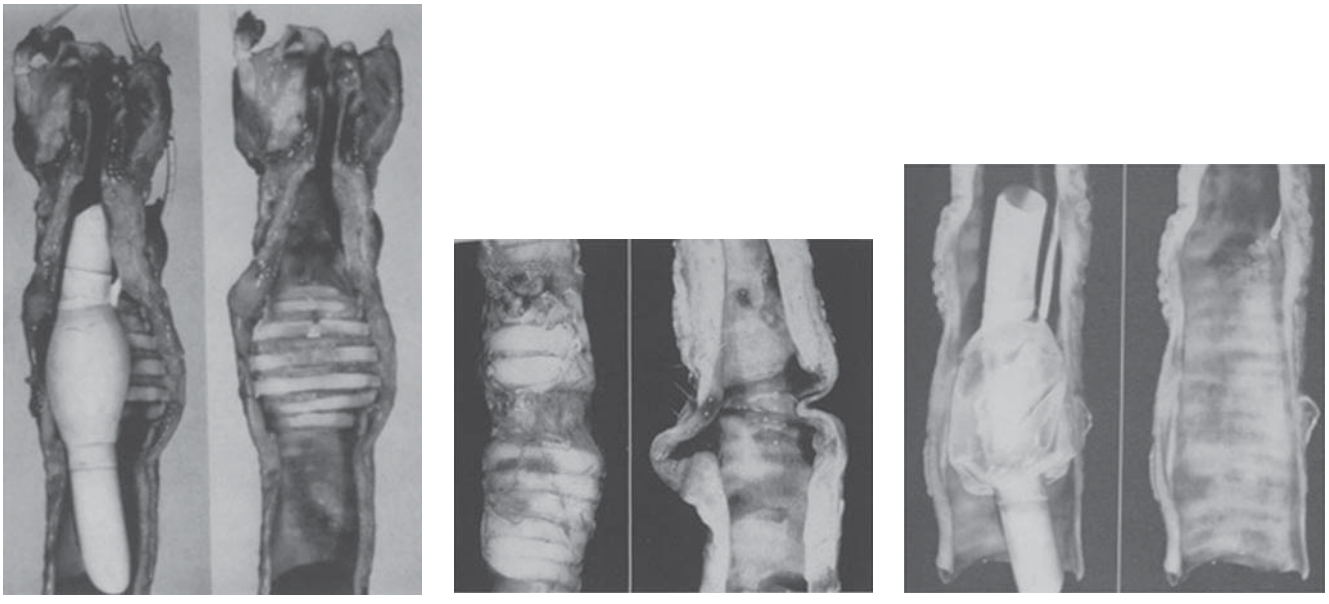

FIGURE 39-17 An experiment in dogs indicated the critical role of high cuff-inflation pressure in causing severe tracheal cuff-site injury. Shown here are severe tracheal ulceration with exposed tracheal cartilage (*left*) and tracheomalacia (*center*) from prolonged intubation with endotracheal tubes (ETTs) with low-volume, high-pressure cuffs. The panel on the *right* shows a normal tracheal surface after prolonged intubation with an ETT with a high-volume, low-pressure cuff. (Modified, with permission, from Cooper and Grillo.[148])

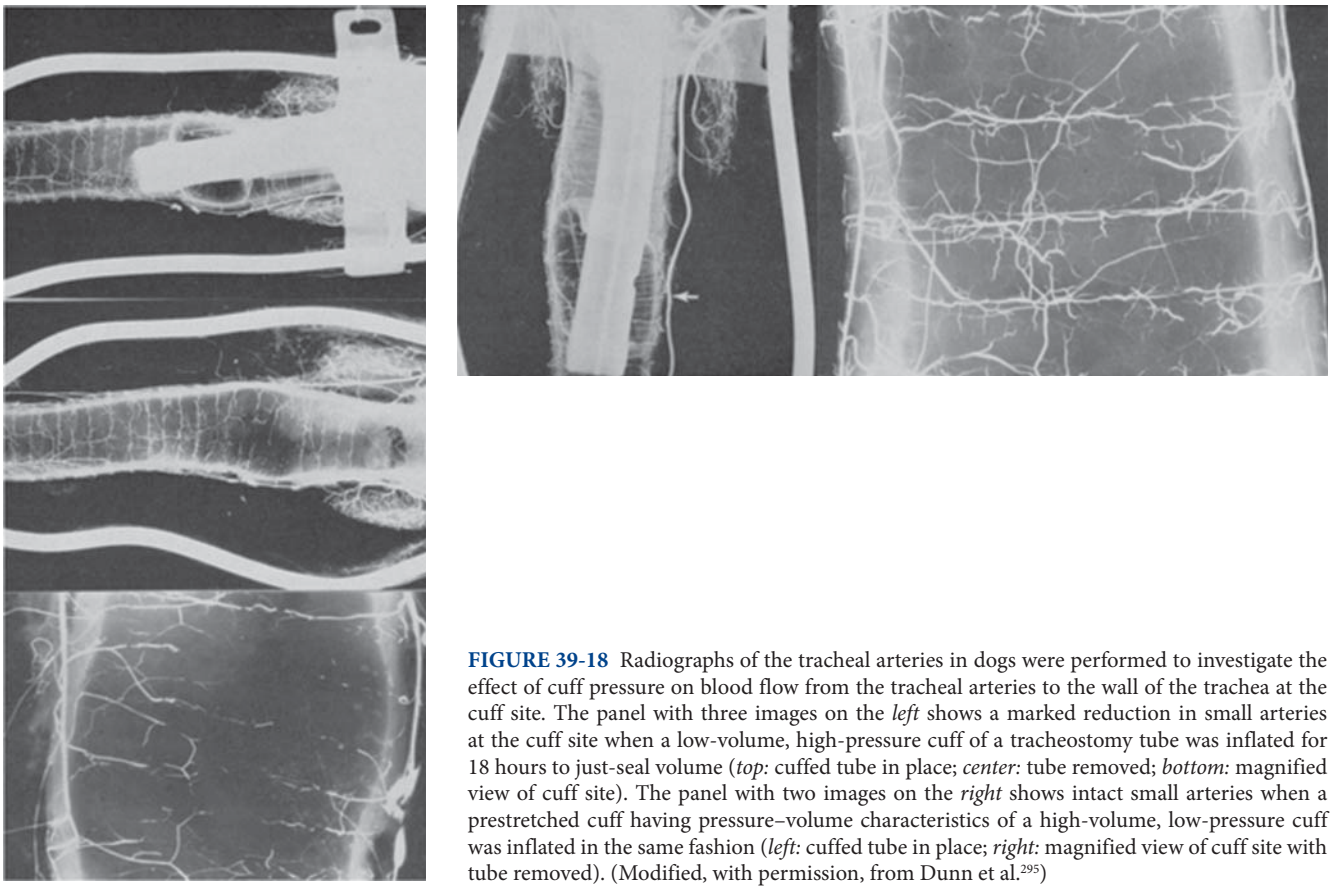

FIGURE 39-18 Radiographs of the tracheal arteries in dogs were performed to investigate the effect of cuff pressure on blood flow from the tracheal arteries to the wall of the trachea at the cuff site. The panel with three images on the *left* shows a marked reduction in small arteries at the cuff site when a low-volume, high-pressure cuff of a tracheostomy tube was inflated for 18 hours to just-seal volume (*top:* cuffed tube in place; *center:* tube removed; *bottom:* magnified view of cuff site). The panel with two images on the *right* shows intact small arteries when a prestretched cuff having pressure–volume characteristics of a high-volume, low-pressure cuff was inflated in the same fashion (*left:* cuffed tube in place; *right:* magnified view of cuff site with tube removed). (Modified, with permission, from Dunn et al.[295])

all are not the same in their pressure–volume relationship and potential for mucosal injury.[254,273,281]

Age. Prospective studies that have examined the influence of age on tracheal cuff-site injury have not found a conclusive relationship.[19,128,129]

Gender. The role of gender in cuff-site tracheal injury from TLI is controversial, as prospective studies have found conflicting results.[19,128,129]

Duration of Translaryngeal Intubation. The relationship between duration of TLI and tracheal cuff-site injury is controversial, probably because observational clinical studies have not been able to control for confounding variables such as cuff pressure, tube movement, and ETT size. We found no statistical association between tracheal cuff-site injury at autopsy and duration of TLI or duration of TLI and tracheotomy together.[19] Other studies have also failed to find a significant relationship between duration of tracheotomy and cuff-site injury.[129,299,300] Only one prospective study found that tracheal cuff-site injury was significantly associated with the duration of TLI.[128]

Hypotension. Few studies have examined the relationship between hypotension and tracheal cuff-site injury in humans. We found no relationship between hypotension and tracheal cuff-site injury at autopsy.[19] In an experimental study of dogs with cuffed tracheostomy tubes, Dunn et al found that intercurrent periods of hypotension did not affect the extent of tracheal injury from tracheostomy tube cuffs.[295]

Corticosteroid Therapy. Two prospective studies reported no association between corticosteroid therapy and tracheal cuff-site injury from TLI.[19,128]

Airway Infection. Nordin reported that bacterial invasion of tracheal mucosa damaged by high cuff inflation pressures begins to occur about 4 hours after the onset of cuff inflation.[259] There is, however, no convincing evidence from clinical or experimental studies that airway infection increases the risk of cuff-site complications.[129,278]

Miscellaneous Factors. Kastanos found a statistically significant association between tracheal injury from TLI and the use of positive end-expiratory pressure.[128] Excessive motion between the inflated cuff and the trachea was implicated in tracheal injury by the studies of Lindholm.[130]

Siobal et al reported a case of tracheoinnominate artery fistula in a burn patient who was intubated for 40 days with an 8-mm internal diameter ETT, which was equipped with a subglottic suction port and held in position by a wire suture

to a molar tooth.[165] Erosion of the left anterior wall of the trachea by the tube tip was attributed to the prolonged period of intubation, fixed position of the tube, and decreased flexibility of the tube as a result of the suction channel feature.

CLINICAL INFLUENCES IN PULMONARY COMPLICATIONS

Pneumonia and Tracheobronchitis. This topic is discussed in Chapter 46. Myriad factors predispose to VAP and ventilator-associated tracheobronchitis while an ETT is in place,[177,179,180,190,301] including the underlying disease(s); impaired host defenses; antibiotic exposure; aspiration; enteral feeding tubes; sinusitis; impaired mucociliary function; ineffective cough; respiratory equipment; hospital transport out of the ICU; ETT biofilm; and increased binding of bacteria to the tracheobronchial epithelium. During intubation, the lower airways of ICU patients are heavily colonized with a variety of organisms. Those isolated most frequently as pathogens in VAP are aerobic gram-negative bacilli (especially *P. aeruginosa, Enterobacteriaceae,* and *Acinetobacter* species) and *S. aureus.*[190] Polymicrobial infections in VAP are common. Anaerobic organisms may also be isolated in cultures of lower respiratory tract secretions in patients with VAP,[302] but their significance in the pathophysiology of VAP remains controversial.[303]

An indwelling ETT is by itself a risk factor for VAP and ventilator-associated tracheobronchitis, because it is a foreign body and it bypasses protective upper airway defenses. Aspiration of contaminated upper airway secretions and leakage of bacteria-laden fluid that pools above the inflated ETT cuff are important mechanisms of entry of pathogens into the lung.[177,304,305] The ETT biofilm also serves as a reservoir for microorganisms, increasing the risk for VAP and ventilator-associated tracheobronchitis.[274,306] Reintubation may be a separate important risk factor for VAP.[307]

Aspiration. Aspiration of gastric and upper airway secretions into the lower airway while an ETT is in place may occur for a variety of reasons.[189] TLI per se invites aspiration of secretions because of stenting of the larynx in an open position, prevention of glottic closure, esophageal compression by the inflated cuff, pooling of secretions above the cuff, creation of channels along folds of cuff fabric,[280] and desensitization of protective upper airway reflexes. Elpern et al, in a prospective study of aspiration in intubated adults, observed that cuff inflation to occlusion does not prevent aspiration, nor does a head-up position in bed.[189] They also noted that nasogastric tubes increased the risk of aspiration, whereas level of consciousness and feeding status did not.

Complications During and After Extubation

In a prospective study of critically ill adults, Jaber et al found that postextubation stridor was associated with traumatic or difficult intubation, prior self-extubation, and increased cuff pressure at the time of ICU admission.[225] They also observed that postextubation stridor increased with duration of TLI,[225] a finding that was also observed by Tadie et al.[221] Efferen and Elsakr reported that postextubation stridor was associated with cuff pressure, corticosteroid therapy at the time of extubation, and a neurologic disorder necessitating TLI.[226] Megarbane et al observed that female gender and intubation time were predictive of postextubation laryngeal injuries in acutely poisoned patients.[220]

The pathogenesis of laryngeal and tracheal stenosis following TLI is related to the healing process of airway injury incurred during TLI. Why some ulcerative lesions heal normally, others with granuloma formation, and others with cicatrix or scar formation is obscure. Table 39-9 summarizes important or potentially important mechanisms of laryngotracheal injury from TLI.

TABLE 39-9: IMPORTANT MECHANISMS OF LARYNGOTRACHEAL INJURY FROM TRANSLARYNGEAL INTUBATION

- Laryngeal ulceration
  - High pressure on the posterior endolarynx
    - Curvature of the endotracheal tube (ETT)
    - Round shape of the ETT
    - Stiffness of the ETT
  - Abrasion (excessive movement at the tube-mucosa interface)
  - Large diameter of the ETT
  - Female gender
  - Oral route of intubation
- Laryngeal granuloma formation
  - Laryngeal ulceration
  - Nasogastric tube
  - Large diameter of the ETT
  - Increasing age
- Laryngeal stenosis
  - Laryngeal ulceration
  - Subsequent tracheotomy
    - Laryngeal inactivity
    - Bacterial invasion
- Tracheal cuff-site ulceration
  - High lateral tracheal wall pressure

IMPORTANT PROSPECTIVE STUDIES OF COMPLICATIONS OF TRANSLARYNGEAL INTUBATION

Because the literature on complications of artificial airways is largely based on retrospective and anecdotal observations, study of this topic is especially prone to potential bias and faulty conclusions. Few techniques of airway management satisfy the criteria of evidence-based medicine. Fortunately, however, a growing number of prospective studies of complications of TLI, tracheotomy, or both

are now available. Large prospective studies of complications of TLI are difficult to perform but they do provide valuable insights.

A growing number of studies comparing complications of TLI with those of tracheotomy or complications of delayed versus early tracheotomy have employed a randomized design.[129,284,308–313] Prospective studies attempting to randomize patients to early tracheotomy have been difficult to perform. Only a few prospective studies have attempted to directly compare complications of TLI alone with those of tracheotomy.[19,129,130,284] A growing number of prospective studies have evaluated airway complications of early versus delayed tracheotomy,[308,309,311–315] but the complications that can be attributed to TLI alone in these studies are difficult to assess.

Rumbak et al randomized 120 adult medical ICU patients to early percutaneous tracheotomy within 48 hours or delayed tracheotomy after 10 to 14 days of TLI.[309] The early tracheotomy group experienced significantly lower mortality, less-frequent pneumonia, fewer days in the ICU, fewer days of mechanical ventilation, and fewer days of sedation. Sugerman et al, however, using a similar study design, found no significant differences between the early and the delayed tracheotomy groups with regard to mortality rate, days in the ICU, or frequency of pneumonia.[308] This section reviews selected prospective clinical studies of laryngeal or tracheal complications of TLI in adults (Table 39-10).

Lindholm's study represents the most comprehensive study of complications of TLI ever performed.[130] He investigated 457 patients for acute and late complications of intubation. Very few late, severe complications and no deaths were attributed to TLI. Large ETT size, ETT stiffness, and excessive laryngeal motion were identified as important risk factors for laryngeal injury. Because, however, the patients were intubated in large part with red rubber and latex tubes with hard cuffs, and the duration of intubation was less than 3 days, the results of the study are not entirely applicable to modern critical care.

TABLE 39-10: SELECTED PROSPECTIVE STUDIES OF COMPLICATIONS OF TRANSLARYNGEAL INTUBATION

Year	References	No. of Patients
1969	Lindholm[130]	457
1981	Stauffer et al[19]	150
1984	Whited[127]	200
1989	Colice et al[52]	82
1994	Santos et al[139]	97
1995	Schwartz et al[70]	238
2004	Bouderka et al[310]	62
2006	Jaber et al[20]	220
2007	Benedetto et al[317]	150
2008	Griesdale et al[21]	136

Stauffer et al compared complications of TLI with those of tracheotomy in 150 critically ill adults in two large teaching hospitals.[19] Survivors were studied for late complications and nonsurvivors were evaluated at autopsy. An attempt to randomize patients into early tracheotomy and prolonged TLI groups was only partially successful. Approximately two-thirds of TLI and two-thirds of tracheotomies had one or more complications, but the complications were judged to be more severe in the tracheotomy group. Laryngotracheal injury at autopsy did not correlate with the duration of TLI. A few patients appeared to tolerate TLI well for up to 3 weeks.

Whited described his personal experience as an otolaryngologist–head and neck surgeon with 200 patients from the critical care units of two teaching hospitals who had TLI from 2 to 24 days.[127] Mirror or fiber-optic laryngoscopy tracheoscopy was performed at extubation and serially thereafter. Fifty survivors (group I) had TLI for 2 to 5 days, 100 (group II) had TLI for 6 to 10 days, and fifty (group III) had TLI for 11 to 24 days. The severity of posterior laryngotracheal injury appeared to increase with the duration of TLI, but statistical analysis was not provided. Chronic posterior commissure stenosis progressing inferiorly to the level of the cricoid ring and into the trachea occurred in 14% of group III patients. Chronic stenosis was more common in patients with TLI followed by tracheotomy than in those with TLI alone. Other variables that might have affected the outcome were not described. The author concluded that TLI for less than 7 days is safe and that TLI beyond 10 days is unacceptable as a routine policy.

Colice et al examined eighty-two adult patients intubated more than 4 days for laryngeal complications of TLI using direct fiber-optic laryngoscopy and careful follow-up.[52] Nonlaryngeal complications were not evaluated. Ulceration and edema of the posteromedial aspects of the vocal cords were observed in 94% of the patients at extubation. Neuromotor activity and performance of a tracheotomy, but not duration of TLI, were associated with increased laryngeal complications. Initial findings at laryngoscopy did not predict the late development of adverse effects.

Santos et al reported risk factors for laryngeal injury from prolonged TLI in critically ill adult men in an initial report in 1989,[316] and updated their findings with a second report in 1994.[139] The latter study described prospective observations in ninety-seven adult men with orotracheal TLI (mean duration: 9 days). Postextubation endoscopic findings in seventy-nine survivors included laryngeal erythema (94%), laryngeal ulceration (76% with resolution within 6 weeks), and laryngeal granulomas (44%). True vocal cord immobility was seen in sixteen (20%) patients and was delayed in onset in half the cases. Duration of TLI was significantly associated with true vocal cord granuloma formation and early and delayed true vocal cord immobility but not with true vocal cord ulceration. The use of a larger ETT (size 8.0-mm internal diameter as compared with size 7.5 mm) was significantly associated with true vocal cord

erythema, ulceration, granuloma formation, and delayed immobility. None of sixty-two patients with TLI alone developed laryngotracheal stenosis.

Schwartz et al prospectively studied 297 consecutive TLIs in 238 critically ill adults in medical and surgical critical care units of a large teaching hospital so as to assess immediate complications of TLI.[70] The most common indications for TLI were respiratory failure (50%), airway protection (17%), ETT change (13%), and cardiac and/or respiratory arrest (10%). Eleven percent of TLIs required three or more attempts at ETT placement. Eight percent were classified as difficult, but none of these were associated with adverse outcomes. Esophageal intubation occurred during twenty-five (8%) of the 297 intubation procedures and was not accompanied by any adverse sequelae. A new infiltrate on the postintubation chest radiograph was observed in 8% of cases, and in half of these (4%) aspiration was suspected as the cause.

Bouderka et al reported results of a prospective, randomized trial of early tracheotomy (days 5 to 6) versus prolonged TLI in sixty-two adults with severe head injury.[310] The two groups were similar in terms of age, gender, and simplified acute physiology score. Clinical symptoms of laryngotracheal complications did not differ between the two groups, but routine endoscopy to evaluate patients for these complications was unfortunately not performed. The early tracheotomy group experienced fewer days of mechanical ventilation both overall and after pneumonia was diagnosed. No differences in ICU stay, frequency of pneumonia, or mortality were observed.

Jaber et al prospectively evaluated immediate complications of 253 intubations in 220 patients in seven ICUs of two teaching hospitals.[20] Seventy-one (28%) of the intubations generated one or more severe complications, including severe hypoxemia (26%), hemodynamic collapse (25%), and cardiac arrest (2%). The presence of acute respiratory failure and shock were independent risk factors for intubation complications, and resident supervision in intubation reduced the risk of complications.

Benedetto et al performed a prospective observational study of urgent TLI in 150 patients in general hospital units at the Massachusetts General Hospital.[317] The overall rate of complications of emergent TLI was 27%, compared with a rate of 22% in elective TLIs. The most common complications observed were multiple (three or more) attempts at TLI and esophageal intubation, both occurring in 9% of cases. These event rates were strikingly similar to those observed by Schwartz et al[70] in another large teaching institution (11% for multiple attempts at TLI and 8% for esophageal intubation).

Griesdale et al examined early TLI complications in 136 patients in a prospective study in a single Canadian teaching hospital ICU.[21] Nearly all intubations were supervised, but 39% generated one or more complications. Like Jaber et al,[20] Griesdale and coworkers observed that severe hypoxemia and hypotension were the most common severe complications of TLI. All intubations were successful, but 13.2% required three or more attempts.

RECOGNITION AND MANAGEMENT OF COMPLICATIONS OF TRANSLARYNGEAL INTUBATION

Recognition of Selected Complications

COMPLICATIONS DURING ENDOTRACHEAL TUBE PLACEMENT

Right Main-Stem Bronchus Intubation. The classic physical examination findings of a patient with right main-stem bronchus intubation (see Fig. 39-3) are greater intensity of breath sounds and expansion of the right hemithorax compared with the left. Right main-stem intubation, however, may be difficult to recognize in many patients, especially those with emphysema, because of distant breath sounds on auscultation and chest hyperinflation.[318] Schwartz et al observed that neither physical examination nor referencing the centimeter markings on the ETT shaft indicated malpositioning of the ETT after emergency TLI.[63] Women are at greater risk than men for malpositioning of the ETT in critical care intubations.[63] Right main-stem bronchus intubation may lead to early hypoxemia and cyanosis, particularly if the patient has underlying lung disease.

Esophageal Intubation. Inadvertent intubation of the esophagus should be recognized immediately by capnography (see the section Prevention of Complications of Translaryngeal Intubation/Complications During Endotracheal Tube Placement/Avoiding Esophageal Intubation, and Chapter 38), although this method is not foolproof. Esophageal intubation may be recognized when manual ventilation after intubation produces poor chest expansion and gurgling sounds on auscultation over the stomach. In some cases, esophageal intubation may be very difficult to detect on physical examination. The patient with an ETT placed in the esophagus may display some degree of chest expansion, and "pseudo" breath sounds may be auscultated as gas enters the stomach. Esophageal intubation should be recognized before a postintubation chest radiograph is obtained. If a radiograph is obtained, however, it may reveal displacement of the ETT slightly away from the tracheal air column. Caution is necessary, however, because slight rotation of the patient may superimpose the tracheal air column over the ETT positioned in the esophagus.

COMPLICATIONS WHILE THE ENDOTRACHEAL TUBE IS IN PLACE

Sinusitis and Otitis. A high index of suspicion is critical to establishing the diagnosis of TLI-associated sinusitis and initiating effective therapy. Sinusitis may present as sinus pain and tenderness, or purulent nasal sinus drainage in an intubated patient, but it is important to emphasize that these findings may be minimal or absent. Sinusitis complicating nasotracheal intubation or use of nasogastric tubes typically

presents with fever, or in some patients, with bacteremia and sepsis syndrome.

Most reports have emphasized the value of CT scanning for accurate diagnosis of intubation-associated sinusitis, because physical examination is generally unreliable and standard sinus radiographs often fail to establish the diagnosis, especially when there is involvement of the ethmoid or sphenoid sinuses.[319] Radiographic maxillary sinusitis is defined as the presence on CT scanning of an air-fluid level or opacification of the maxillary sinus. Opacification of the other sinuses is common in intubated patients. Otitis is detected by routine otoscopic examination, which should also be performed in evaluation of fever of unknown origin in the intubated patient.

Nasal and Oral Injury. Nasal and oral complications during TLI are recognized by daily careful examination of the nose and mouth.

Laryngeal Injury. Recognition of laryngeal injury during TLI is rarely successful, because the ETT hides the injured areas from observation. Posterior ulceration of the larynx is hidden from view during fiber-optic endoscopy unless the ETT is removed, which is dangerous and impractical. Supraglottic and glottic edema is sometimes assessed by direct or indirect laryngoscopy during TLI. There are conflicting reports about the value of laryngoscopy in assessing laryngeal injury during TLI.[140,143] Routine endoscopy of the pharynx and larynx during TLI is not currently advised. Furthermore, endoscopic findings in the larynx during TLI do not clearly guide the timing of tracheotomy or predict long-term laryngeal sequelae of TLI.[52,246]

Tracheal Injury. Tracheal cuff-site injury cannot be detected during TLI unless fiber-optic bronchoscopy is performed while the ETT is retracted upward. This practice has no proven value, however, and is not indicated in decision making about extubation or conversion to tracheotomy. When the ratio of cuff-site diameter to tracheal transverse diameter on a chest radiograph exceeds 1.5, severe damage to the tracheal wall is present.[152] Eighteen (13.5%) of 135 intubated adult patients developed this complication as a result of cartilaginous destruction, and those who survived eventually developed tracheal stenosis or tracheoesophageal fistula.[152] Therefore, patients in whom tracheal dilation develops during TLI should be followed closely for months because of the potential for tracheal stenosis.

COMPLICATIONS DURING AND AFTER EXTUBATION

Laryngeal Injury. Persistent hoarseness, stridor, or dyspnea after extubation should always raise the question of serious laryngeal complications of TLI, including granuloma formation, laryngeal muscle paresis or paralysis, severe ulceration, laryngeal stenosis, cricoarytenoid ankylosis, or synechia formation.[125,130,242] The physician should also be aware that dyspnea, hoarseness, and stridor appearing weeks to months after extubation may indicate serious laryngeal (or tracheal) stenosis and should not be dismissed as simply being related to the underlying lung disease.[240] Glottic or subglottic stenosis may take weeks or months to develop after seemingly uneventful TLI and extubation.

The evaluation of patients with suspected serious laryngeal injury after TLI should include physical examination and laryngoscopy. Physical examination may reveal prolonged inspiratory phase, harsh tracheal sounds and palpable thrill over the larynx on inspiration, and inspiratory intercostal retractions. Upper airway stridor transmitted to the thorax should not be misinterpreted as a sign of bronchoconstriction.

Laryngoscopy is necessary in all cases. Vocal cord movement may be evaluated initially by mirror laryngoscopy. If any abnormalities are detected, direct laryngoscopy should be performed. The finding of bilateral vocal cord abduction could be related to cricoarytenoid arthritis or recurrent laryngeal nerve injury.[242] Recurrent laryngeal nerve injury is suggested by absence of vocal cord motion, while in posterior glottic stenosis there is some motion of the cords on inspiration and phonation.[242] Glottic synechiae and laryngeal granulomas are usually readily apparent at the time of direct laryngoscopy.

Imaging the larynx is very helpful in the diagnosis of TLI-induced laryngeal injury. Older imaging techniques such as soft-tissue radiographs and linear tomography have been replaced by CT scanning with multiplanar reconstruction capability to create axial, coronal, and sagittal reformatted images.[320] Magnetic resonance imaging plays a lesser role than CT imaging. Radiographic studies and fiber-optic laryngoscopy are more sensitive than the history and physical examination in detecting laryngeal injury from TLI.

The maximal expiratory-to-inspiratory flow–volume loop is sometimes performed in the evaluation of patients with suspected laryngeal (or tracheal) injury from TLI. The classic feature of unilateral vocal cord paralysis on a flow–volume loop is attenuation of inspiratory flow rates. The classic feature of bilateral vocal cord paralysis or laryngeal (or tracheal) fixed stenosis is attenuation of both inspiratory and expiratory flow rates with a "boxed-off" appearance to the flow–volume loop (see Fig. 39-13A). Classic patterns of these types of injury are not always seen, however, because the flow–volume loop is neither sensitive nor specific. A completely normal flow–volume loop, on the other hand, makes functionally significant laryngeal (or tracheal) disease unlikely.

Tracheal Stenosis. Symptomatic tracheal stenosis after extubation is very uncommon in the modern era of soft-cuff ETTs. Like laryngeal stenosis, tracheal stenosis may not become apparent for weeks, months, or even years after extubation. [321] Typical symptoms of tracheal stenosis include progressive dyspnea on exertion, cough, difficulty clearing sputum, and in some cases, stridor. Unfortunately, these findings are commonly attributed to underlying disorders such as bronchitis, asthma, chronic obstructive pulmonary disease, or resolving acute respiratory distress syndrome.[240]

The diagnosis of tracheal stenosis requires a high degree of clinical suspicion based on a history of TLI (or tracheotomy) weeks to months earlier. Initial symptoms of cough, hoarseness, and difficulty clearing lower airway secretions are followed by dyspnea and stridor. Stridor and progressive respiratory distress, however, may not occur until the tracheal diameter is reduced to approximately 5 mm or less in adults.[247] Physical examination may be normal in patients with mild to moderate degrees of tracheal stenosis. In severe cases, stridor is the key finding. Flow–volume loops demonstrate fixed airway obstruction if there is a tight fibrous ring at the stenotic segment (see Fig. 39-13A). A 50% reduction in tracheal caliber (<8-mm diameter), however, may be needed in order to produce an abnormal flow–volume relationship.[322]

Confirmation of the diagnosis of tracheal stenosis is possible with multidetector CT scanning, including axial imaging, multiplanar reconstruction, and creation of "virtual bronchoscopy" images, all of which are highly accurate in comparison with fiber-optic bronchoscopy.[251,323] Multislice three-dimensional CT imaging offers remarkably clear images of tracheal stenosis.[324] Fiber-optic or rigid bronchoscopy may be employed in some cases.

Management of Selected Complications

COMPLICATIONS WHILE THE ENDOTRACHEAL TUBE IS IN PLACE

Sinusitis. Effective management of sinusitis during TLI requires early recognition, appropriate radiographic studies (see "Complications During and After Extubation" above), and culture and sensitivity of aspirated sinus fluid. Nasotracheal and nasogastric tubes should be removed. Consultation with an otolaryngologist–head and neck surgeon is advised. Aspiration of maxillary sinus fluid yields fluid for Gram stain and cultures for bacteria (aerobic and anaerobic) and fungi, allowing selection of appropriate antimicrobial therapy. Repeated aspiration may be necessary in some patients. Sinus irrigation or lavage via an indwelling catheter is sometimes required. Treatment with nasal decongestants for short periods is commonly employed.

COMPLICATIONS DURING AND AFTER EXTUBATION

Laryngeal Complications. Laryngeal edema from mucosal trauma by the ETT may cause stridor, which appears minutes to several hours following extubation. Kriner et al prospectively observed that twenty (4.3%) of 462 patients who were intubated for more than 24 hours developed postextubation stridor.[325] Female gender, longer duration of TLI, and larger ratio of ETT diameter to laryngeal size were risk factors for postextubation stridor in this series. Fundamental elements of management of postextubation stridor include supplemental oxygen, close monitoring of vital signs and oxygen saturation, removal of secretions from the upper airway, and positioning the head and neck to maintain airway patency. The patient should be reassured and anxiety managed appropriately. Because most cases of postextubation stridor are caused by laryngeal edema, management should be directed with this in mind. Parenteral corticosteroids, aerosolized epinephrine, and inhalation of a helium–oxygen gas mixture are the mainstays of empiric therapy.[144] Helium–oxygen gas mixtures may help reduce the patient's work of breathing. Helium–oxygen mixtures with more than 40% oxygen are generally ineffective. Reintubation is commonly required if the above measures are not successful. Kriner et al noted that seven (35%) of twenty patients with postextubation stridor required reintubation.[325]

Helium–oxygen therapy has also been described for temporary relief of increased work of breathing in patients with bilateral vocal cord dysfunction complicating TLI.[230] Prevention of recurrent postextubation stridor is discussed (see the section Prevention of Complications of Translaryngeal Intubation/Complications During and After Extubation/Avoiding Stridor).

The cuff-leak test is valuable in planning for extubation, because little or no leak around the deflated cuff helps to predict the presence of laryngeal edema and postextubation stridor.[326] Jaber et al observed that a cuff-leak volume of less than 130 mL (or less than 12% of tidal volume set at 10 to 12 mL/kg) was useful in identifying critically ill adult patients at risk for stridor after extubation.[225] Others have reported that cuff leaks of less than 10%[288] or 15.5%[327] of tidal volume help to identify patients at risk for reintubation from laryngeal edema. Chung et al reported the sensitivity and specificity of the cuff-leak test to be 88.6% and 90.0%, respectively.[223] Recent reports indicate that the negative predictive value of the cuff-leak test (air leak is observed) is 96% to 97%, while the positive predictive value (air leak is not observed) ranges from 12% to 25%.[325,328,329]

As stated earlier, limited motion of the vocal cords long after extubation reflects posterior glottic fibrosis or ankylosis of the cricoarytenoid joint.[106] The goal of management is restoration of the voice, prevention of aspiration, and provision of adequate airflow. Management by an experienced otolaryngologist–head and neck surgeon is essential. Surgical and nonsurgical techniques to improve laryngeal function in patients with vocal cord paresis/paralysis are available.[106,330–332] Patients with bilateral vocal cord paralysis may require emergent tracheotomy.[106]

Treatments for laryngeal granulomas (see Figs. 39-9B and C and 39-12) are directed at their causes, which include vocal abuse and gastroesophageal reflux disease as well as TLI. Granulomas from TLI are often managed with fiber-optic laryngeal surgery[333] or surgical resection with very good results. Other therapeutic approaches for laryngeal granulomas have been described, including inhaled corticosteroids,[334] injection of corticosteroids,[106] injection of botulinum toxin,[335] and radiation.[336] Wang et al, however, observed that vocal process granulomas, regardless of etiology, may completely resolve without steroid treatment and spontaneously achieve complete remission in more than 80% of cases without excision or other intervention.[337]

Laryngeal stenosis requires surgical intervention. Surgical options depend upon the location of the stenotic lesion and include laser therapy,[338] dilation procedures, stenting, laryngofissure, resection,[339,340] keel insertion, and other reconstructive procedures.[341,342] Posterior commissure scarring is difficult to treat surgically.[238,242] Repeated surgical operations for laryngeal stenosis may be required. In many cases, permanent tracheostomy is necessary. Czigner et al treated twenty-nine patients with subglottic stenosis, which was related to TLI or tracheotomy in most cases, with resection of the stenotic segment and end-to-end anastomosis, achieving a success rate of 96%.[343] Pena et al reported very similar results.[341]

Tracheal Complications. Tracheal granulomas are managed by endoscopic removal. Small granulomas may resolve spontaneously. Management of tracheal stenosis depends upon its severity. Patients with mild degrees of tracheal stenosis (arbitrarily defined as <25% reduction in airway diameter) and no symptoms require only periodic follow-up to look for progressive stenosis. Those with greater degrees of airway narrowing and symptoms require more aggressive management. In severe cases with 50% to 75% narrowing of the trachea, emergent medical and surgical intervention is necessary.

Surgical options in patients with severe tracheal stenosis include dilation procedures,[344,345] stent placement, electrocautery, laser photoablation,[338] and resection of the stenotic segment with reanastomosis.[248,346,347] Tracheal reconstruction for tracheal stenosis is usually successful. Grillo and Donahue reported good or satisfactory results with surgery in 94% of 503 patients with postintubation tracheal stenosis.[347]

PREVENTION OF COMPLICATIONS OF TRANSLARYNGEAL INTUBATION

Most of the complications of TLI are preventable. Skilled intubation technique, seasoned clinical judgment, and meticulous care and monitoring of the intubated patient are the key elements in avoidance of TLI complications. Because intubation and reintubation put a patient at risk for airway injury, noninvasive alternatives to TLI, such as use of the laryngeal-mask airway or the esophageal-tracheal Combitube, should always be considered, particularly in difficult and emergency airway management situations.[348,349] A review of three randomized or controlled clinical trials of emergency TLI in the field demonstrated no benefit of TLI compared with bag-valve-mask ventilation techniques on survival or neurologic outcome.[350] In patients with respiratory failure from acute exacerbation of chronic obstructive pulmonary disease, noninvasive positive-pressure ventilation decreases the need for TLI and has advantages, such as decreased mortality, rate of complications, and length of hospital stay.[351] An early important step is choosing the appropriate route of TLI for each patient with awareness of the advantages and disadvantages of each.[352] Principles of airway management to prevent complications of artificial airways are described in Chapter 38 and elsewhere.[120,185,353,354]

Complications During Endotracheal Tube Placement

Most of the complications that occur during ETT placement can be prevented by assiduously following the principles and procedures of airway management described in Chapter 38. The intubator should be aware of common pitfalls in attempting to place an ETT in proper position (Table 39-11).

SELECTING THE CORRECT ENDOTRACHEAL TUBE

The ETT selected should have a high-volume, low-pressure soft cuff. All ETTs used in modern critical care should meet standards required by the F29 Committee on Anesthetic and Respiratory Equipment, American Society for Testing and Materials.[267] The ideal ETT should be compliant at body temperature to help conform to the anatomic shape of the patient's airway, thereby reducing force on the posterior larynx. It also should be kink resistant and have a soft cuff that seals the airway and prevents aspiration at minimal lateral tracheal wall pressures.[263,281]

For anesthetic intubation, Stenqvist et al have advocated the use of size 6-mm or 7-mm (i.e., the size of the internal diameter) ETTs in order to reduce pressure on the laryngeal contact points.[355] For use in the patient with respiratory failure in the ICU, however, small tubes have obvious disadvantages, including difficulty in suctioning and increased

TABLE 39-11: COMMON PITFALLS IN PERFORMING TRANSLARYNGEAL INTUBATION

Inadequate training, practice, and experience in intubation
Failure to assemble necessary intubation equipment and drugs before starting the procedure
Selection of the incorrect route of intubation
Inadequate sedation, muscle relaxation, or topical anesthesia
Failure to prepare the nose with vasoconstrictors, analgesics, and/or decongestants before nasal intubation
Failure to oxygenate and ventilate the patient with bag-and-mask ventilation before intubation
Improper positioning of the head and neck
Use of the laryngoscope blade as a lever to pry the airway open
Use of the teeth as a fulcrum to turn the laryngoscope
Failure to visualize the vocal cords
Forcing the endotracheal tube (ETT) forward against tissue resistance
Prolonged intubation attempts without regard for progressive hypoxemia and acidosis
Advancing the ETT deep into the airway after successfully passing the tube through the larynx
Equipment malfunction

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airflow resistance that may increase the work of breathing and delay weaning from mechanical ventilation.[356] A size 8.0-mm to 8.5-mm tube in men or a size 7.5-mm to 8.0-mm tube in women is usually selected for oral intubation, while a tube that is 0.5-mm to 1.0-mm smaller is usually selected for nasal intubations.[185]

PREVENTING INTUBATION TRAUMA

Intubation trauma may be avoided by skilled airway management strategies (see Chapter 38). These include the initial use of bag-and-mask technique to oxygenate and ventilate the patient, thereby avoiding the necessity for "crash" intubation. The importance of adequate preoxygenation before attempting TLI cannot be overemphasized.[357,358] Attempts to visualize the glottis with the laryngoscope should be brief and limited in number. Mort reported that the relative risk of airway complications was significantly higher when three or more laryngoscopic attempts were made.[72] Eleven percent of the 297 TLIs in critically ill adults prospectively studied by Schwartz et al required this number of attempts.[70]

The value of skill and experience in intubation cannot be overstated. For example, nearly all reports of pharyngeal perforation from TLI emphasize that this complication occurs in emergency intubations performed by inexperienced intubators. Skill in intubation may be gained by mannequin or simulation training.[359–362] Bishop et al compared intubation by experienced intubators and novices, observing that novices required twice as long to intubate and had significantly higher intubation "impulses" (force of intubation multiplied by duration of effort) than experienced intubators.[359] Schmidt et al documented a lower rate of complications when anesthetic TLI was supervised by attending physicians.[23] These observations underscore the benefits of training, skill, and experience in intubation technique.

Chapter 38 discusses appropriate management strategies for the difficult intubation. Critical care providers should be familiar with current clinical practice guidelines to manage the patient with a difficult airway.[363]

Preventing Nasal Bleeding. Nasal intubation should be avoided in patients with coagulation disorders, thrombocytopenia, or platelet dysfunction. Careful examination of the nasal passage before intubation is essential, and the more patent side should be selected. Softening the nasal ETT with warm water before intubation may make it more compliant, decreasing the frequency and severity of nasal hemorrhage.[364] Application of a topical decongestant-vasoconstrictor and a topical anesthetic before nasotracheal intubation is recommended.

PREVENTING HYPOVENTILATION AND HYPOXEMIA

Monitoring of ventilation and oxygenation after intubation is critical (see Chapter 38). Unrecognized hypoventilation is among the most common preventable complications of intraoperative anesthesia. Recent guidelines emphasize the importance of preventing hypoventilation by confirming proper ETT placement (see the section Avoiding Esophageal Intubation and Avoiding Right Main-Stem Bronchus Intubation)[349] and by appropriately monitoring ventilation and oxygenation in the sedated patient.[365] Guidelines of the American Society of Anesthesiologists indicate that all patients undergoing sedation/analgesia should be monitored with pulse oximetry and with observation or auscultation of ventilatory function.[365] Monitoring of exhaled carbon dioxide should be considered for all deeply sedated patients and for moderately sedated patients whose ventilation cannot be directly observed.[365]

PREVENTING CARDIOVASCULAR REACTIONS TO TRANSLARYNGEAL INTUBATION

The tachycardic-hypertensive response and cardiac arrhythmias that may accompany laryngoscopy and TLI are potentially preventable.[92,366] The routine use of drugs to prevent these cardiovascular reactions to TLI is not advised, but prophylactic treatment should be considered in patients with hypertension, cardiac disease, or cerebrovascular disease.[366] A wide variety of drug classes and specific drugs are available for this purpose.[366]

AVOIDING ESOPHAGEAL INTUBATION

Esophageal intubation represents a misadventure in intubation with potentially disastrous consequences. A number of strategies have been described to avoid and to recognize this complication.[10,367–370] McCulloch and Bishop reviewed the efficacy of fifteen different methods to determine correct ETT placement and avoid esophageal intubation.[10] Pulse oximetry to assure adequate oxygenation and quantitative monitoring of carbon dioxide levels of expired gas are now standards of care in the operating room. No method to detect esophageal intubation is absolutely foolproof, but capnography comes closest to the mark.[367] It is superior to chest auscultation[370,371] and methods that employ a self-inflating bulb[372] or a lighted stylet.[370] Monitoring of end-tidal CO_2 levels after intubation gives a characteristic repeated waveform if the ETT is properly located in the trachea. Failure of capnography to detect esophageal intubation is very rare.[373] Although colorimetric CO_2 indicators are helpful in detecting esophageal placement of an ETT,[368,369] they still have the potential for indicating tracheal placement even though the ETT is in the esophagus.[374]

Recent international guidelines for emergency cardiovascular care call for both primary confirmation of correct tracheal placement of the ETT by physical examination and secondary confirmation by an end-tidal CO_2 detector or an esophageal detector device.[349] These steps are followed by careful chest auscultation and a chest radiograph. Use of an ETT holder to prevent subsequent dislodgment is also advised in these guidelines.[349]

AVOIDING RIGHT MAIN-STEM BRONCHUS INTUBATION

Physical examination of the chest is not reliable in determining proper positioning of the ETT.[375] Brunel et al reported that 60% of patients with main-stem bronchus intubations had equal breath sounds on chest physical examination.[318] Therefore, in general, it is always desirable to obtain a chest radiograph after intubation[318,376] unless fiber-optic bronchoscopy is performed to confirm proper positioning. By chest radiograph (or bronchoscopy) the tip of the ETT should be approximately 4 to 5 cm above the carina in adults, or at about the level of the third or fourth thoracic vertebra on the chest radiograph.[377–379] When the tip of the ETT is approximately 4 cm above the carina, the upper end of the ETT cuff is approximately 2 cm below the vocal cords.[379]

Endobronchial intubation is usually caused by intubator inexperience and is therefore preventable with proper training and supervision.[65,68,379] Intubators must resist the impulse to thrust the ETT too deeply into the trachea after the tube enters the glottis. Insertion to a depth of 21 cm in women or 23 cm in men from the upper incisor teeth or gums is a reasonable first step to avoid endobronchial intubation.[65,68] This approach will probably avoid endobronchial intubation, but in some patients it may result in positioning the ETT too high in the trachea, risking laryngeal compression or accidental extubation. Cherng et al reported that the correct oral ETT length in adults with the head in a neutral position was correlated with body height.[378] They advocated estimating the length of the tube (in centimeters) from 5 cm above the carina to the angle at the right side of the mouth with this equation: (body height in centimeters/5) – 13.[378] After a chest radiograph confirms proper positioning of an ETT, the tube should be marked with indelible ink at the level of the lip or nasal alae to avoid subsequent inadvertent tube dislocation.

Complications While the Endotracheal Tube Is in Place

A number of practices may be helpful in preventing complications during TLI (Table 39-12). A careful physical examination of the patient should be performed by the physician at least daily, including examination of the mouth, nose, ears, sinuses, neck, and chest. The entry site of the ETT should be inspected carefully after removing adhesive tape or ETT holders as necessary (Fig. 39-19).

Nasal ala ulceration (see Fig. 39-4) may be prevented by positioning the ETT so that it points downward straight out the nose, by avoiding tight taping of the tube to the nose, by selecting a nasotracheal tube that is not too large for the patient, and by other approaches.[380,381] Oral ulceration (see Fig. 39-7) may be avoided by minimizing the direct pressure transmitted to the lips and soft tissues of the oral cavity from the shaft of the ETT and ventilator tubing. Oropharyngeal airways should not be used routinely.

TABLE 39-12: SELECTED MEASURES TO REDUCE THE RISK OF COMPLICATIONS WHILE THE ENDOTRACHEAL TUBE IS IN PLACE

- Perform a careful bedside examination daily
  - Include mouth, nose, ears, and sinuses
- Avoid nasal ulceration
  - Position the nasotracheal tube so that it points downward
  - Avoid too large a nasotracheal tube
  - Avoid taping the endotracheal tube (ETT) tightly to the nose
- Avoid oral ulceration
  - Minimize direct pressure on the lips and soft tissues of the oral cavity from the shaft of the ETT
  - Support the weight of the attached ventilator tubing
  - Use oropharyngeal airways only if necessary
- Select the best ETT for the patient
  - Use high-volume low-pressure soft cuffs only
  - Avoid very large ETTs (size ≥9.0 mm) to reduce the risk of laryngeal injury
- Manage cuff inflation carefully
  - Limit intracuff pressure to ≤20 mm Hg, 25 mm Hg at the maximum
  - Consider a trial of a foam cuff ETT if higher inflation pressures are required
  - Check and record intracuff pressures every 8 hours
  - Check for high cuff pressures after general anesthesia with nitrous oxide and other anesthetic gases
  - Use the minimal occluding pressure technique for cuff inflation
  - Avoid overinflation of soft cuffs
  - Watch the chest radiograph for tracheal cuff-site dilation
- Avoid deliberate or inadvertent self-extubation
  - Use extremity restraints and sedate the patient if necessary
  - Reassure the patient to allay anxiety
  - Be certain the ETT is properly located in the trachea, with the tip approximately 4 to 5 cm above the carina (for an adult of average height)
- Suction the airway carefully
  - Avoid excessive movement of the ETT
  - Use sterile gloved technique
  - Oxygenate and ventilate the patient adequately during suctioning
  - Limit suctioning to a maximum of 10 to 15 seconds at a time
  - Suction secretions when necessary, not routinely
- Avoid transmission of mechanical forces directly to the patient
  - Use elastic connectors and swivels
  - Support the weight of ventilator tubing
  - Do not tie ventilator tubing to the bedrails
- Minimize abrasion of the laryngeal and tracheal mucosa
  - Minimize attempts to talk, swallow, and move the head and neck
  - Control coughing and aggressively treat agitation, seizures, and rigid posturing
  - Sedate the patient if necessary
- Use nasogastric tubes judiciously and only if necessary
  - Avoid large nasogastric tubes
- Attach the ETT to a source of warm, humidified gas
- Give the patient reassurance and emotional support
  - Facilitate and encourage written communication
- Remove the ETT as soon as possible

MANAGING CUFF PRESSURE

Only ETTs with low pressure cuffs should be used in adult critical care. The cuff inflation pressure should be limited to

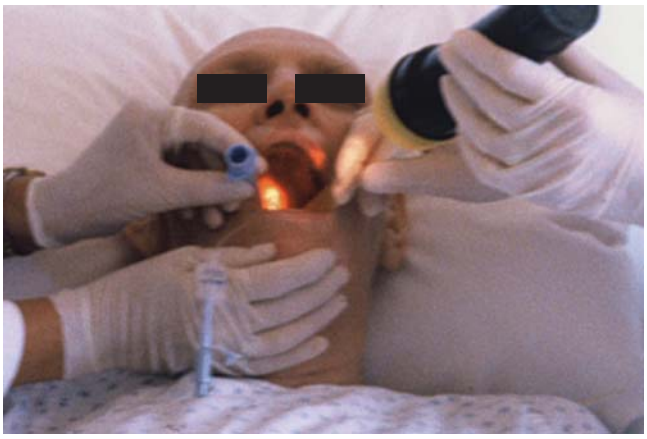

FIGURE 39-19 During translaryngeal intubation the nose and mouth should be inspected carefully every day to detect evidence of nasal or oral injury from the endotracheal tube.

less than 20 to 22 mm Hg (27 to 30 cm H_2O) if possible.[382] If higher cuff pressures are required, the cuff pressure should certainly not be allowed to exceed 25 mm Hg (34 cm H_2O). If this goal cannot be achieved, consideration should be given to replacing the ETT with a foam-cuff tube. A cuff pressure monitoring device that records the pressure in the cuff and manometer simultaneously should be used (Fig. 39-20).

Critical care practitioners should be aware that it is necessary to check the ETT cuff for excessive pressure after general anesthesia with nitrous oxide (N_2O) and other anesthetic gases, because these gases diffuse into the cuff.[383] In patients undergoing surgery with general anesthesia that included 50% N_2O, Tu et al noted that ETT soft-cuff pressures exceeded 80 cm H_2O and that cuff-site injury correlated with cuff pressure.[383] ETT cuff pressure should be checked at least every 20 to 30 minutes during and after anesthesia with N_2O.

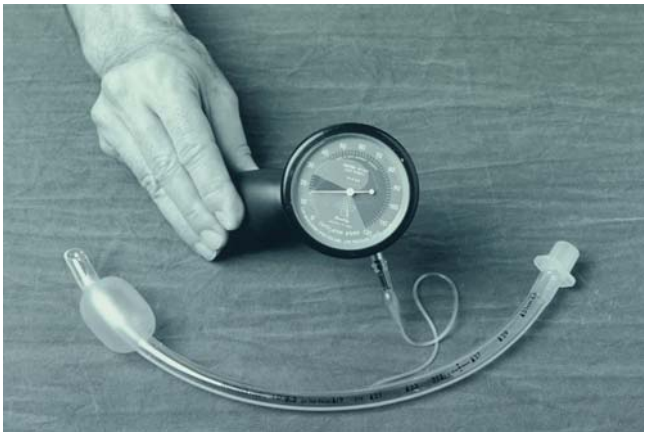

FIGURE 39-20 The pressure in the endotracheal tube cuff should be set and checked every nursing shift to help avoid tracheal cuff-site injury. Cuff inflation pressure should be limited to less than 20 mm Hg (27 cm H_2O) if possible. The cuff pressure monitoring system shown here (Posey Cufflator Endotracheal Tube Inflator and Manometer, Posey Company, Arcadia, CA) records the pressure in the cuff and aneroid manometer simultaneously.

The "minimal occluding pressure" technique[273] is advised for maintaining cuff inflation, although some practitioners prefer the "minimal leak" technique.[384] Regardless of the technique of cuff inflation that is used, overinflation of soft cuffs should be avoided. The addition of only a few extra milliliters of air to the soft cuff may raise intracuff pressures sharply, increasing lateral tracheal wall pressure and risking tracheal mucosal injury.[258,292,293] Cuff pressures should be recorded at least every 8 hours or once every nursing shift. Routine monitoring of intracuff pressures is desirable, despite the shortcoming that it always overestimates lateral tracheal wall pressure.[385]

High cuff inflation pressures should be taken seriously. The patient should be watched carefully for signs of excessive cuff pressure, including widening of the tracheal air column on the standard chest radiograph.[152] Rising peak airway pressures during mechanical ventilation require higher cuff inflation pressures in order to prevent cuff air leak. A prospective study of fifteen patients undergoing mechanical ventilation for surgery revealed a linear relationship between peak airway pressure and minimal occluding cuff pressure, and in this series a cuff pressure of 25 mm Hg corresponded with a peak inflation pressure of 35.3 mm Hg (48 cm H_2O).[386]

AVOIDING UNPLANNED EXTUBATION

The patient should be constantly reassured to reduce anxiety. Extremity restraints should be applied if necessary and the patient sedated if it appears that self-extubation is likely. Mechanically ventilated patients who are severely agitated are significantly more likely to self-extubate than those who are not agitated.[204,387] Tung et al observed in a retrospective case-control study that ICU patients who self-extubated were more than twice as likely as controls to be agitated.[201]

Self-extubation tends to be repetitive, so constant vigilance is necessary. Staff awareness of the potential for self-extubation and the appropriate use of restraints and sedation reduce the risk of its occurrence. Proper positioning of the tip of the ETT approximately 4 to 5 cm above the carina also reduces the risk of inadvertent self-extubation such as during movement, patient transport, or extension of the head and neck.[206] Proactive nursing care aimed at avoiding excessively long periods of intubation provides a protective benefit.[388]

USING SKILLED SUCTIONING TECHNIQUES

Complications of tracheal suctioning during TLI include pain, coughing, hypoxemia, cardiac arrhythmias, bronchoconstriction, and mucosal damage. Consequently, it is important to suction the trachea carefully and never routinely.

Multiuse closed-system tracheal suction catheters save time, eliminate the need to disconnect the patient from the ventilator, and are preferable to open suctioning in patients with severe hypoxemia.[389] There is, however, no consensus that they should be used to prevent VAP.[304]

Open suctioning of the trachea should be performed with clean or sterile gloves, a sterile, single-use catheter, and sterile fluid.[304] Tracheal suctioning should ideally be performed by two attendants so as to avoid excessive movement of the ETT during suctioning and to maintain adequate oxygenation and ventilation. The patient should be adequately oxygenated and ventilated and suctioning intervals limited to a maximum of 10 to 15 seconds.

AVOIDING TRANSMISSION OF MECHANICAL FORCES FROM THE ENDOTRACHEAL TUBE DIRECTLY TO THE PATIENT

Elastic connectors and swivels between ventilator tubing and the ETT should be used. The weight of ventilator tubing should be supported by a folded towel on the patient's chest or by overhead supports. The ventilator tubing should not be tied to the bedrails. An ETT holder with integrated bite-block can help secure the position of the ETT and prevent the patient from biting and occluding the tube.

MINIMIZING ABRASION OF THE LARYNGEAL AND TRACHEAL MUCOSA

Any motion of the ETT during TLI applies shearing forces to the mucous membranes of the mouth, and more importantly, the glottis and trachea, promoting airway injury. Attempts at talking, swallowing, and moving by the patient should be discouraged. Coughing should be controlled and aggressive measures taken to manage agitation, seizures, and rigid posturing. The ventilator tubing, ETT, and patient should be thought of as one unit and moved together in order to minimize movement at the interface between the ETT and the patient's airway. Nasogastric tubes should be used only if necessary.

MISCELLANEOUS PREVENTIVE STRATEGIES

The ETT should be attached to a source of warm, fully humidified gas to promote clearing of airway secretions and to avoid desiccation of the tracheobronchial mucosa. If a heat and moisture exchanger is used, especially for prolonged periods of time, close observation of ETT patency and airway resistance is necessary because of the risk of tube occlusion. The patient should be reassured and given emotional support throughout the period of TLI. This may help avoid complications such as self-extubation and those caused by excessive motion and agitation. Because ventilated patients experience a high level of frustration and stress related to their difficulty in communication,[390] care providers need to be especially attentive to patients' communication needs. Finally, the ETT should of course be removed as quickly as possible.

MODIFYING THE DESIGN OF THE ENDOTRACHEAL TUBE

Investigators have attempted to reduce the rate of complications of TLI by modifying the design of the ETT. Such innovations have led to the introduction into clinical practice of devices such as the foam-cuff ETT and the ETT with a suctioning lumen above the cuff. The foam-cuff tube described by Kamen and Wilkinson reduces lateral tracheal wall pressure to less than 15 mm Hg.[391] Experimental innovations have included shaping the ETT to match the anatomic contour of the airway,[392] using a balloon on the shaft of the ETT,[126,261] covering the ETT shaft with foam,[316] lengthening the cuff to provide a larger contact area on the tracheal mucosa,[393] using two cuffs,[394] and adjusting the cuff design to prevent leakage of fluid into the lungs.[395] Self-regulating devices to control cuff pressure have been designed,[255] but they have not gained widespread acceptance.

Complications During and After Extubation

Respiratory care techniques to avoid complications of extubation are reviewed elsewhere.[185,396] The patient should be adequately oxygenated and ventilated before extubation. The cuff should be fully deflated before the ETT is removed, and the pool of secretions above the cuff should be suctioned from the trachea immediately upon cuff deflation. The rate of failed extubations was reduced by a quality improvement program that addressed risk factors for failed extubation.[397]

AVOIDING STRIDOR

Patients with a high risk of postextubation stridor (female gender, prolonged TLI, smaller leak volume on cuff-leak test) should be considered as candidates for prophylactic administration of corticosteroids to prevent or attenuate laryngeal edema. Older studies showed little or no benefit of single doses of corticosteroids to prevent laryngeal edema and postextubation stridor,[398,399] but several recent reviews and meta-analyses indicate a clear benefit of multiple doses of corticosteroids administered 12 to 24 hours before extubation in reducing the occurrence of stridor and the need for reintubation.[400–402]

Patients who have displayed one episode of postextubation stridor requiring reintubation represent a serious therapeutic challenge for subsequent attempts at extubation. In this situation, because no particular therapeutic regimen has been studied carefully in adults and proven to be of benefit, all measures are empiric. No matter what measures are employed, experience indicates the need for repeated intubation of such patients. In one study, such patients required a mean of 2.9 intubations.[224] A trial of parenteral corticosteroids should be considered, but no controlled studies of this approach in adults have been reported. Nebulized epinephrine and helium–oxygen gas inhalation are also reasonable approaches. Weymuller et al[108] proposed a rigorous regimen

in anticipation of a second episode of postextubation stridor, including general anesthesia in the operating room, followed by direct laryngoscopy. Deeb et al recommended immediate telelaryngoscopy for all patients who appear to require tracheotomy because of failed extubation.[143]

IMPORTANT UNKNOWNS

In spite of accumulated experience in airway management of critically ill patients spanning six decades, there is still much that is unknown about complications of TLI and their avoidance. Considering the major advances of the last few decades, it is reasonable to expect even more advances in the decades ahead. It is likely that some of the following questions will be addressed:

1. Are there better techniques to assure correct ETT placement into the trachea?
2. Can subsets of patients requiring TLI who would benefit from early tracheotomy be identified?
3. Is there an optimal size of ETT for individual patients based on gender and height?
4. Is there a better shape for the ETT to avoid posterior laryngeal injury?
5. Is abrasion of the mucosa as a result of motion between the patient and the ETT at the level of the posterior glottis an important risk factor for posterior glottis injury?
6. Would reducing ETT shaft stiffness decrease the risk of posterior glottis injury?
7. Is there a better cuff design to minimize tracheal surface injury?
8. What is the appropriate balance between cuff inflation pressure and airway peak inflation pressure, considering the competing needs of preventing tracheal mucosal ischemic injury and reducing leakage of secretions from above the cuff?
9. What is the optimal composition of the ETT shaft in relationship to its wall thickness, compliance, inner diameter, pressure-flow relationship, and biofilm accumulation?
10. What is the appropriate level of training and experience permissible to perform TLI?

THE FUTURE

Extensive experience with TLI over the last six decades has provided a huge database of ETT-related complications, mechanisms of airway injury, recommendations for management of the intubated patient, and strategies for prevention, early recognition, and treatment of the complications. Large prospective studies of complications of TLI provide special insight into the true frequency of complications and the related risk factors. Retrospective observations, individual case reports, and small case series, however, have also added to our growing knowledge about airway complications of TLI. The expanding literature has allowed us to record and classify seemingly countless examples of airway injury from TLI as well as tracheotomy. Since the development of high-volume, low-pressure ETT cuffs more than 40 years ago, however, major advances to prevent complications of TLI in critical care have not been forthcoming.

Opportunities to reduce the impact of complications of TLI include the following:

1. Performing large multicenter prospective studies of complications of TLI in critically ill adults and children to evaluate the optimal timing of tracheotomy in subsets of critically ill patients.
2. Promoting training and credentialing in advanced airway management, including management of the difficult airway, for personnel involved in critical care at all levels—paramedical personnel, emergency department staff, and critical care unit practitioners.
3. Supporting research in new design and composition of artificial airways, including research to make ETTs more compliant, especially at the level of the posterior larynx, to design new and safer cuffs, and to reduce biofilm on tube surfaces.
4. Performing further prospective studies of the use of alternatives to TLI, including the tracheoesophageal Combitube, the laryngeal-mask airway, and noninvasive positive airway pressure devices.
5. Developing clinical practice guidelines for managing TLI in critically ill patients.

SUMMARY AND CONCLUSIONS

Complications of TLI in critically ill adults are reviewed and classified according to the time period in which they occur: during ETT placement, while the ETT is in place, and during and after extubation. This chapter reviewed mechanisms of these adverse events and described steps to recognize, manage, and prevent complications of TLI. As the literature on complications of TLI expands, new insights to improve airway management of the critically ill patient continue to develop and evolve.

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CARE OF THE MECHANICALLY VENTILATED PATIENT WITH A TRACHEOTOMY

John E. Heffner
David L. Hotchkin

Although Egyptian tablets depict use of tracheotomy for medical applications nearly 5600 years ago,[1] initial descriptions of the procedure in Western literature did not appear until the middle of the sixteenth century.[2] By 1718, "tracheotomy" became accepted terminology for the surgical technique that was then primarily used for relief of airway obstruction and removal of aspirated foreign bodies. Typically gruesome clinical results relegated tracheotomy to a reviled role in airway management and gained it a designation as the "scandal of surgery."[3] The diphtheria epidemics of the nineteenth century popularized tracheotomy.[4] Tracheotomy did not become widely accepted, however, until 1909, when Chevalier Jackson standardized surgical techniques and decreased the operative mortality from 25% to less than 1%.[5]

Advances in tube design during the 1960s and 1970s and improved management techniques further promoted acceptance of tracheotomy for long-term airway access for critically ill, ventilator-dependent patients. The advent of percutaneous dilational tracheotomy (PDT) further widened the application of tracheotomy by allowing the procedure to be performed in the intensive care unit (ICU) by nonsurgeons.[6] Up to 24% of patients undergoing mechanical ventilation and 6% of critically ill patients in general have a tracheotomy performed.[6–12] In North Carolina, nearly a threefold increase in the application of tracheotomy for prolonged mechanical ventilation was observed from 1993 to 2002.[9] Although only 7% of ventilated patients underwent tracheotomy in that study, they accounted for 22% of all mechanical ventilation patient charges.

Four indications exist for a tracheotomy in critically ill patients: (a) maintenance of airway patency for patients with functional or mechanical upper airway obstruction, (b) provision of airway access for suctioning retained airway secretions, (c) prevention or limitation of aspiration in patients with glottic dysfunction, and (d) management of patients who require long-term airway access for ventilator support.[13] Acceptable outcomes from tracheotomy remain dependent on the skill of the operator who performs the procedure and expertise of interdisciplinary teams charged with managing

patients from the critical care phase of their illnesses through transitions to hospital wards and long-term care facilities until successful decannulation occurs.[14,15]

TECHNIQUES OF SURGICAL AIRWAY ACCESS

Standard Surgical Tracheotomy

A *standard surgical tracheotomy* provides tracheal access through a temporary incisional tracheostoma between cartilaginous rings (Fig. 40-1). The stoma spontaneously closes after removal of the tracheotomy tube.

Standard surgical tracheotomy is a well-tolerated procedure with an operative mortality of less than 1% when performed as an elective procedure in stable, ventilator-dependent patients. In contrast, most,[16] but not all,[17] centers report a higher complication rate when surgical tracheotomy is performed as an emergency procedure. Some groups report successful emergency tracheotomy when performed on awake patients.[18] Most centers, however, have replaced emergency surgical tracheotomy with specialized endotracheal intubation techniques to secure a difficult airway,[19] emergency cricothyroidotomy,[20] and emergency percutaneous techniques.[21–27]

Percutaneous Tracheotomy

Percutaneous tracheotomy refers to several techniques that insert a standard or modified tracheal airway with a Seldinger technique below the first or second tracheal rings using a device to cut and spread the trachea[28] or a forceps or dilator technique to cannulate and dilate tracheal tissue between cartilaginous rings (see Fig. 40-1).[29–31]

Ciaglia first described percutaneous dilatational tracheotomy (PDT) wherein a Seldinger technique allowed the insertion of sequential dilators to place a tracheotomy tube.[30] The procedure has evolved from the use of sequential dilators to insertion of a single dilator that increases in caliber from tip to base where it matches the diameter of a tracheotomy tube (Ciaglia Blue Rhino, Cook Critical Care Inc., Bloomington, IN) (Fig. 40-2).[32] The single-dilator Blue Rhino technique results in faster insertion times as compared with the sequential dilator technique,[27,33,34] and a lower risk of posterior tracheal injury.[27,35,36]

Recently, the Ciaglia PDT has been further modified with use of a balloon dilator (Ciaglia Blue Dolphin, Cook Critical Care Inc., Bloomington, IN), which is placed across the anterior tracheal wall and inflated to dilate the stoma by radial force, thereby avoiding anterior–posterior compression of tracheal structures that can fracture cartilaginous rings. The procedure has not yet been established as being superior to the Blue Rhino technique.[37,38]

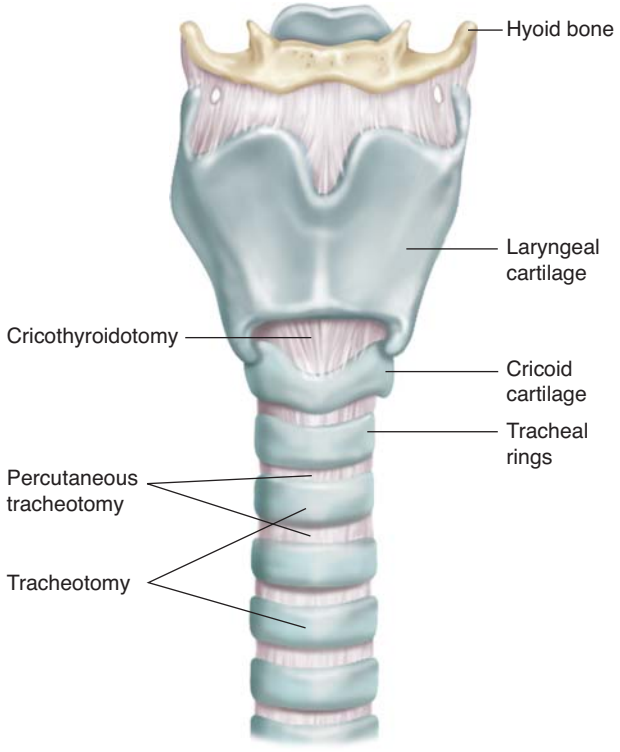

FIGURE 40-1 Anatomic location of stoma placement for different forms of surgical airway access.

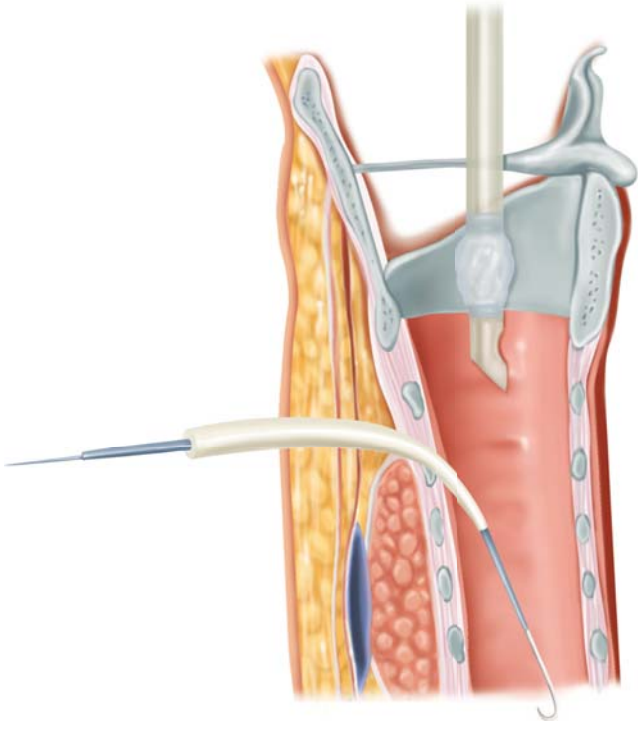

FIGURE 40-2 Insertion of a stoma dilator for percutaneous dilatational tracheotomy. (Courtesy Cook Critical Care, Bloomington, IN.)

The Ciaglia PDT technique is the most commonly performed percutaneous tracheotomy procedure in the United States and is frequently used in Europe.[39–41] Nonsurgeons can perform the procedure with low complication rates, with few patients requiring conversion to a surgical tracheotomy.[42] Controversy remains, however, among otolaryngologists, with only 29% of otolaryngology residency programs teaching PDT; however, programs that do include training in PDT use the Ciaglia Blue Rhino technique and endorse its safety.[43,44]

Other techniques for percutaneous tracheotomy include a specialized guidewire dilating forceps with a groove that allows loading of a guidewire onto forceps, which dilate the trachea, thread the wire, and insert a tracheotomy tube by Seldinger technique (Portex guidewire dilating forceps kit, Sims, Inc, Philadelphia, PA).[45] The guidewire dilating forceps technique provides quick, safe, and effective placement of a tracheotomy for critically ill patients.[46–51] Guidewire dilating forceps require the same time to completion as the Ciaglia single-dilator method.[52,53] Comparative studies have shown both higher,[54] similar,[46,52,53] and lower[50] complication rates with the guidewire dilating forceps as compared with the Ciaglia Blue Rhino technique, with each having unique complications.[55] Long-term follow-up studies demonstrate acceptable rates of tracheal stenosis and other chronic airway complications with guidewire dilating forceps,[56–59] although one study of 208 patients observed a 38% incidence of a changed voice and a 12% incidence of persistent, severe cough. Patients with short, fat necks, conditions that prevent neck extension, an enlarged thyroid isthmus, a previous tracheotomy, coagulopathy, or anticoagulation therapy have successfully undergone the guidewire dilating forceps technique.[60]

Frova et al described a single-step technique (PercuTwist, Rusch, Kernen, Germany) that threads a screw-type dilator between tracheal rings to allow insertion of a specially designed tube.[61] This technique causes less compression of the anterior tracheal wall than does the Ciaglia technique. Early experience with PercuTwist reported variable success with difficulties in learning the procedure and problems with damage to tracheal structures.[34,62–65] More recent reports using bronchoscopic guidance compared PercuTwist with other percutaneous techniques and reported similar complication rates and speed of completion of the procedures.[66–68]

Fantoni proposed translaryngeal tracheotomy for placing a tracheotomy in a reverse direction from within the airway through the tracheotomy tract.[69] The operator places a needle into the trachea between the second and third tracheal rings. With bronchoscope guidance, a guidewire is passed retrograde through the needle into a cuffed, rigid bronchoscope, which is then removed from the airway. A tracheotomy tube with a tapered proximal end is loaded onto the cephalad end of the guidewire and pulled through the airway and the needle tract. Comparative studies suggest that translaryngeal tracheotomy is equally effective and less traumatic than the Ciaglia PDT technique.[70–73]

All percutaneous techniques require a learning curve to gain skills for completing the procedures quickly and safely.[74,75] Centers that emphasize close supervision of trainees note no differences in complication rates by seniority of operator.[76] Because PDT is the primary technique used in most ICUs, it is the percutaneous technique discussed in the remainder of this chapter.

Contraindications to PDT have decreased with increasing experience with the procedure. Conservative relative contraindications have included age younger than 16 years, bleeding diatheses, severely calcified tracheal rings, and anatomic abnormalities, such as obesity and thyromegaly, that obscure landmarks.[35,77–79] Greater experience with PDT, however, has allowed its application by experienced practitioners in patients with body mass indices equal to or greater than 27 kg/m^2 [80] and equal to or greater than 35 kg/m^2.[81] Preoperative ultrasonography allows selection of patients with anatomic abnormalities of the neck for successful PDT.[82,83] Trauma and burn patients with known or suspected cervical injury, patients 5 to 6 days after anterior spinal fusion, and patients with previous tracheostomies have also undergone successful PDT.[83–89] Studies report successful PDT for patients with thrombocytopenia,[90,91] coagulopathies secondary to liver disease,[92] and systemic heparinization.[91,93] PDT has been performed successfully for patients with acute respiratory failure and dependence on high levels of positive end-expiratory pressure (mean: 16.6 cm H_2O; range: 12 to 20 cm H_2O positive end-expiratory pressure).[94]

Purported advantages of PDT as compared with standard surgical tracheotomy include speed of the procedure (less than 10 minutes), ICU placement without operating room transport, avoidance of general anesthesia, decreased cost, reduced operating room use, and limited personnel requirements that include a single operator, a bronchoscopist, a nurse, and a respiratory therapist.[95,96] Such simplifications decrease costs,[97] avoid complications from intrahospital transport, and eliminate dependency on the operating room schedule, thereby decreasing the time from the decision to place a tracheotomy to when it is actually performed.[98] Some centers, however, obviate some of these benefits by performing standard surgical tracheotomy in the ICU.[99–109] Standard surgical tracheotomy in the ICU has similar costs and complication rates comparable to PDT if performed under controlled circumstances with all of the resources that would be available in the operating room.[108,109]

Percutaneous tracheotomy has a potential advantage over standard surgical tracheotomy by dilating rather than incising cervical tissues thereby producing a tracheostoma that fits snugly around the tracheotomy tube.[110] This tight fit has potential for improving anchoring of the tracheotomy tube, decreasing the incidence of inadvertent extubation (1.4% incidence),[43] compressing blood vessels in the stoma tract thus decreasing postoperative bleeding (2% to 4% incidence),[35,43,111] and diminishing the incidence of wound infections observed with conventionally placed surgical stomas.[111] The smaller skin incision also may result in a better cosmetic appearance after extubation.[111,112]

Many observational studies and a smaller number of randomized, controlled trials[73,86,95,96,98,104,111–119] have addressed the potential benefits of PDT by comparing the outcomes of the procedure with those of standard tracheotomy. These trials, however, are relatively small, often employ varying tracheotomy techniques, have considerable spectrum bias, usually exclude patients with relative complications to PDT, and measure heterogeneous outcomes with differing definitions between studies. Five meta-analyses have critically analyzed these studies and come to varying conclusions.[109,120–123] The meta-analysis by Dulguerov et al concluded that PDT had a higher complication rate than standard tracheotomy, but the analysis suffered from methodological flaws (double counting) and included retrospective studies.[109] The three most recent meta-analyses[109,122,123] have the usual limitations from heterogeneity of primary studies, but conclude that PDT and surgical tracheotomy have comparable major complication rates. The analyses differ regarding relative rates of early postoperative complications, but Delaney et al performed a subgroup analysis by type of PDT and found a similar rate of postoperative bleeding for PDT as compared with surgical tracheotomy performed in the operating room.[123] General conclusions from these analyses indicate that the choice of technique should be individualized by an interdisciplinary approach and PDT can be performed more quickly with similar outcomes as compared with surgical tracheotomy performed in the operating room or at the bedside in appropriately selected patients.[109] A shorter time from the decision to perform tracheotomy to its actual completion may result from PDT.[98,111] Prospective comparative data of surgical versus PDT for patients with underlying bleeding diatheses, neck anatomic abnormalities, and other risk factors for complications do not exist.[124] Also, up to 7% of PDT procedures require conversion to surgical tracheotomy because of technical difficulties.[122]

Cricothyroidotomy

Cricothyroidotomy, or more specifically *surgical cricothyroidotomy,* is a surgical technique for placing an airway through the cricothyroid space (see Fig. 40-1). The term has also been applied to percutaneous placement of a cannula by Seldinger technique (*cannula* or *percutaneous* cricothyroidotomy) or a needle (*needle* cricothyroidotomy) through the cricothyroid space to establish an emergency airway. Because of its simplicity and the superficial location of the cricothyroid space, cricothyroidotomy has become the preferred procedure for emergency airway placement for patients who cannot undergo translaryngeal intubation.[125–128] After training on simulators or cadavers, operators can complete surgical or cannula cricothyroidotomy in less than 60 seconds.[129–131] Some centers, however, prefer emergency PDT after failed intubation attempts.[21–27] Up to 62% of patients have vertically oriented arteries and veins overlying the cricothyroid membrane, which can complicate cricothyroidotomy.[132]

Most intensivists do not employ cricothyroidotomy for elective, long-term airway access in critically ill patients because of concern for delayed airway damage, which has been reported to occur more commonly in patients with 6 to 7 days of prior translaryngeal intubation.[133–137] More recent studies propose that cricothyroidotomy has a low complication rate and represents a reasonable option for critically ill patients with challenging neck anatomy.[106,138,139] These studies were retrospective, however, and did not provide systematic patient follow-up to detect long-term airway complications.

Cricothyroidotomy presents potential long-term risks to vocalization after decannulation because the tube inserts through the cricothyroid membrane, which lies within 1 cm of the true vocal cords, and can thereby cause glottic and direct vocal cord scarring and also prevent anterior pivoting of the laryngeal cartilage, which is required to stretch the vocal cords.[140,141] Up to 78% of patients treated with a cricothyroidotomy experience hoarseness.[140–144] No studies, however, have compared the relative risk of voice changes after cricothyroidotomy as compared with tracheotomy,[125] which have been reported to cause vocalization problems in 24% of cardiovascular surgery patients after tracheotomy.[145]

Because of concerns for long-term airway damage, traditional recommendations propose converting emergency cricothyroidotomies to tracheostomies within 72 hours for patients who require continued airway support.[146] Such recommendations, however, have not been studied. Small case series report serious complications in approximately 50% of ventilator-dependent trauma patients undergoing conversion and longer hospitalizations as compared with patients maintained with their initial cricothyroidotomies.[18,147] A meta-analysis of 1134 patients undergoing emergency cricothyroidotomy reports a 2.2% incidence of subglottic stenosis overall and a 1.1% incidence in trauma patients, with only 0.3% of trauma patients requiring reconstructive airway surgery.[125] The study emphasized that the primary studies had considerable deficiencies, no studies support routine conversion, and a need exists for further investigations in light of the potential risks of conversion to tracheotomy.

Although cricothyroidotomy has been recommended for long-term airway support after median sternotomy to avoid mediastinitis, recent reports report an acceptably low risk of mediastinitis when tracheotomy is performed after cardiac surgery.[148–151] The advent of PDT has further decreased concern regarding contamination of fresh sternal incisions,[150–153] although PDT remains an independent predictor of deep sternal infections (odds ratio [OR] 3.22, 95% confidence interval [CI] 1.14 to 9.31, $p < 0.0001$) after cardiac surgery.[154]

Currently, cricothyroidotomy serves as the primary approach for emergency airway support when translaryngeal intubation fails and as a secondary approach for elective long-term airway access in support of mechanical ventilation. When performed electively, most,[134,136,142] but not all,[106,138,147] clinicians reserve cricothyroidotomy for patients intubated less than 7 days. Cricothyroidotomy should also be avoided if possible for patients who depend occupationally on their voice, such as singers or actors,[144] despite absence of comparative outcome data with tracheotomy.[125]

Minitracheotomy

A *minitracheotomy* is a percutaneous technique first described by Matthews et al in 1984 for inserting through the cricothyroid membrane a specialized 4-mm uncuffed tube that accommodates a 10 Fr suction catheter (see Fig. 40-1).[155–157] Performed at the patient's bedside, minitracheotomy provides direct access to the airway for suctioning tracheal secretions without interfering with the patient's cough or speech. The catheter can be capped when not in use for airway suctioning. Because of the tube's small caliber and uncuffed design, a minitracheotomy does not provide airway access for mechanical ventilation, although it has been used during elective otolaryngologic procedures,[158] in patients undergoing jet ventilation,[159] for patients with sternal dehiscence,[160] and for the management of sleep apnea.[161]

The procedure may provide benefit for patients with adequate spontaneous respirations who appear at risk for secretion-related deterioration of lung function.[157,162–168] Patients at high risk for pulmonary complications after thoracic or upper abdominal surgery may benefit from the prophylactic placement of a minitracheotomy at the end of the operative procedure.[162] It has also been used as a transition from PDT for patients who have weaned from mechanical ventilation but who cannot manage secretions.[169] Little outcome data exist, however, to demonstrate efficacy of minitracheotomy with a recent meta-analysis of primary studies demonstrating no benefit in terms of mortality or ICU length of stay for high-risk patients undergoing thoracotomy and lung resection.[170]

Minitracheotomy is usually well tolerated, although 1% develop life-threatening complications[170] and 6% to 57% develop minor complications, such as temporary discomfort, voice changes, subcutaneous emphysema, bleeding, and dyspnea.[156,170–173] Life-threatening complications include pneumothorax after misplacement into paratracheal tissue, profuse bleeding from anterior jugular veins, and esophageal puncture.[174–177] Long-term studies have not reported subglottic stenosis after minitracheotomy.[2,157,163]

SURGICAL TECHNIQUES FOR TRACHEAL CANNULATION

Open Surgical Tracheotomy

Elective standard tracheotomy is performed in an operating room under general anesthesia or an ICU for patients if adequate lighting, personnel, and equipment can provide the resources available in an operating room. The patient's neck is hyperextended with a rolled towel placed between the shoulder blades to bring the trachea and larynx into a superficial and elevated position. The surgeon identifies anatomic landmarks by palpating the cricoid cartilage, tracheal rings, and thyroid cartilage. Some surgeons perform ultrasound to identify structures.[178]

Unless the patient has a vertical scar from a previous tracheotomy, most surgeons perform a 2- to 3-cm transverse incision 2 cm above the suprasternal notch midway between the sternal notch and thyroid cartilage over the second tracheal ring with subsequent dissection of the subcutaneous tissues and platysma. A vertical incision then separates the sternohyoid and sternothyroid muscles from the midline allowing retraction of the strap muscles to reveal the thyroid isthmus. The thyroid isthmus can be pulled superiorly or inferiorly out of the surgical field, but may need to be divided and oversewn to allow visualization of tracheal rings. Vessels can bleed substantially and require electrocautery or suture ligation. Although the anterior jugular veins lie lateral to the incisional plane, communicating venous branches may need to be divided.

The trachea is elevated and stabilized by placing a cricoid hook under the cricoid cartilage or first tracheal ring or using lateral traction sutures around the third or fourth tracheal rings. A vertical incision between the second and third or third and fourth tracheal rings is made with a scalpel, avoiding electrocautery because of flash fire risks. A tracheal wall flap (Björk flap) attached inferiorly to the anterior tracheal wall can be created or a section of the tracheal wall removed. The translaryngeal endotracheal tube is pulled back under direct vision above the tracheal incision. Some surgeons pass the endotracheal tube further into the airway, positioning the tip by bronchoscopic guidance just above the carina, which allows the endotracheal tube cuff to block incisional blood from entering the lower airway.[179]

After positioning the endotracheal tube, the tracheal incision is gently dilated laterally sufficiently to allow insertion of a tracheotomy tube. The tube size is selected by airway inspection, choosing a tube approximately two-thirds the diameter of the tracheal lumen at the level of the stoma. Some surgeons measure the depth of the stoma track and the angle between the stoma and trachea in all patients to determine a need for a nonstandard tube.[180] Specialized tubes are usually required for patients with obesity, short necks, or other anatomic variations,[78] with special attention directed toward assessing the depth of pretracheal tissue before tube insertion.[181] The nonstandard internal diameters of tracheotomy tubes from different manufacturers should also be recognized.[182] After inflation of the tube cuff and confirmation of adequate ventilation, the endotracheal tube is removed. Some surgeons use bronchoscopy to confirm correct tracheotomy tube positioning and to suction bloody secretions.[183] The tracheal traction sutures are removed because they serve little value in facilitating recannulation of the trachea if inadvertent decannulation later occurs.

Percutaneous Dilational Tracheotomy

The PDT Blue Rhino single-dilator Seldinger technique utilizes a kit that contains a J-wire guide, Teflon catheter with introducer needle, a Teflon introducer dilator, a translucent Teflon guiding catheter, and a single curved dilator.

Some operators first examine the neck after the application of positive end-expiratory pressure with the patient in the horizontal position and the neck slightly extended to detect aberrant jugular veins that traverse the operative field.[169] Others examine the neck by ultrasonography to both detect aberrant vessels and select an insertion site.[178,184] The patient is preoxygenated with 100% O_2 and positioned with the head extended as for a standard surgical tracheotomy.[185] Patients with mild to moderate respiratory acidosis may benefit from increasing the minute ventilation before the procedure.[185] Even with a normal baseline partial pressure of carbon dioxide (P_{CO_2}), 26% of patients experience an increased P_{CO_2} by equal to or greater than 3 to 4 mm Hg during insertion of a bronchoscope, with risks for intracranial hypertension in neurosurgical patients[185] unless minute ventilation is adjusted upward.[186] A 2-cm transverse skin incision is made over the second tracheal interspace. Protrusion of fat into the wound is a reliable measure of adequate depth of the incision.[185] Blunt dissection through the incision identifies the anterior tracheal wall.

A fiber-optic video bronchoscope is inserted through the endotracheal tube to visualize the puncture site and ensure its midline position, orientate the endotracheal tube above the needle insertion site, provide suction for pulmonary toilet, and avoid puncturing the posterior tracheal wall.[111,187,188] After withdrawal of the endotracheal tube above the first tracheal ring and reinflation of the cuff, a syringe with the catheter-introducer needle is advanced between the first and second or second and third tracheal rings. Some operators use the bronchoscope to transilluminate the needle insertion site or depress the insertion site with mosquito forceps under bronchoscopic visualization to ensure precise needle insertion[189] and adequate withdrawal of the endotracheal tube above the needle insertion site.[187,190] After air is aspirated through the needle, the J-wire is passed into the trachea toward the carina and the needle is removed. The wire must remain freely mobile throughout the procedure or perforation of the posterior tracheal wall should be suspected.[185] The curved dilator is passed over the wire until the trachea has been dilated sufficiently to receive the tracheotomy tube, which is loaded onto an introducer and inserted over the guidewire. Dilation of the trachea may be difficult in young patients with healthy tracheal tissue.[191]

Some physicians employ methods other than bronchoscopy to ensure proper placement of the tracheotomy tube. A "modified PDT" employs direct palpation of the trachea without bronchoscopy.[192] This technique, however, produces a larger stoma similar to a standard surgical tracheotomy and obviates the advantages from PDT of a snug stoma.[189] Others use an external laser light source for transillumination to obviate bronchoscopy.[193] Intratracheal placement of the needle and dilator guided by capnographic monitoring of exhaled CO_2 has been reported in a randomized trial of fifty-five patients to have similar outcomes as with bronchoscopy.[194] Insertion of a light wand into the trachea can also guide PDT by transilluminating pretracheal tissue.[195]

Most operators, however, use bronchoscopy to guide PDT because of its multiple advantages.[35,123,196] Bronchoscopy ensures withdrawal of the endotracheal tube above the surgical site,[197] decreases risk of injury to the posterior membranous portion of the trachea,[35,198,199] allows early recognition of tracheal puncture if it occurs,[199] and may lower risk of pneumothorax and pneumomediastinum.[35] Bronchoscopy facilitates translaryngeal reintubation if the endotracheal tube inadvertently moves above the glottis.[185] The endotracheal tube size must be 7.5 mm or greater to accommodate the bronchoscope.[185]

Preoperative assessment with ultrasonography may ensure proper placement of a PDT, avoidance of vascular structures, and detection of a deep lying trachea that would indicate a need for surgical tracheotomy.[200,201] One study in seventy-two patients found that ultrasound imaging altered the originally selected needle insertion site in 24% of patients because overlying vascular structures and/or thyroid tissue.[202] Ultrasonography also may be of value in patients with obesity, short necks, and other anatomical variations.[82] Ultrasonography may be increasingly used as an adjunct to bronchoscopic PDT with the advent of highly portable ultrasonographic equipment.[203]

The airway becomes unstable during PDT when the endotracheal tube cuff is withdrawn into the endolarynx. An additional variation of technique employs removal of the endotracheal tube and insertion of a laryngeal mask airway,[204–207] microlaryngeal tube,[208] or 4-mm pediatric endotracheal tube.[209]

Cricothyroidotomy

The cricothyroid membrane is located by palpation of the prominence of the cricoid cartilage. The membrane is 9 to 10 mm in height and trapezoidal in shape, with a surface area of 3 cm^2. It lies 9 to 10 mm beneath the true vocal cords.[126,210]

To perform a surgical cricothyroidotomy, the patient is positioned as for a standard tracheotomy.[127,128] A horizontal 2-cm skin incision is carried through the subcutaneous tissue to the thyroid cartilage. In the emergency setting, a vertical skin incision avoids severing the anterior jugular veins.[78] The lower border of the cricothyroid membrane is incised transversely, and a tracheal hook is placed under the thyroid cartilage. A Trousseau dilator is inserted through the membrane with gentle vertical dilation to allow passage of a 6- or 7-mm tube. The outside diameter of the tube is limited by the height of the cricothyroid membrane (usually 9 mm).

Percutaneous cricothyroidotomy avoids a surgical incision[211] and represents the preferred route in some algorithms for managing difficult airways.[212] Several prepackaged kits are available (Quicktrach Kit, Teleflex Medical, Research Triangle, NC; Portex Minitrach II Kit, Smiths Medical, Dublin, OH; Melker Kit, Cook Critical Care, Bloomington, IN). The various techniques for percutaneous

cricothyroidotomy, necessary training for competency,[213] application of ultrasound guidance,[203,211] and comparative outcomes[130,211,214–216] are discussed elsewhere.

Minitracheotomy

Minitracheotomy can be performed either by a scalpel or Seldinger technique.[156,164] A scalpel kit has a blade that protrudes 1.4 cm from a plastic guard that limits the depth of penetration through the cricothyroid membrane. After positioning as for standard tracheotomy, the cricothyroid membrane is located and marked by palpating the cricoid cartilage. After tissue infiltration with local anesthetic, the guarded scalpel is inserted through the midline of the cricothyroid membrane into the trachea to produce a 1-cm stab incision. The lubricated curved introducer is passed through the incision. A minitracheotomy cannula is then passed over the introducer, which is then removed from the airway.

The Seldinger technique uses a 16-gauge needle that is passed through the cricothyroid membrane. After confirmation of correct placement by aspiration of tracheal air, the needle is angled caudally and a guidewire inserted. The needle is then removed and a minitracheotomy tube loaded over a vein dilator is passed over the guidewire. Once in place, the minitracheotomy tube should be plugged when not in use for suctioning to prevent the inhalation of dry ambient air.

COMPLICATIONS OF TRACHEOTOMY

Techniques and tube designs are sufficiently advanced to allow the safe application of tracheotomy in most ventilator-dependent patients. Although 9% to 40% of patients will experience some type of complication, most of these are minor and the mortality rate is less than 1% (Table 40-1).[17,217–220] The frequency and seriousness of complications correlate with an institution's and operator's expertise in airway management and the use of strict management protocols.[220,221]

Intraoperative Complications

CARDIORESPIRATORY ARREST

Sudden cardiorespiratory arrest is the most feared complication of tracheotomy, occurring in fewer than 1% of patients. Underlying etiologies include vasovagal reactions, misplacement of the tracheotomy tube, tension pneumothorax, arrhythmias, and pulmonary edema after relief of transient upper airway obstruction.[35,222,223]

HEMORRHAGE

Major hemorrhage occurs rarely as an early complication because it can be avoided by identifying anterior jugular veins, vascular anomalies, and the thyroid isthmus to avoid inadvertent transection. Tracheotomies performed below the fourth tracheal ring risk injury to the innominate artery.

Minor hemorrhage occurs in 1% to 40% of surgical tracheotomies, with bleeding rates depending on operator experience and presence of bleeding diatheses.[99] Recent PDT series report less than 2% to 4% bleeding rates,[42,76] although bleeding is the most common individual complication of the procedure.[35,76]

TABLE 40-1: COMPLICATIONS OF TRACHEOTOMY

Aspiration pneumonia
Cardiopulmonary arrest during the procedure
Herniation and fracture of tracheal rings
Inadvertent decannulation
Mediastinitis
Peristomal cellulitis
Pneumomediastinum and pneumothorax
Poor stoma healing after decannulation with scar, keloid, or tracheocutaneous fistula
Posterior tracheal wall perforation
Stomal erosion or breakdown
Stoma site infection
Stomal hemorrhage
Subglottic stenosis or atresia
Surgical emphysema
Tracheal dilation
Tracheal granulomas with obstruction
Tracheal ring rupture
Tracheal stenosis
Tracheoesophageal fistula
Tracheoinnominate fistula
Tracheomalacia

PNEUMOTHORAX AND PNEUMOMEDIASTINUM

Pneumothorax and/or pneumomediastinum occur in 0% to 4% of patients,[97,99,106,119,224] as a result of dissection of air through the incision into the mediastinum, rupture of a lung bleb if transient airway obstruction occurs, or direct injury to the apical pleura.[225] Massive mediastinal insufflation can result from tube misplacement into paratracheal tissue.[226,227]

RECURRENT LARYNGEAL NERVE INJURY

The recurrent laryngeal nerves lie along the tracheoesophageal recesses. A properly placed midline surgical tracheotomy incision should not injure the nerves in their deep positions, but risk of injury is increased in patients with altered cervical anatomy.

TRACHEOESOPHAGEAL FISTULA

Improper technique can puncture or lacerate the posterior membranous tracheal wall and cause an acute tracheoesophageal fistula. Most contemporary studies report an incidence

rate of 0% to 1% of tracheal perforation during PDT performed with bronchoscopic guidance.[198,217,219,220,228,229]

Early Postoperative Complications

HEMORRHAGE

Wound hemorrhage may first present during the early postoperative period when an injured blood vessel ruptures when the patient coughs or moves. Resolution of intraoperative hypotension or dissipation of tissue epinephrine infiltrated during tracheotomy may also cause bleeding to present after the patient leaves the operating room. Prolonged oozing that persists for longer than 2 to 3 days is usually attributable to coagulopathy.[93] Onset of hemorrhage 48 hours or more after surgery suggests a tracheoinnominate fistula.[230] Immediate airway hemorrhage may be less common with PDT as compared with surgical tracheotomy, with rates less than 2%,[42] although instances of massive, fatal airway hemorrhage with PDT have been reported.[231,232]

SUBCUTANEOUS EMPHYSEMA

Subcutaneous emphysema occurs in less than 10% of patients undergoing surgical tracheotomy.[224,233] Positive pressure escapes from the airway around an inadequately sealed tracheotomy tube cuff and decompresses into cervical tissue planes. Avoiding gauze packing in the tracheotomy wound decreases the risk of subcutaneous emphysema. Use of a fenestrated tube during the first week after tracheotomy promotes subcutaneous emphysema because the fenestrations may shift into the stoma tissue tract.[234] Misplacement of a tube into paratracheal tissue may first present with subcutaneous emphysema.[68] Pneumoperitoneum may also occur after tracheotomy.[235] After correction of the underlying cause, subcutaneous air is usually resorbed spontaneously.

INADVERTENT DECANNULATION

Inadvertent decannulation is a life-threatening complication, particularly during the first 72 hours after tracheotomy. During this period, the stoma tract has not fully developed and parastomal tissue can obscure the tracheal window during recannulation efforts. Blind attempts to replace the tracheotomy tube usually result in misplacement into the pretracheal fascia and external airway compression.

Ventilator-dependent patients who experience early inadvertent decannulation should be reintubated through the translaryngeal route if upper airway obstruction is not a factor. The tracheotomy tube can then be reinserted under more controlled conditions. If emergent recannulation of the stoma tract is necessary because of upper airway obstruction, the patient should be positioned as for surgical tracheotomy with a hyperextended neck. Pulling on tracheal traction sutures may allow visualization of the tracheal window. Initial insertion of a smaller size cannula or placement of a guide catheter, such as an intubation stylet, over which a tracheotomy tube is passed, may assist recannulation.

If the tracheal lumen is not clearly seen, a pediatric laryngoscope may assist exploration of the wound and airway visualization. In thick-necked individuals, initial placement of a cuffless pediatric translaryngeal endotracheal tube followed by recannulation with a larger tracheotomy tube later may be required. A fiber-optic bronchoscope or laryngoscope may serve as a guiding stylet to assist tracheotomy tube reinsertion. Regardless of the approach, recannulation should be attempted only by skilled and adequately prepared operators because of the high risk of misplacement.

The 1% to 7% incidence of early inadvertent decannulation can be decreased by appropriately securing the tracheotomy tube.[99] Tracheotomy tape should wrap closely around the neck, allowing sufficient space for insertion of a single finger. Tape should not be secured over gauze dressings that may later shift. Although avoided by some surgeons, suturing the tracheotomy plate to the skin is an additional preventative approach. Risks of accidental decannulation are especially high in obese patients, who benefit from selection of an appropriately configured tube to fit through the stoma tract.[181]

STOMA WOUND INFECTION

Although rapidly contaminated with nosocomial pathogens,[236] only 11% to 30% of surgical tracheostomies[17,111,237] and 4% to 9% of PDT procedures[111,237] are complicated by wound infections, probably because the stoma is left open to drain secretions. Patients with purulent wound drainage without tissue infection usually respond to local tracheostoma care. Systemic antibiotic therapy is reserved for parastomal cellulitis and signs of deep tissue infection. Necrotizing stomal infections can dissect into cartilaginous tracheal structures, adjacent major blood vessels, and the mediastinum.[238] This complication requires drainage, débridement, and replacement of the tracheotomy tube with a translaryngeal endotracheal tube.[239]

PNEUMONIA

All ventilator-dependent patients are at risk for ventilator-associated pneumonia (VAP). Tracheotomy has theoretic potential for both increasing the rate of VAP by promoting drainage of colonized stomal pathogens into the lungs and for decreasing VAP rates by allowing removal of the endotracheal tube and promoting normal glottis closure, which may prevent aspiration. However, up to 35% of patients with a tracheotomy experience aspiration,[240–242] which is most often silent.[242] No evidence exists that aspiration occurs more commonly in ventilator-dependent patients after conversion to a tracheotomy.[243]

Although observational studies indicate that VAP occurs more commonly in patients with a tracheotomy as

compared with patients intubated through the translaryngeal route,[244–246] it is difficult to control these studies for duration and severity of respiratory failure.[247] One study examined risk factors for VAP with multivariate analysis and reported tracheotomy as an independent predictor of VAP (adjusted OR = 3.56).[248] Studies also report an increased rate of VAP in patients undergoing tracheotomy while receiving sedation[249] or after placement of an internal jugular central venous catheter.[250] A retrospective case-control study, however, reported tracheotomy as an independent predictor of a lower rate (episodes per 1000 mechanical ventilator days) of VAP.[251] The relationship between tracheotomy and risk for VAP appears to be highly complex, with many interactions with other clinical factors, which prevent strong conclusions regarding whether tracheotomy is associated with a higher or lower incidence of VAP in patients undergoing mechanical ventilation.

TUBE OBSTRUCTION

Partial obstruction of tracheotomy tubes decreases airflow and increases work of breathing for patients receiving partial assist modes of mechanical ventilation (intermittent mechanical ventilation or pressure support). Obstruction usually results from inspissated secretions or clotted blood, but may occur with incorrect selection of cannula size that places the tip of the tracheotomy tube against the tracheal wall or carina. Tracheotomy tubes with a removable inner cannula decrease the incidence of obstruction by secretions.[252] Tubes with adjustable flanges can be malpositioned in the airway resulting in obstruction of the lumen.[222] Obstruction can also occur when the tip of the tube causes injury to the tracheal wall with invagination of edematous or granulation tissue into the tube lumen[188,253] or when patient repositioning abuts the tube against the tracheal wall.[254]

Late Complications

Up to 65% of patients undergoing tracheotomy in the ICU experience some type of late complication, which may correlate with the duration of preexisting translaryngeal inubation.[255] The seriousness of these complications requires physicians to monitor patients for complications before and after decannulation.

POOR AIRWAY ALIGNMENT

The short length and standardized design of tracheotomy tubes combined with anatomical variation of patients' airways promote malpositioning of the tube tip within the tracheal lumen. Malpositioning increases airflow resistance and ventilatory workload contributing to failure of weaning from mechanical ventilation. One study of mechanically ventilated patients with a tracheotomy at an acute care weaning center reported that 10% of patients had more than 50% occlusion of tube lumens by tracheal tissue, which was associated with prolonged weaning.[256] Replacing a tracheotomy tube with one of different design can improve alignment within the trachea.

TRACHEAL AND LARYNGOTRACHEAL STENOSIS

Tracheal stenosis occurs at the level of the cuff, tracheostoma site, or tip of the tube. Low pressure–high volume cuffs lower, but do not eliminate, risk of tracheal stenosis at the cuff site.[257,258] Inappropriate cuff overinflation or use of too small of a tracheotomy tube that requires cuff overinflation to maintain an airway seal can convert a low-pressure to a high-pressure cuff system. High intracuff pressures transmit to the tracheal mucosa as high cuff tensions that generate pressure necrosis. Resultant mucosal ulcerations become confluent and expose cartilaginous rings that become infected, which leads to weakening of the anterior and lateral tracheal walls.[255] Necrosis generates fibrous scars and transmural airway narrowing. Nontransmural tracheal stenosis can also develop when cartilaginous structures remain undamaged but granulation tissue and proliferative scars in a weblike pattern narrow the airway. The greatest area of scar formation is usually within 3.5 cm of the stoma and ranges from 0.5 to 4 cm in length.

Tracheal stenosis can occur at the distal tip of the tracheotomy tube if a malpositioned tube abuts tracheal mucosa. A tracheotomy tube design should be selected that ensures collinearity with the tracheal lumen, and traction on the tube or ventilator hoses should be avoided.

The stoma has become the most common site for tracheal stenosis after surgical tracheotomy and PDT.[114,122,219,258–262] The airway is narrowed in an anterolateral dimension with relative preservation of the posterior wall. Contributing factors include an overly large tracheal incision and excessive movement of the tube against the tracheal stoma. Fracture of cartilaginous rings during PDT also leads to tracheal stenosis. Patient-related risk factors include female gender, obesity, diabetes mellitus, hypertension, cardiovascular disease, and current smoking.[258]

Tracheotomy can also cause laryngotracheal stenosis above the stoma site.[259,263] One observational study reported a higher incidence of suprastomal stenosis with PDT (24% of patients with more than 50% of lumen) as compared with surgical tracheotomy (7% of patients).[264] A study in cadavers demonstrated the potential of PDT to damage the cricoid cartilage and structures above the stoma site, which may promote subglottic stenosis.[265] A meta-analysis that compared complications from PDT and surgical tracheotomy, however, found no differences in risk of subglottic stenosis.[122]

Clinical manifestations of tracheal stenosis may develop while the tracheotomy tube is in place, but more commonly occur 2 to 6 weeks after decannulation. Delayed onset as late as 4 months after extubation may also occur. Patients with compromised pulmonary function or neuromuscular disease may not manifest symptoms of tracheal stenosis until an episode of bronchitis with increased airway secretions occurs.

The symptoms and signs of tracheal stenosis may be obscured by the patient's underlying disease, but typically include difficulty clearing secretions, dyspnea unresponsive to bronchodilators, exertion-related dyspnea, cough, monophasic wheezing, stridor, and pneumonia. Patients with normal underlying lung function may be relatively asymptomatic until the tracheal lumen is decreased by more than 50%. Clinically important tracheal stenosis occurs in 1% to 11% of patients after 1 year of follow-up.[59,114,219] Because of the nonspecific nature of the clinical manifestations of tracheal stenosis, patients with deteriorating respiratory function and a history of previous intubation should undergo evaluation.

The diagnostic evaluation relies on imaging and endoscopic studies to detect airway narrowing, which may be fixed or dynamic.[266] Chest radiographs and standard chest computed tomography (CT) scans have limited sensitivity, but three-dimensional spiral CT reconstruction imaging provides a valuable adjunct.[267,268] Pulmonary function tests are insensitive (require 80% narrowing) and nonspecific indicators of upper airway obstruction and provide limited diagnostic utility.[269] Direct bronchoscopic visualization remains the gold standard. Most patients with airway stenosis are candidates for corrective interventions either by tracheal resection and reconstruction, neodymium:yttrium-aluminum-garnet (Nd:YAG) laser therapy, mechanical or balloon dilation, or placement of a stent.[270,270–273]

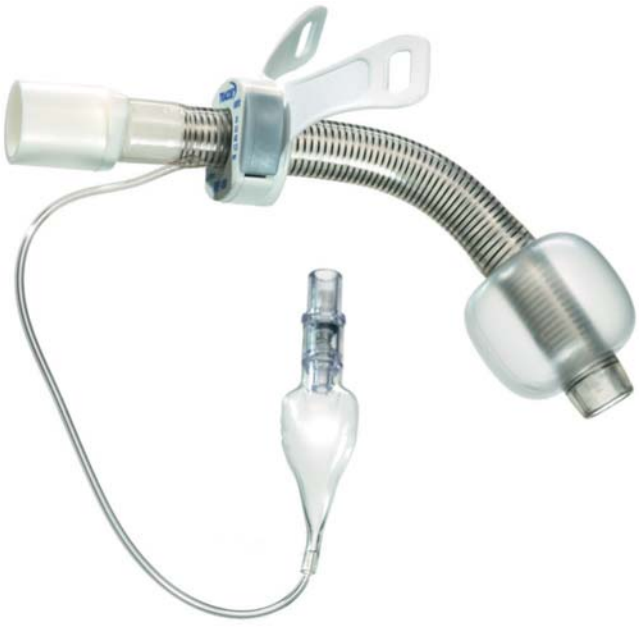

FIGURE 40-3 Flexible tracheotomy tubes with adjustable flanges allow customization of a tube for fitting patients with difficult anatomy or a special need to place the cuff over a specific segment of the airway. (Courtesy TRACOE Medical, Frankfurt, Germany.)

TRACHEOMALACIA

Extensive destruction and necrosis of tracheal cartilages by the tracheotomy tube and ensuing infection of deep tracheal tissue causes tracheomalacia. This complication promotes expiratory tracheal collapse, which can present before or after decannulation. This complication should be suspected in patients who require overdistension of the tracheotomy cuff to maintain an adequate seal.[274] Patients may require a longer tracheotomy tube, bronchoscopic stenting, surgical resection, or tracheoplasty.[183,273]

TRACHEOESOPHAGEAL FISTULA

A tracheoesophageal fistula occurs in less than 1% of patients and results from pressure necrosis of the tracheal and esophageal mucosa caused by the tube cuff.[43,275–277] Risk factors include high cuff pressures, high ventilator-induced airway pressures, excessive tube movement, prolonged intubation, presence of a nasogastric tube, and diabetes mellitus.[276,278] During the course of intubation or after extubation, patients demonstrate increased cough and/or tracheal secretions. Symptoms may only occur after eating solids or swallowing fluids. Patients undergoing mechanical ventilation may experience gastric distension or frequent belching, and chest radiographs may show an air-filled esophagus or gastric distension. Recurrent aspiration may manifest as pneumonia.

A high index of suspicion for tracheoesophageal fistula is required for critically ill patients who have compatible symptoms that may mimic other swallowing or pulmonary problems. The diagnosis is made by tracheoscopy and esophagoscopy, which determine the location and extent of the fistula. Positioning the cuff of an adjustable tracheotomy tube distal to the fistula (Fig. 40-3) and placement of a gastric tube limit airway soiling by aspirated gastric contents. A jejunostomy tube provides nutritional support. Because spontaneous closure rarely occurs, surgical correction is required, which must be delayed until after weaning from mechanical ventilation to avoid anastomotic dehiscence. Primary closure can correct small tracheal fistulae, but most patients require tracheal resection and reconstruction.[276,279] Tracheoesophageal fistulae are universally fatal if left uncorrected.

TRACHEOARTERIAL FISTULA

A tracheoarterial fistula is a major, potentially life-threatening complication of tracheotomy that occurs in less than 1% of patients.[280–283] The innominate artery is most commonly involved because it is nine to twelve tracheal rings below the cricoid cartilage within reach of the tip, and sometimes the cuff, of the tracheotomy tube. In some patients, the innominate artery can traverse the midline just below the tracheotomy stoma where the "elbow" of the tube just above the cuff can induce pressure necrosis.[284] Arterial erosions, however, may also involve the common carotid artery, inferior thyroid artery, the thyroid ima artery, the innominate vein, and the aortic arch.[285] Improper traction on the tracheotomy tube by ventilator tubing, placement of the tracheal window below the fourth tracheal ring, misalignment of the tube with the

tip against the tracheal mucosa, high cuff pressures, prolonged intubation, excessive patient movement or posturing, sepsis, malnutrition, and corticosteroid therapy increase the risks for this complication.[286–289]

Massive airway hemorrhage and asphyxia are the feared complications of tracheoarterial fistula. Hemorrhage can occur as early as several days or as late as 7 months after tracheotomy with the peak incidence between the first and third weeks.[280,283,286,290,291] Up to 50% of patients who experience an episode of airway hemorrhage later than 72 hours after a tracheotomy have an underlying tracheoarterial fistula.[286] Pulsations of the tracheotomy tube and "spotty" herald hemorrhages may portend massive hemorrhage. Any airway bleeding 72 hours after tracheotomy warrants consideration of fiberoptic endoscopy in an operating room environment in case airway manipulation precipitates massive hemorrhage.[230,280] Three-dimensional CT scanning may establish the diagnosis for stable patients.[292] Patients who present with massive hemoptysis should be managed with overinflation of the tracheotomy tube cuff or insertion of a translaryngeal tube with positioning of the cuff over the fistula in an effort to tamponade bleeding. A finger inserted into the stoma tract may allow compression of the innominate artery anteriorly against the sternum (Fig. 40-4).[286,287]

A tracheoarterial fistula represents a surgical emergency and patients require a median sternotomy with ligation and resection of the artery because tissue infection obviates vascular repair.[280,283,285,293] Interruption of the innominate artery is usually tolerated without neurologic sequelae.[280,285,293]

TRACHEOCUTANEOUS FISTULA AND STOMAL SCARS

Epithelialization of the stoma tract may prevent the stoma from closing spontaneously after decannulation. The parastomal platysma or a sternohyoid muscle flap can then be pulled over a surgical stoma repair followed by skin closure.[294–296] Some patients develop excessive scarring at a closed stoma site, which can be managed through reconstructive surgery that fills lost deep tissue bulk, corrects any tracheal skin tugging, and produces a tension-free closure that falls more naturally into the neck folds.[297]

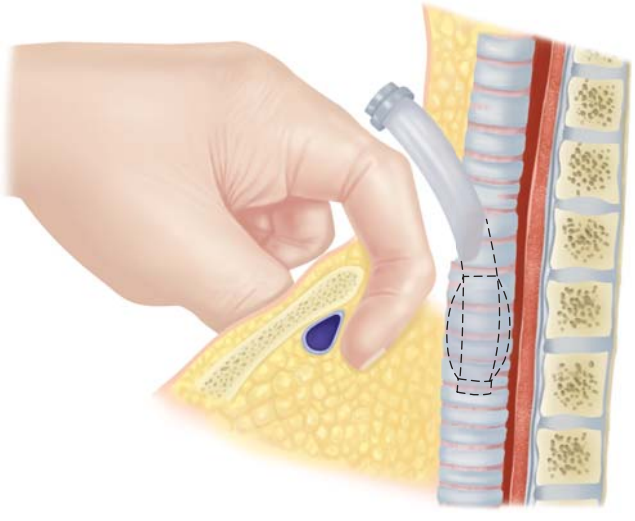

FIGURE 40-4 Hand position for finger tamponade of the innominate artery in a patient with a bleeding tracheoinnominate fistula.

TRACHEAL RING FRACTURE AND HERNIATION

A PDT risks fracture and herniation of tracheal rings because the technique dilates rather than incises intercartilaginous tissue and produces an anteroposterior vector of force at the tracheal insertion site.[298–303] Damaged rings can protrude into the airway causing tracheal narrowing[304] or promote tracheomalacia if extensive loss of cartilaginous support occurs.[305] The frequency of clinically important complications after tracheal ring fractures is unknown. One study followed sixteen patients with tracheal ring fractures and found no instances of tracheal stenosis.[306]

TIMING OF TRACHEOTOMY DURING MECHANICAL VENTILATION

Although translaryngeal endotracheal tubes are relatively well tolerated, patients who require prolonged ventilation eventually benefit from tracheotomy (Table 40-2).[307,308] Selecting patients for tracheotomy and identifying the ideal time for the procedure, however, remain clinical challenges with physicians demonstrating considerable practice variation.[41,309–311] Clinical trials that randomize patients to "early" versus "late" tracheotomy to inform timing decisions face major difficulties.[312] Investigators must be able to identify accurately soon after intubation those patients who will most likely require prolonged ventilation so as to avoid performing unnecessary tracheotomies.[313] Unfortunately, experts doubt their own abilities to predict prolonged intubation during the first days of ventilation.[314] Recent trials report that a large proportion of enrolled patients randomized to control, nontracheotomy groups based on their high risk

TABLE 40-2: ADVANTAGES OF TRACHEOTOMY AS COMPARED WITH PROLONGED TRANSLARYNGEAL INTUBATION

Decreased airway resistance for promoting weaning from mechanical ventilation
Earlier transfer of ventilator-dependent patients from the ICU
Enhanced oral nutrition and oral hygiene
Enhanced phonation and communication
Improved airway suctioning
Increased comfort with opportunities to decrease sedation
Increased patient mobility
Less direct endolaryngeal injury
More secure airway and decreased risk of inadvertent decannulation

of needing prolonged ventilation actually undergo early extubation.[315,316] Collected study data should ideally include comprehensive short-term (e.g., pneumonia, incisional bleeding, duration of mechanical ventilation, patient comfort) and long-term (e.g., tracheal stenosis, speech problems, dysphagia) outcomes, which often have nonstandardized definitions, imprecise or costly approaches to detection, and dependency on case mix.

Additional study design challenges include (a) physician reluctance to allocate patients to the early tracheotomy group when assigned by randomization, (b) difficulties with blinding providers to group allocation, (c) standardizing patient care with protocols for other critical care interventions and approaches to weaning and extubation, and (d) standardizing the tracheotomy technique (i.e., PDT versus surgical tracheotomy). Consequently, most existing prospective trials have limitations because of small and heterogeneous study populations, variations in defining "early" versus "late" tracheotomy, and various methodological flaws that complicate meta-analyses.

These limitations indicate that timing tracheotomy for critically ill patients remains a complex decision that requires individualization of care. No data exist to establish a standard time when tracheotomy must be performed to avoid airway injury related to continued translaryngeal intubation. Moreover, the risks of performing tracheotomy are acceptably low so that it can be safely applied when patients appear likely to benefit from the procedure. Recommendations to "calendar watch" and avoid tracheotomy if at all possible for at least 14 to 21 days because of its attendant risks have become obsolete. Patients should be selected for tracheotomy by considering the unique circumstances of the patient at hand and the likelihood based on existing studies that the benefits of tracheotomy outweigh its inherent risks as compared with the competing risks of prolonging translaryngeal intubation (Table 40-3). Patient and family values and preferences should also influence the decision.

In considering potential benefits, a tracheotomy provides opportunities to improve a patient's comfort and sense of well-being.[316–318] For patients receiving intravenous sedation, some,[319,320] but not all,[316,321] studies indicate that drug requirements to maintain comfort are decreased after tracheotomy. By freeing the oropharynx, tracheotomy promotes oral hygiene and nutrition and facilitates articulated speech,[322–325] allows early mobilization,[312,326] and permits transfer from the ICU to more comfortable and family-centered settings for patients who remain ventilator dependent.[327] More effective oral care and decreased sedative requirements may decrease risks of ventilator-associated pneumonia.[328,329] The largest available randomized trial that assessed impact of tracheotomy timing on pneumonia risk, however, reported no differences between patients undergoing early versus late tracheotomy.[315]

The shorter length and rigid structure of tracheotomy tubes have been stated to decrease airway resistance and promote weaning from mechanical ventilation.[330,331] The resistance to airflow of translaryngeal endotracheal tubes in situ increases beyond in vitro predictions because thermolabile tubes assume angulated configurations and become inspissated with secretions, both of which promote turbulent airflow.[332,333] Studies conflict, however, about whether or not the lower measured resistance of tracheotomy, as compared with endotracheal tubes, produces meaningful benefits. Lin et al noted no clinically important differences in pulmonary mechanics before and after tracheotomy.[334] Three studies, however, noted small decreases in work of breathing after tracheotomy that became more significant with increasing respiratory rates, in addition to decreases in airway resistance, pressure–time product, and auto–positive end-expiratory pressure.[335–337] No changes in tidal volume, respiratory rate, or dead space ventilation were observed.[335–338]

Tracheotomy provides an opportunity to further decrease work of breathing by removing the inner cannula during spontaneous breathing weaning trials.[339] Enhanced ability to suction through a tracheotomy may promote removal of airway secretions, which increase airway resistance of endotracheal tubes; decreased secretions may promote weaning from mechanical ventilation for patients with borderline ventilatory reserve.[336,340]

Most prospective randomized trials report that early tracheotomy within 7 days of intubation decreases duration of mechanical ventilation.[4,315,320,327,341–344] Prospective studies of early tracheotomy also decreases ICU stay, possibly by promoting weaning and allowing transfer of ventilated patients with a stable airway to the wards.[4,315,320,327,344] Some retrospective[10,345,346] and prospective[347] cohort studies indicate that earlier tracheotomy decreases total hospital stay. Other

TABLE 40-3: COMPLICATIONS AND DISADVANTAGES OF PROLONGED TRANSLARYNGEAL INTUBATION

Airway perforation
Aspiration pneumonia
Cricoid cartilage abscess
Damage to intrinsic laryngeal muscles
Dislocation or subluxation of the arytenoid
Granulation tissue forming interarytenoid adhesion
Healed fibrous glottic nodules
Inadvertent extubation
Mucosal ulceration
Nasal septal fractures with nasotracheal intubation
Nosocomial sinusitis
Otitis media
Oversedation
Patient discomfort
Posterior glottic stenosis
Subglottic stenosis
Tracheal stenosis
Ulcerative lesions of the nares and pharynx
Vocal cord fixation from fibrosis of the cricoarytenoid joint
Vocal cord laceration
Vocal cord paralysis
Subglottic web formation

retrospective studies note no differences in hospital length of stay.[348,349] Of note, however, the largest prospective randomized trial to date of early tracheotomy did not find any effect on duration of hospital stay even though time in the ICU was decreased.[315] This study, however, excluded patients with chronic obstructive pulmonary disease and pneumonia. If future randomized studies demonstrate tracheotomy does not decrease hospital stay, any decreases in duration of ICU stay would be expected to result in only small total decreases in total costs of hospitalization.[350]

One randomized trial of early PDT reported decreased hospital mortality for patients in medical ICUs who received early (32% mortality, 2 days before tracheotomy) versus late (62% mortality, more than 14 days before tracheotomy) PDT.[320] The study, however, limited enrollment to patients with an Acute Physiology and Chronic Health Evaluation score of greater than 25, which limits its generalizability to patients with lower mortality risks.[351] Other prospective trials[4,315,316,327,341,343,344] and a retrospective review of a large dataset[352] demonstrate no mortality benefit. Most retrospective and prospective studies of trauma and burn patients report no benefit on mortality between early and late tracheotomy.[236,341,343,344,346,348,349,353–357] Guidelines exist, however, that recommend early tracheotomy for trauma patients estimated to require ventilation for more than 7 days.[358]

Inadvertent extubation occurs in 8.5% to 21% of ventilator-dependent patients[317,359–361] and exposes patients to risks of adverse cardiopulmonary events that include nosocomial pneumonia.[360,362–364] Tracheotomy decreases the risk of self-extubation.[319,320,360,365]

Tracheotomy allows removal of a translaryngeal endotracheal tube and interrupts ongoing injury by the endotracheal tube to intralaryngeal structures. Risks of prolonged translaryngeal intubation include oropharyngeal injury, pressure necrosis of the larynx resulting in subglottic stenosis, and nosocomial sinusitis.[366–368] The decision to perform tracheotomy would be simplified if evidence existed that the risk of laryngotracheal injury correlated with duration of endotracheal intubation. Aggregate data indicate that some degree of clinically important laryngeal injury occurs in 10% to 19% of patients managed with prolonged translaryngeal intubation.[369] It is not clear, however, that laryngeal injury can be predicted by the duration of endotracheal intubation or the detection of acute airway lesions in intubated patients.[370–373] No support exists, therefore, that "calendar watching" with the performance of tracheotomy after a specific duration of translaryngeal intubation prevents long-term airway injury.

In contrast to calendar watching, many clinicians endorse "the anticipatory approach" to timing tracheotomy that tailors the decision to perform a tracheotomy to an individual patient's unique needs.[308,369,374,375] With this approach, the decision to perform of tracheotomy centers less on "when" tracheotomy should be performed and more on "for whom." Patients with respiratory failure first receive necessary critical care to allow stabilization. Patients who appear likely to achieve extubation within the first several days of ventilation are not considered for tracheotomy. If patients remain ventilator dependent for several days and appear likely to require ventilation for 7 or more days, a tracheotomy can be considered. The actual decision to perform the procedure, however, depends on multiple patient-dependent factors that determine whether the patient will likely experience the benefits associated with tracheotomy and on patient and family values. The decision can usually be made for most patients within the first week of intubation.[376]

The anticipatory approach requires daily reassessments of patients to estimate the likelihood that weaning and extubation remains unlikely because the accurate prediction of prolonged ventilation with various scoring systems remains elusive.[6,315,377–390] A standardized protocol to assess patients for tracheotomy may result in more appropriate application of the procedure and less practice variation.[391]

SPECIAL PATIENT CARE CONSIDERATIONS

After tracheotomy, ventilator-dependent patients benefit from a well-organized treatment plan and an interdisciplinary team experienced in tracheotomy management. Skills in evaluating patients for oral communication and nutrition, avoiding airway-related complications, initiating an airway weaning protocol, and recognizing complications after decannulation improve patient outcome.[392] These skills are especially important as pressures increase for earlier transfer of patients with tracheotomy tube to wards or intermediate care units.

Management of Tube Cuff Pressure

Tube cuff pressures should be maintained between 18 mm Hg (approximately 24 cm H_2O) to 25 mm Hg (approximately 34 cm H_2O). Cuff pressures greater than 25 mm Hg can tamponade mucosal capillaries and cause mucosal ischemia, leading to tracheal stenosis.[393] Intracuff pressures below 18 mm Hg may promote microaspiration and nosocomial pneumonia.[394–396] Various techniques exist to estimate cuff pressure, such as finger palpation of the external inflation bulb, minimal occlusive volume, and subjective assessment of tension required on a syringe to inflate the cuff. None, however, reliably substitutes for direct cuff pressure measurements with a pressure gauge.[397–401] In the absence of routine cuff pressure monitoring, up to 45% of critically ill patients have excessively high endotracheal tube cuff pressures.[402] Unfortunately, use of manometry to monitor cuff pressure does not ensure the avoidance of excessively high inflation pressures because of measurement practice variation.[403,404] Chest radiographs can detect overdistension of the tracheal lumen by a hyperinflated cuff and provide an additional safeguard against overinflation.[405] Tube cuffs from different manufacturers may seal airways at different pressures.[406]

Several factors contribute to elevated cuff pressure. High peak airway pressures externally compress the cuff surface raising intracuff pressure and tracheal wall tension.[407] Patients undergoing general anesthesia experience a rapid increase in cuff pressure as anesthetic gases infuse into the air-filled cuff.[408] An inappropriately small tracheotomy tube can also cause increased tracheal wall tension with resultant delayed airway stenosis by necessitating cuff overinflation to maintain an airway seal.[409] Elevated cuff pressures may signify the presence of tracheal dilation (e.g., tracheomalacia), which requires cuff overdistension to produce a seal.[274] Transport to high altitude can also increase cuff pressure.[410]

Standards of respiratory care call for recording cuff pressures measured by a calibrated device and recording pressures once a shift or whenever the tube is changed or other events occur that may alter cuff pressure.[411] Cuff pressure should be monitored with the use of a syringe, stopcock, and manometer that allow simultaneous communication between all three compartments while pressure is being adjusted and measured.[411] Use of the minimal leak technique or palpation of the pilot balloon is not recommended.[409,411]

Swallowing

Normal swallowing is a complex physiologic event comprised of simultaneous and sequential contractions of muscles of the oral–facial region, pharynx, larynx, and esophagus. To initiate swallowing, upward and backward motion of the tongue moves a food bolus to the posterior oral cavity or oropharynx,[412–414] where stimulation of neuroreceptors triggers pharyngeal swallowing and halts respiration, typically in the expiratory phase.[415–418] The pharyngeal swallow comprises five overlapping events that protect the airway and clear the pharynx of ingested material. These events are (a) elevation and retraction of the soft palate, (b) elevation and anterior displacement of the hyoid bone and larynx, (c) laryngeal closure, (d) pharyngeal contraction, and (e) opening of the pharyngoesophageal region.[412,419–424]

Contraction of the pharyngeal constrictors occurs coincident with forceful retraction of the tongue, which propels the bolus posteriorly to assist pharyngeal clearance.[424] Contractions of the thyrohyoid and submental extrinsic tongue muscle group elevate and move forward the hyoid bone and larynx as a functional unit. This hyolaryngeal complex movement closes the larynx to prevent aspiration and pulls the cricoid cartilage anteriorly and away from the posterior pharyngeal wall, thereby opening the pharyngoesophageal segment region to permit entry of the bolus into the cervical esophagus.[420–426] The pharyngoesophageal segment becomes compliant by synchronized relaxation of the cricopharyngeal muscle. The larynx then descends toward its resting position and respiration resumes characterized by a small expiratory airflow.[415–417] Once in the cervical esophagus, the bolus is propelled by primary and secondary esophageal peristaltic muscle contractions.[427,428] These contractions continue until the bolus progresses into the stomach through the passively relaxed lower esophageal sphincter.

A tracheotomy tube and/or inflated cuff may interfere with the mechanics of swallowing (Fig. 40-5). A tube can anchor the hyolaryngeal complex and prevent its normal excursion during swallowing causing incomplete airway closure and penetration of liquid and food into the laryngeal vestibule with aspiration below the vocal folds.[429,430] Prevention of the normal upward and forward mobility of the hyolaryngeal complex impedes anterior displacement of the cricoid cartilage leading to incomplete opening of the cervical esophagus and retained pharyngeal contents, which may be aspirated into the open airway after completion of the swallow. An inflated tube cuff may disturb esophageal motility and slow esophageal clearance causing retrograde flow of ingested material into the pharynx with aspiration. Coexisting gastroesophageal reflux disease with esophageal refluxate increases the risk for aspiration.[431] Preexisting translaryngeal intubation presents an additional risk factor for aspiration even in patients who do not progress to tracheotomy with more than 50% of patients experiencing dysphagia after prolonged translaryngeal intubation.[432]

Tracheostomized patients at risk for aspiration should undergo a systematic assessment to determine the nature of any swallowing disorder to prevent aspiration and facilitate weaning to decannulation. Coordination of services between speech therapists and critical care providers provides resources for assessing aspiration risk, monitoring the extent of aspiration, and managing risk to prevent complications during tracheotomy use, weaning, and postdecannulation (Table 40-4).[433–436]

Nutrition

Feeding patients with a tracheotomy through a nasoenteric tube increases the risk of aspiration and pneumonia. Up to 69% of patients with a tracheotomy aspirate at least once every 48 hours regardless of mental status.[395,437]

Although a tracheotomy offers opportunities to resume an oral diet, patients recovering from critical illness with a tracheotomy in place commonly have severe swallowing dysfunction,[242,438,439] either from underlying disease or effects of the tube itself.[440,441] Before resuming oral feeding, patients should undergo evaluation by an interdisciplinary team that includes a speech-language pathologist trained in swallowing assessment.[433,441,442]

Communication: Voice, Speech, and Language

A tracheotomy disrupts normal speech production. For patients previously intubated with an endotracheal tube, however, a tracheotomy may improve patient well-being by increasing options for communication.[375,433,443–448] Personal isolation and an inability to communicate during mechanical

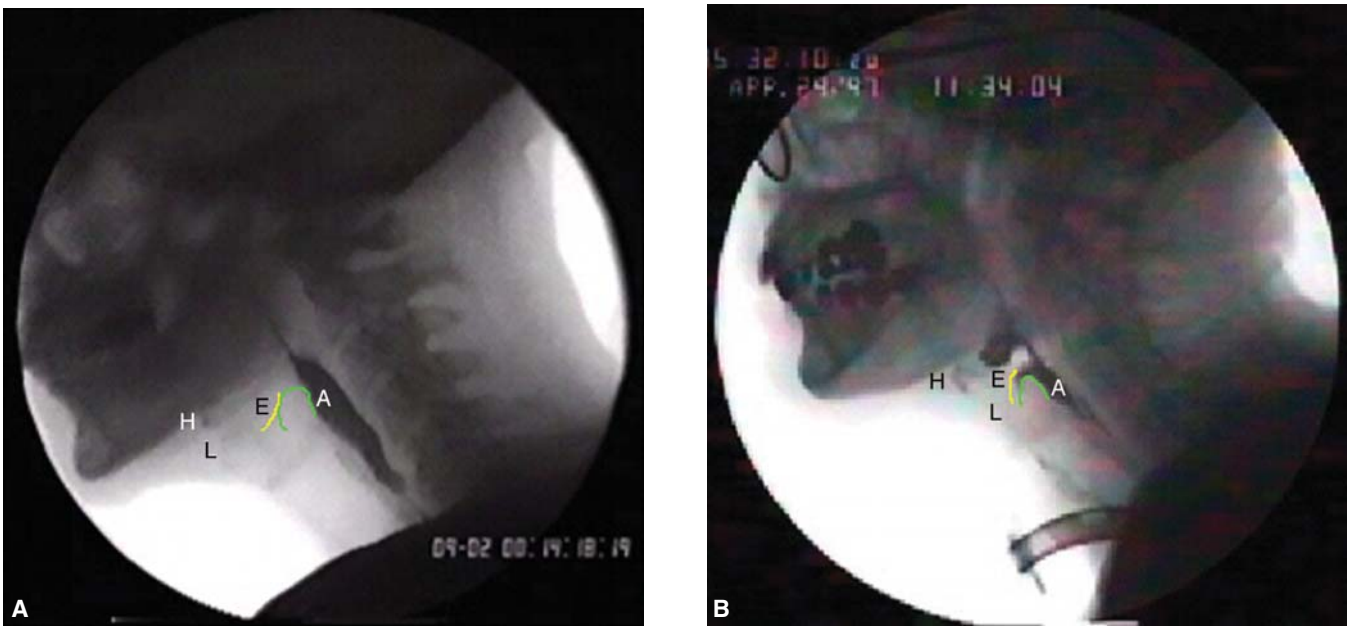

FIGURE 40-5 **A.** Superior and anterior displacement of the hyoid (*H*) and larynx (*L*) results in approximation of the arytenoid cartilages (*A*) and epiglottic petiole (*E*), and release of the posterior cricoid area from the posterior pharyngeal wall. **B.** The hyoid (*H*) and larynx (*L*) are anchored by the inflated tracheotomy tube cuff leading to incomplete approximation of the arytenoid cartilages (*E*) to the epiglottic petiole (*E*) with resultant penetration, aspiration, and incomplete opening of the cervical esophagus.

ventilation are leading factors in increasing anxiety in patients, families, and health care providers.[324,325,444,448–451]

Several techniques for promoting verbal communication can be tailored to the individual patient's ability to participate in speech therapy. Patients may also graduate through increasingly more complex techniques as medical conditions allow. Table 40-5 outlines the clinical features and applications of these techniques.

TABLE 40-4: CLINICAL WARNING SIGNS SUGGESTIVE OF SWALLOWING IMPAIRMENT AND ASPIRATION

- Adventitious lung sounds
- Articulatory imprecision
- Breathy vocal quality
- Decreased frequency of swallow
- Decreased laryngeal sensation
- Decreased orofacial sensation
- Delayed cough
- Drooling
- Gas-induced cough
- Harsh vocal quality
- Hoarse vocal quality
- Immediate cough
- Impaired resonance
- Labored chewing
- Labored oral transport
- Laryngeal elevation
- Orofacial weakness
- Reduced O_2 saturation
- Sounds of swallow
- Strained vocal quality
- Wet vocal quality

Patients undergoing positive-pressure ventilation with moderate to low minute ventilation requirements may be able to whisper during brief periods of partial cuff deflation. Patients mechanically ventilated because of neuromuscular disease can be managed by a cuffless or fenestrated tracheotomy tube during positive pressure ventilation and retain the ability to speak.[452–454] A portion of the ventilator-delivered tidal volume enters the lower trachea and flows around the tracheotomy tube toward the upper airway during inspiration allowing the patient to talk.

The above approach limits speech to inspiration and a short portion of expiration. Speech throughout the respiratory cycle can be promoted by partial cuff deflation as described above, prolongation of the ventilator's inspiratory phase, and application of low levels of positive end-expiratory pressure.[443,455,456] The resultant continuous air leak around the cuff allows more spontaneous speech.[457] Pressure-support ventilation in the presence of a leak around a tracheotomy tube causes an increase in inspiratory time and volume,[458–460] both of which may theoretically assist speech production.

Specialized tracheotomy tubes, termed *pneumatic speaking tubes* or *talking tubes,* promote speech by supplying pressurized gas mixtures to the trachea above the tube cuff.[461–464] The gas escapes through the glottis allowing whispered or vocalized speech. A pressurized gas source is connected to

TABLE 40-5: METHODS OF COMMUNICATION FOR INTUBATED PATIENTS

Communication Option	Advantages	Disadvantages	Considerations	Select Patient Use
Lip reading, mouthing	• Follows a natural communication style • Closely resembles normal speech movement • Limited training required • Makes use of oral motor functions • Allows for natural production of facial expression • Communication letter board assists communication	• Decreased understanding of mouthed messages • May result in patient frustration • Unnatural for patient to decrease rate and length of message • Very limited for orally intubated patients	• Patient should be alert • Requires intact motor functioning • Works best for nasally intubated patients • Requires proper tube taping technique in orally intubated patients for maximal oral movement • Patient at times requires encouragement to mouth words • Patients often require cueing to decrease rate and length of messages	• Can be used with a variety of nonparalyzed patients • Can be used with patients who are unable to use other alternatives for communication
Gestural language (yes–no [Y–N] responses, facial expressions, hand gestures)	• Y–N responses result in effective and rapid communication of basic needs • Appropriate facial expressions can greatly enhance communication and emotion • Message intent is usually understood	• Limited interpretation • Difficulty expressing complex or lengthy messages • Requires coordination and dexterity	• Establish Y–N response mode and communicate to staff and family (strive for natural Y–N responses with head nods) • Patients may require encouragement to use consistently	• Especially helpful for patients with oral intubation and/or oral motor dysfunction
Written communication	• Can be used for effective expression of basic needs and wants	• Timely method of communication • Requires significant patient endurance and alertness • Limited expression of complex ideas and emotion • Often difficult to read patient writings • May require staff assistance • Requires interpretation (language, writing style, etc.) by receiver	• Requires: motor coordination, strength of upper extremity, use of arm free from medical restraints, adequate visual acuity and perception, and supplies at bedside • May require prepositioning for writing comfort and visibility • Use a felt-tip marker or other antigravity dark marking device • Provide a clipboard for firm writing surface • Provide glasses before writing attempts	• Can be used as an alternative to other communication options

Communication boards (picture, alphabet, and word boards)	• Effective communication of basic needs	• Timely communication process • Communication limited to items on board • High degree of frustration with alphabet use • Requires coordination for pointing response • Requires intact visual acuity/ perception • Potential source of contamination when board used from room to room • Requires immediate accessibility, patient training, and staff patience	• Provide glasses to prescription lens wearers • Board should be kept at bedside • Position board and size of characters to meet patient's needs	• Can be used with a variety of nonparalyzed patients • Can be used with patients who are unable to use other alternatives for communication
Augmentative communication devices ("parrot," "voice-aided," "text-to-speech" computer software and tablet apps, direct selection, and scanning devices)	• Effective communication of *basic* needs but newer software (i.e., tablet apps) capable of sophisticated touch screen text-to-speech • Provides a programmed speaking voice when text selected or typed • Communication programs can be highly individualized to the patient • Easy access to provide complete phrases • Provides a means for more sophisticated, complex communication • Requires minimal energy once patient is familiar with device • Timely communication process	• Must be programmed or existing software modified to meet patient needs • Communications limited to items on the board or touchscreen unless patient can type • May be frustrating because of limited options or difficulty with typing or use of touchscreen • Requires operator training • Requires concentration for selection of appropriate phrases • Requires coordination for pointing response • Potential source of contamination if device is used from room to room • Requires visual acuity • Requires maintenance (software update, battery charging, electrical safety, repairs) • May be costly to the patient (equipment, support of speech therapy)	• Patient and family need to be included in programming and selection of communication choices • Provide glasses to prescription lens wearers • Device should be kept at the bedside	• Can be used with a variety of nonparalyzed patients • Can be used with patients who are unable to use other alternatives for communication

(*continued*)

TABLE 40-5: METHODS OF COMMUNICATION FOR INTUBATED PATIENTS (*CONTINUED*)

Communication Option	Advantages	Disadvantages	Considerations	Select Patient Use
Electrolarynx with or without oral adapter and intraoral electronic larynx (multiple brands)	• Provides a voice without using vocal cords • Provides auditory component to speech productions for better understanding • Allows verbal communication of basic needs and emotions • Makes use of oral motor functioning • Useful when tracheotomy cuff cannot be deflated for other speaking techniques	• Poor mechanical quality of voice (monotonal) • Requires assistance from staff, significant patient and staff training, dexterity and hand coordination, and intact oral and motor functioning • Patient must be alert and cooperative • Patient must have energy reserve to use effectively • Oral adapter may be uncomfortable and awkward	• Dentures should be in place • Mouth and lips should be moist • Demonstrated technique to patient and family and allow for return demonstration • Allow time for experimentation for this and other options (including oral adapter)	• To be used with tracheotomy patients (free use of mouth for motion)
Deflated/cuff leak methods (cuff leak on ventilator, T-piece)	• Allows use of own voice through vocal cords' natural communication styles • Results in efficient communication • Requires minimal staff assistance if patient can tolerate deflation • No cost requirements	• May be limited to use for short periods depending on tolerance level of patient • Requires staff assistance to deflate and monitor cuff • Methods contraindicated for acute or medically unstable patients • Requires intact oral motor functioning and respiratory reserve • Requires staff training (to monitor cuff pressures and exhaled volumes)	• Patients must be alert • Patients with copious secretions should be suctioned before deflation • Procedure must be fully explained to the patient • Ventilator-dependent patients require cueing for proper voice initiation • T-piece users must have T-piece occluded for voice to be audible • Ventilator adjustments often needed	• For use with ventilator patients who are stable with cuff leak/deflation and who have complex communication needs • Excellent for chronic/long-term ventilator and tracheotomy patients (especially nonventilator-dependent patients) • Nasotracheal or T-piece patients (stable respiratory status)
Tracheotomy phonation valves (Olympic, Passy-Muir, Boston Medical)	• Allows for phonation and production of patient's own voice • Natural communication method • Some can be used on ventilated patients	• May be limited to use for short periods • Requires staff assistance to plug in most patients • Requires intact oral and motor functioning • Patients without respiratory reserve may not tolerate • Works poorly on patients with stiff lungs or with copious secretions	• Provide support and encouragement during initial valve applications • Close observation is required • Valve is routinely removed when not in use in acute setting	• For use in long-term and chronic tracheotomy patients • Some may be used for ventilated patients

a cannula that travels through the wall of the tracheotomy tube and exits at its greater curvature. A gas flow rate of 1.5 to 10 L/min successfully produces intelligible speech in 75% of properly selected patients.[465] Prognostic indicators for successful use of pneumatic speaking tubes include adequate mental status, availability of a well-trained speech-language pathologist for training and positive reinforcement, absence of laryngeal pathology such as vocal fold paralysis, patient motivation, and encouragement from the critical care staff and patient's family.[466]

Pneumatic speaking tubes may fail because the pressurized gas may flow retrograde through the tracheostoma around the tube. Because this retrograde flow can cause subcutaneous emphysema in patients with recent tracheotomies, pneumatic tubes are contraindicated during the first 5 to 7 days after surgery. Pneumatic tubes may also fail because secretions or granulation tissue above the cuff may occlude the exit port for gas flow.[467]

Other complications of pneumatic speaking tubes include desiccation and inflammation of laryngeal mucosal structures caused by the drying effect of the gas flow. Warming and humidification of the gas source along with intermittent use of the technique can prevent the onset of laryngitis. An air mixture rather than pure oxygen should be used to avoid further airway injury from hyperoxia.[468]

An "electrolarynx" is a valuable device for promoting speech that has a high rate of success in critically ill patients with a tracheotomy.[469,470] These devices consist of a vibrator unit with an attached handheld battery pack that generates a vibratory tone with variable loudness and pitch. Held firmly against the patient's neck midway between the mandibular angle and the notch of the thyroid cartilage or attached with an intraoral stem that applies intraoral vibrations when inserted through the mouth, the electrolarynx substitutes for the vocal cords as an amplifier for speech. More than 90% of mentally alert patients with a tracheotomy can learn to use an electrolarynx successfully.[469] Critical care team members may require frequent in-servicing on correct application of the device because of the loss of enthusiasm that develops when patients do not quickly learn the technique.

Patients being weaned from mechanical ventilation who have achieved periods of spontaneous ventilation can speak with the assistance of a fenestrated tracheotomy tube.[457] Fenestrated tubes with an inner cannula can provide airway access for mechanical ventilation and a system for speech when the inner cannula is removed. Occlusion of the tracheotomy tube with a gloved finger or plug can divert airflow through the upper airway allowing whispered or vocalized speech. Deflation of the tube cuff can further improve expiratory airflow through the larynx.

A fenestrated tracheotomy tube can also be combined with a one-way "phonation valve" (e.g., Passy-Muir valve, Passy and Passy, Irvine, CA) that allows inspiratory airflow through the tube but closes during expiration diverting airflow through the larynx (Fig. 40-6).[471] Phonation valves can be applied to the tracheotomy tube of spontaneously breathing patients and patients undergoing positive pressure ventilation. In the latter setting, it is essential that the patient is being ventilated with the tracheotomy cuff deflated and no upper airway obstruction exists. Commercially available one-way valves vary in their airflow resistive properties[464,472] and effectiveness for promoting understandable speech.[473]

FIGURE 40-6 Passy-Muir one-way valves that allow articulated speech through the native airway for spontaneously breathing patients with a tracheotomy or patients undergoing mechanical ventilation through a tracheotomy tube. (Courtesy Passy-Muir Tracheotomy Valves, Passy-Muir Inc., Irvine, CA).

Weaning from Tracheotomy and Decannulation

Patients recovering from prolonged respiratory failure may either tolerate rapid decannulation or require stepwise tracheotomy weaning. The presence of underlying cardiorespiratory or neuromuscular disease increases the likelihood that a period of weaning will be required.

Evaluation for decannulation begins with an interdisciplinary evaluation after the patient demonstrates success with spontaneous breathing for 48 hours.[474] Persistent difficulties with spontaneous ventilation through the tracheotomy tube may occur if the tube is malpositioned in the airway causing partial obstruction[256] or has a narrow internal diameter. Unfortunately, guidelines do not exist to inform clinical practices and extensive practice variation occurs between centers in evaluating patients for decannulation.[475] Moreover, standardized decannulation protocols akin to protocols for weaning patients from mechanical ventilation have not been adequately studied to determine their effectiveness.[14,391,476,477] Extensive practice variation occurs, therefore, with weaning patients from tracheotomy.[478]

Essential criteria for considering patients for decannulation include level of consciousness, cough effectiveness, volume of airway secretions, oxygenation, effectiveness of swallowing, and ability to breathe spontaneously with the tracheotomy tube capped.[479] The ability to manage secretions is assessed by deflating the tube cuff and observing the patient for clinical signs of aspiration or retained secretions.[480] Capping the tracheotomy tube and observing the patient during spontaneous respiration for 30 minutes allows evaluation for the presence of upper airway obstruction.[481,482] Increased inspiratory effort, stridor, or dyspnea provide evidence that the patient might benefit from

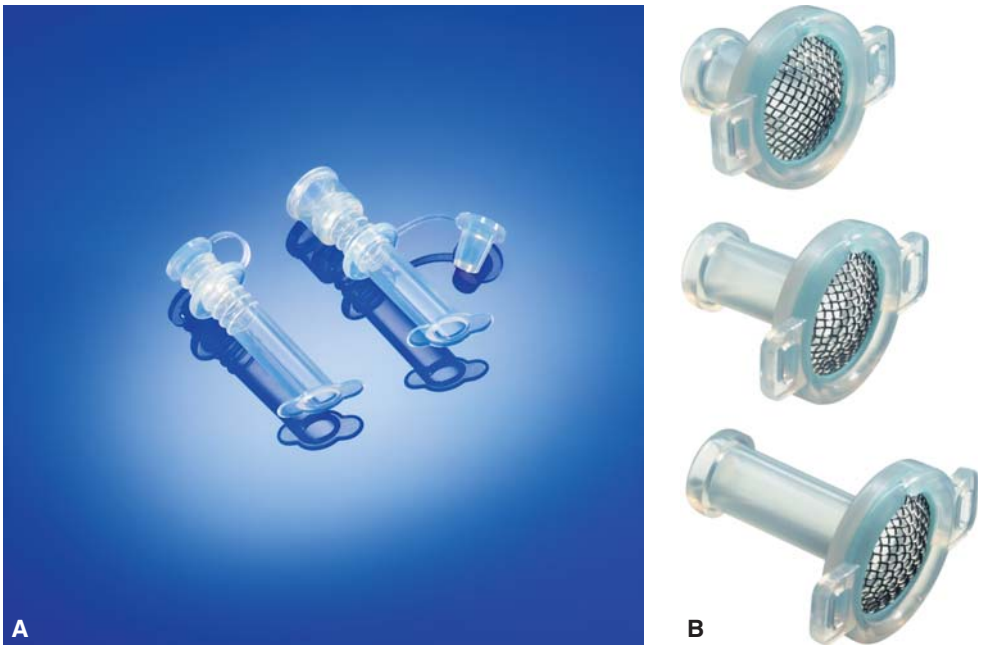

FIGURE 40-7 A stoma stent can maintain patency of the stoma after tracheotomy tube decannulation for patients who require ongoing airway access for suctioning or replacement of a tracheotomy tube if failure of decannulation occurs. Some stents are more adaptable for either long-term use (**A**, Montgomery Long-Term Cannula, courtesy Boston Medical Products, Westborough, MA) or shorter-term use (**B**, TRACOE Stoma Button, courtesy TRACOE Medical, Frankfurt, Germany), but each has allied attachments to promote articulated speech or provide oxygenation with humidification.

downsizing the tracheotomy tube[477] or tracheoscopy to evaluate for vocal cord or subglottic abnormalities.[482] Some centers routinely examine the airway by fiber-optic endoscopy before decannulation.[483] Difficulty with spontaneous breathing while the tracheotomy is capped in the absence of airway abnormalities may indicate ventilator muscle weakness and potential benefits from weaning toward cannulation with a capped tracheotomy tube supplemented by noninvasive face-mask ventilation.[484]

Patients with moderate airway secretions and severely compromised lung function may not tolerate spontaneous breathing with partial obstruction of their airway with a tracheotomy tube. Such patients may benefit from a tracheotomy plug, also termed *stoma stent* or *stoma maintenance device,* which frees the airway but allows airway suctioning and maintenance of the stoma track for reinsertion of a tracheotomy tube if needed (Fig. 40-7).[411]

After prolonged ventilation, the failure rate of decannulation ranges from 5% to 20%.[485] Up to 40% of patients may require translaryngeal intubation with readmission to the ICU.[485] Most patients fail within the first 4 to 24 hours with retained secretions representing the major factor.[485]

PATIENT PROGNOSIS AND QUALITY IMPROVEMENT

Patients who require tracheotomy for respiratory failure have a worse prognosis as compared with other ventilator-dependent critically ill patients and experience substantial health care costs.[486] They represent the most resource-consuming diagnostic categories for many acute care hospitals.[487,488] Their hospital mortality rate ranges from 49% to 78% if they undergo tracheotomy in the ICU.[6,489–491] Among those who survive hospitalization, 24%, 30%, and 42% are no longer alive at 100 days, 6 months, and 2 years after discharge, respectively,[489] and the presence of a tracheotomy is an independent predictor of long-term functional debility[492] and mortality.[493] If decannulation occurs before hospital discharge, 92% of patients are alive 1 year later,[489,494–496] but lack of decannulation before transfer from the ICU to a ward has an independent association with hospital mortality[497,498] with highest mortality among patients with obesity or neurologic injuries. Among mixed medical and surgical patients who survive acute hospitalization after tracheotomy, 57% are successfully weaned and 30% decannulated before hospital discharge.[489] At 1 year, 9% of patients who require prolonged mechanical ventilation have no functional dependency, 26% are alive with moderate dependency, and 65% are either alive with complete functional dependency or dead.[486] Older patients with more comorbid conditions are more likely to require discharge to post–acute care facilities.[486] Incremental costs per quality-adjusted life-year exceed $100,000 in older age groups.[499]

Unfortunately, clinical outcomes are significantly worse than projected by patients' surrogates and physicians at the time they make the decision to proceed with tracheotomy.[500] Efforts to develop predictive models to estimate long-term outcomes for critically ill patients being considered for tracheotomy have had variable results.[388,498,501]

Unfortunately, specialist clinicians in the ICU demonstrate practice variation for tracheotomy care that often does not conform to best clinical practices[310,502] and delays decannulation.[503] Combined with increasing trends for earlier transfer of patients from the ICU to hospital wards and post–acute care hospitals, an increasing number of patients with a tracheotomy are managed outside of the ICU by providers with limited knowledge and skills in airway care.[14,504,505] Some centers have approached this challenge to quality care by developing interdisciplinary teams that provide tracheotomy care both in the ICU and after transfer to a non-ICU setting.[15,392,474,506–508] Studies are limited regarding the impact of tracheotomy teams on patient outcomes, but a recent meta-analysis reported that all existing studies found that tracheotomy teams decreased time to decannulation, length of stay, and adverse events.[509]

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XI

COMPLICATIONS IN VENTILATOR-SUPPORTED PATIENTS

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41

COMPLICATIONS ASSOCIATED WITH MECHANICAL VENTILATION

Karin A. Provost
Ali A. El-Solh

Critically ill patients are at risk of succumbing to their primary disease or the undesired sequelae associated with their therapy. Although frequently lifesaving, the use of positive airway pressure therapy has numerous undesired physiologic and clinical complications. These complications have their origins in the endotracheal or tracheostomy tube, the positive-pressure ventilation (PPV), or from therapies delivered during the care of mechanical ventilation. Other complications may result from coexisting illness or comorbid conditions. Although not commonly recognized as important effects of PPV or positive end-expiratory pressure (PEEP), alterations in organ functions ought to be recognized and addressed accordingly to reduce morbidity and mortality.

GASTROINTESTINAL TRACT COMPLICATIONS

The interaction between PPV and the gastrointestinal tract in critical setting is a complex one. Gastrointestinal changes are reported frequently in critically ill patients receiving PPV. The true incidence of gastrointestinal complications is not known, but it is reported to be up to 100% for those receiving PPV for more than 3 days. Splanchnic hypoperfusion seems to play a pivotal role in the pathogenesis of these complications, including mucosal damage, motility disorders, and mesenteric ischemia (Fig. 41-1).[1] Unlike many other vascular beds, the splanchnic exhibits limited autoregulation when faced with reduction in mean arterial pressure.[2] Without altering total blood flow to the organs of the digestive tract, sympathetic stimulation redistributes blood flow to the muscularis of the wall by decreasing mucosal perfusion.[3] This poses severe ischemic changes to the mucosal layer because the mucosa is metabolically more active than the muscle layer and is more vulnerable to the destructive effects of a compromised blood supply.

Mechanical ventilation influences the gastrointestinal function by impacting systemic hemodynamics via high PEEP or potentially injurious ventilator strategies such as a high tidal volume (V_T). The effect of PEEP on splanchnic

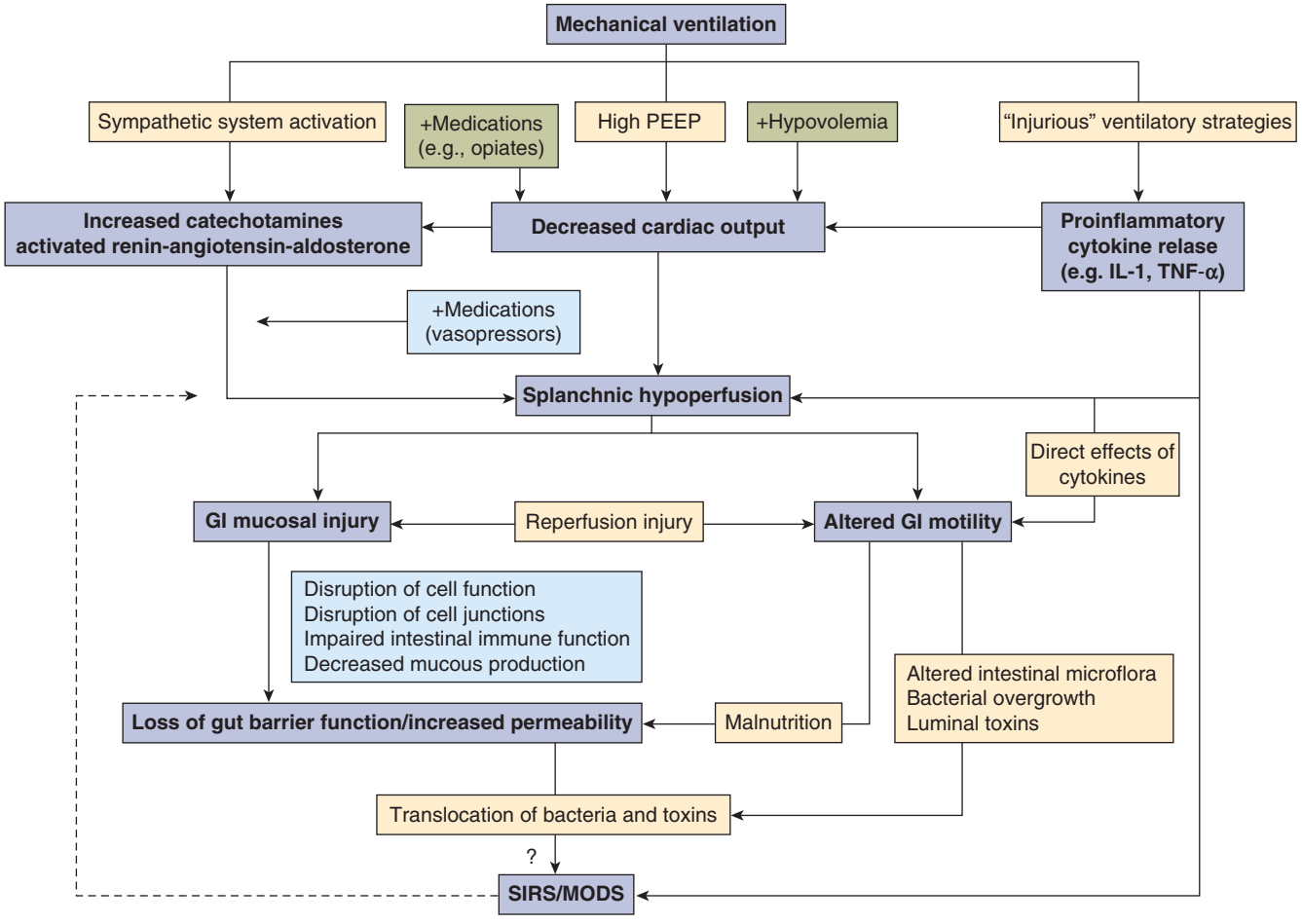

FIGURE 41-1 Suggested mechanisms for the development of gastrointestinal (GI) complications during mechanical ventilation. *IL,* interleukin; *MODS*, multiple-organ dysfunction syndrome; *PEEP*, positive end-expiratory pressure; *SIRS*, systemic inflammatory response syndrome; *TNF*, tumor necrosis factor. (Used, with permission, from Mutlu.[1])

blood flow has been shown in animal models to be dose-dependent.[4] PEEP decreases venous return and reduces preload, which in turn reduces cardiac output and results in splanchnic hypoperfusion.[5] The reduction of splanchnic blood flow is limited at PEEP levels below 10 cm H_2O but it is more pronounced at PEEP levels of 15 to 20 cm H_2O.[6] In rats, the addition of 10 cm H_2O of PEEP resulted in reduction of cardiac output and mesenteric blood flow by 31% and 75%, respectively.[7] PEEP also promotes plasma-renin-angiotensin-aldosterone activity, as well as catecholamine release, which limits splanchnic hypoperfusion.[4,7] Interestingly, high PEEP levels interfere with mesenteric leukocyte–endothelial interaction. In rats with healthy lungs, 10 mbar of PEEP was associated with an increase in the number of rolling, adherent, and migrated leukocytes when compared with anesthesia alone or with mechanical ventilation with 0 or 5 mbar PEEP.[8]

Alternatively, mechanical ventilation with high V_T can modify the inflammatory responses irrespective of the underlying lung injury. Experimental data suggest that mechanical ventilation with high V_T and zero end-expiratory pressure induces not only cytokine release (tumor necrosis factor [TNF]-α and interleukin [IL]-8) but also translocation of cytokines from the lungs to the systemic circulation and vice versa.[9,10] These cytokines lead to a number of clinical sequelae in the gastrointestinal tract including splanchnic hypoperfusion and intestinal smooth muscle impairment.[11,12]

Indirectly, medications administered to patients on mechanical ventilation can have deleterious effects on gastrointestinal function. Opiates and sedatives, such as benzodiazepines, can decrease gut motility and impair venous return.[13] Other agents, like vasopressors or inotropes,[14,15] may alter hemodynamic parameters that, in turn, reduce mesenteric blood flow and put a critically ill patient at risk of developing stress-related mucosal disease.[4]

Stress-Related Mucosal Disease

EPIDEMIOLOGY

Stress-related mucosal disease is the most common cause of gastrointestinal bleeding in patients receiving mechanical ventilation. An estimated 74% to 100% of critically ill

patients have endoscopically detectable lesions in the gastric mucosa within hours after admission.[16,17] These lesions are most frequently reported in the acid-producing areas of the stomach in contrast to peptic ulcers, which are more common in the antrum and the duodenal bulbs. Overt stress-related gastrointestinal bleeding occurs in up to 5% of critically ill patients.[18] Other studies have demonstrated an even lower incidence of clinically significant bleeding, ranging from 0.17% to 1.5%.[19] The risk increases with increasing number of days of mechanical ventilation and length of intensive care unit (ICU) stay.[20] Other contributing factors include major surgery, head trauma, severe burns, sepsis, glucocorticoids, and renal and hepatic disease on admission.[20] Unsurprisingly, clinically significant gastrointestinal bleeding has been linked to prolonged ICU length of stay by as much as 11 days and to a markedly increased mortality, although the primary cause of mortality is attributable to the primary disease process rather than gastrointestinal hemorrhage.[20]

PATHOPHYSIOLOGY

The pathophysiology of stress-related mucosal disease underlines a complex interaction of opposing vectors (Fig. 41-2).[21] Under normal physiologic conditions, the integrity of the mucosa depends on a delicate balance between injurious factors (gastric acid, enzyme secretion) and protective mechanisms (mucous production, prostaglandins).[22] Gastric acid is considered essential for stress ulceration but it is not the sole factor in the pathogenesis of mucosal disease. In the setting of decreased splanchnic blood flow, oxygen radicals are released, prostaglandins synthesis is reduced, and nitric oxide production is exaggerated. These changes perpetuate the release of inflammatory cytokines and triggers cell death.[23] As a result, increased back diffusion of hydrogen ions and pepsin occurs without the mitigating effect of bicarbonate-rich mucous layer and the protective effect of prostaglandins. Collectively, the imbalance between the noxious gastric acid and the impaired reparative mechanisms

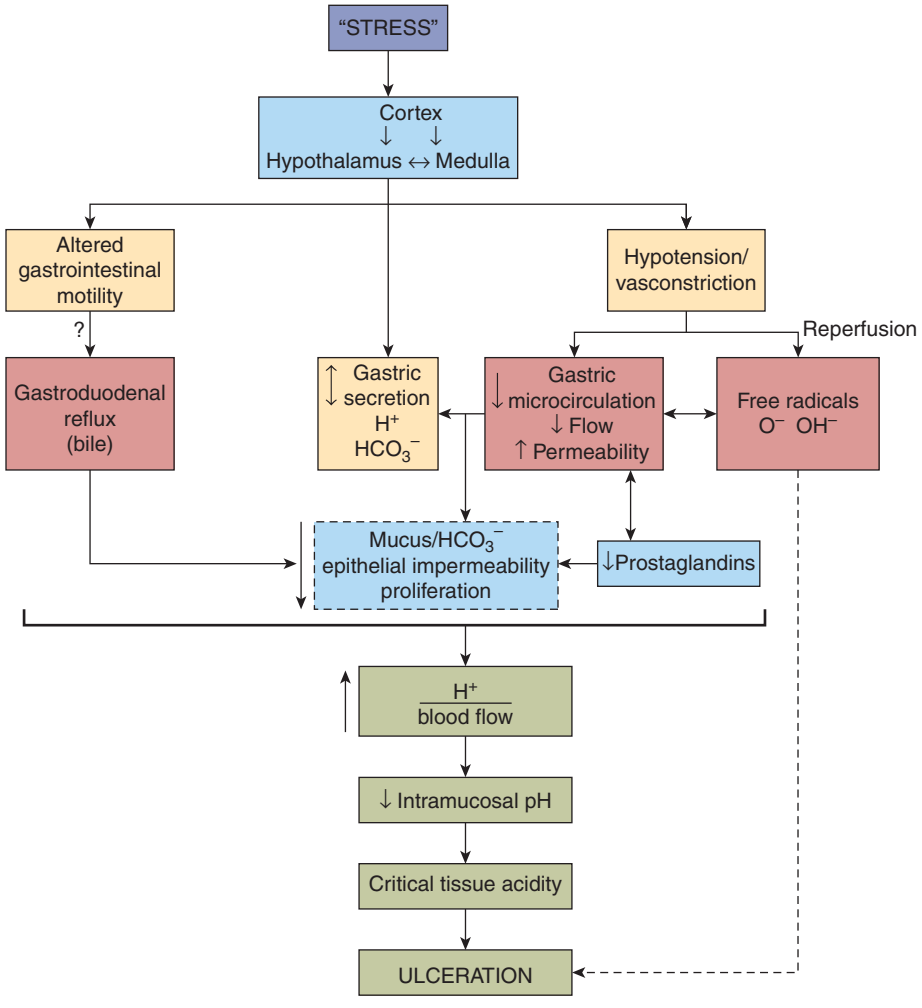

FIGURE 41-2 Proposed mechanisms for the development of stress ulceration during mechanical ventilation. (Used, with permission, from Bresalier.[21])

predisposes patients on mechanical ventilation to stress-related mucosal injury.

THERAPEUTIC INTERVENTIONS

The mainstay of the clinical management of stress-related mucosal bleeding in patients who are mechanically ventilated is prevention. Several classes of antistress agents have been introduced since antacids were first evaluated in 1976.[24] Antacids directly neutralize luminal gastric acid, bind pepsin and bile acids,[25] and may stimulate prostaglandin release from the mucosa.[26] The efficacy of antacids in preventing clinically significant stress-related bleeding has been demonstrated in randomized controlled trials.[27] The frequent dosing interval needed to achieve and maintain a pH greater than 4, however, is one of the disadvantages of this therapy. In addition to impairing the absorption of other medications, aluminum-containing antacids may be associated with hypophosphatemia and toxic aluminum levels in renal-failure patients, while magnesium-containing antacids may be associated with diarrhea and hypermagnesemia. Sucralfate is another agent that shields the gastric mucosa by forming a protective barrier from the acid in the gastric lumen, stimulating mucous and bicarbonate secretion, and enhancing prostaglandin release.[28] A meta-analysis of the efficacy of sucralfate compared with that of histamine-2-receptor antagonists and antacids for the prophylaxis of stress ulcers indicated that sucralfate was at least as effective as the other agents.[29] Sucralfate is generally well tolerated but may cause constipation, and aluminium toxicity may occur in patients with renal failure. Misoprostol, a synthetic prostaglandin E_1 analog with gastric cytoprotective and antisecretory properties, has also demonstrated effectiveness in preventing gastric injury and complications induced by nonsteroidal antiinflammatory drugs.[30] Its use is limited, however, by the high rate of diarrhea and the need for multiple daily doses.

The introduction of histamine-2-receptor antagonists and proton pump inhibitors eclipsed the use of antacids, and medications in these classes are currently the standard therapy for stress-related mucosal disease. Although continuous infusions may be more effective in suppressing gastric acid,[31] no studies have demonstrated improved safety, more effective prophylaxis, or a lower rebleeding rate with either method. A major concern of using histamine antagonists is the development of tolerance, which occurs within 42 hours after intravenous administration by both bolus and continuous infusion.[32] Histamine antagonists are also associated with adverse chronotropic and inotropic effects and, experimentally, may induce a dose-dependent coronary vasoconstriction.[25] The clinical significance of these effects is unclear.

Proton pump inhibitors irreversibly bind the hydrogen-potassium-adenosine triphosphatase, the enzyme responsible for secreting acid into the gastric lumen. Unlike histamine antagonists, proton pump inhibitors do not seem to develop tolerance with sustained therapy. Although both histamine antagonists and proton pump inhibitors can elevate intragastric pH to more than 4, proton pump inhibitors are more likely to maintain a pH above 6.[18] Yet in a meta-analysis of randomized, controlled trials that directly compared proton pump inhibitors with histamine antagonists in prevention of stress-related upper gastrointestinal bleeding in ICU patients, both agents were equally efficacious in preventing stress-related bleeding.[33]

The safety consideration of acid-suppressive therapies has been a concern after several studies suggested that acid-suppressive agents may increase the risk of pneumonia.[34,35] Numerous small studies[36,37] have examined this issue in ICU patients, but multicenter randomized studies did not demonstrate any significant difference in pneumonia rates between sucralfate and histamine antagonists[38] or between proton pump inhibitors and histamine antagonists.[33] Other potential adverse effects for acid-suppressing agents include higher rates of *Clostridium difficile*-associated diarrhea[39] and enteric infections.[40] None of these associations, however, have been confirmed in randomized trials.

Because acid injury may potentiate mucosal ischemic changes, enteral nutrition could potentially decrease stress ulceration by raising intragastric pH. Several studies in mechanically ventilated patients[41] and in burn patients[42] have associated enteral feeding with a lower incidence of stress-related bleeding. Other studies in critically ill patients, however, have demonstrated that enteral feeding does not have a significant effect on increasing gastric pH and therefore may be ineffective in affording gastroprotection.[43,44] Definite recommendations regarding the role of enteral nutrition for stress-ulcer prophylaxis are not possible at the present because of lack of prospective, randomized trials.

Motility Disturbances

Several studies indicate that abnormal gastrointestinal motility is common in mechanically ventilated patients.[45,46] The prevalence of abnormalities in gastric emptying is estimated to be as high as 50%.[15] Using manometric evaluation, it was demonstrated that the contractile activity of the stomach is severely depressed in patients receiving PPV—but persistent, albeit reduced, in the duodenum.[47] These abnormalities are thought to result from the dysfunction of the interstitial cells of Cajal that act as the controller of gastrointestinal motor activity.[48] Several factors are implicated in the pathophysiology of altered gut motility, including preexisting diseases, release of endotoxin[49] and corticotropin-releasing factor[50] during severe stress, and drugs routinely used in the management of patients on mechanical ventilation (e.g., sedatives and opioid analgesics, catecholamine vasopressors, anticholinergics, and α_2-adrenergic receptor agonists). Hyperglycemia has been considered as a risk factor to impair pyloric and antral contractions in healthy volunteers.[51] A relationship, however, between hyperglycemia and delayed gastric emptying remains unclear.

Current recommendations for the treatment of impaired gastrointestinal motility focus on optimizing fluid intake, correcting electrolyte disturbances, and minimizing the use

of drugs that slow gut motility. Prokinetic agents are not routinely recommended though a recent survey revealed standard prokinetic use in 39% of critically ill patients.[52] A combination therapy of erythromycin and metoclopramide provides the most effective regimen in improving the delivery of nasogastric nutrition.[53] Owing to a rapid tachyphylaxis following erythromycin or metoclopramide administration, however, therapeutic use should be limited to 3 days. Newer therapeutic approaches, such as μ-opioid receptor antagonists and cholecystokinin-1 receptor antagonists, hold promise in alleviating motility disorders but have not been studied so far in critical illness.

If treatment of gastric stasis fails or is contraindicated, the stomach can be bypassed with an intestinal feeding tube. Early enteral feeding can be more successful if feeds are delivered directly to the small intestine. Postpyloric tubes have been shown to be equally effective as prokinetic treatment in patients who failed nasogastric feeding,[54] but there is currently no evidence to support routine use of these tubes in critically ill patients.

Acalculous Cholecystitis

Acalculous cholecystitis is a serious and potentially life-threatening illness in critically ill ventilated patients if unrecognized. The condition accounts for 5% to 10% of all cases of acute cholecystitis.[55,56] The etiology of the disease remains unknown, although PPV for more than 72 hours is considered a risk factor.[55] Other predisposing conditions include shock, dehydration, multiple transfusions, total parenteral nutrition, and drugs (opiates, sedatives, ceftriaxone) (Table 41-1).[57,58] Clinical assessment may not be reliable, particularly in intubated and sedated patients. Ultrasonography remains the diagnostic test of choice, although computed tomography has the advantage of being more sensitive in diagnosing acalculous cholecystitis.[59,60] Evidence of gallbladder wall thickness greater than or equal to 4 mm, pericholecystic fluid or subserosal edema without ascites, intramural gas, or a sloughed mucosal membrane are considered diagnostic criteria for acute acalculous cholecystitis. Hepatobiliary scintigraphy is compromised by frequent false positives and is more helpful in excluding rather than confirming the diagnosis.[59] The mainstay of therapy for acalculous cholecystitis has been cholecystectomy, but for the critically ill patients percutaneous cholecystostomy is considered an alternative to open procedures.[61]

TABLE 41-1: PREDISPOSING FACTORS FOR ACALCULOUS CHOLECYSTITIS IN CRITICALLY ILL PATIENTS

Decreased motility
- Surgery
- Burns
- Mechanical ventilation
- Narcotic analgesics

Decreased cystic artery blood flow
- Arteriosclerosis
- Diabetes
- Shock
- Cardiac failure

Infection
- Salmonella
- Cholera
- Campylobacter
- HIV

Obstruction of cystic duct
- Lymphadenopathy
- Metastatic malignancy

HEPATIC COMPLICATIONS

The normal adult liver has a dual blood flow and oxygen supply. Approximately two-thirds of hepatic blood flow and one-half of the oxygen supply is derived from the portal vein while the rest is provided by the hepatic artery. Institution of PPV has significant implications on hepatic perfusion. The reduction in cardiac output observed during PPV causes a proportional drop in global hepatic blood flow.[62,63] In addition, the descent of the diaphragm during PPV results in a direct compression of the liver parenchyma and a dramatic rise in intraabdominal pressure. The combination of these two forces leads to an increase in hepatic vascular resistance, which, in turn, impedes portal venous flow. Maintenance of spontaneous breathing during airway pressure release ventilation results in higher hepatic venous oxygen saturation and better hepatic lactate elimination as compared with full ventilator support at equal airway pressure limits.[64]

The addition of PEEP further complicates the picture. In clinical studies of patients with acute lung injury secondary to septic shock, an increase in PEEP to 15 cm H_2O resulted in decrease hepatic vein oxygen saturation compared to 10 cm H_2O.[65] Similarly, PEEP levels of 15 cm H_2O but not 10 cm H_2O was associated with a decrease in hepatic glucose production. After liver transplantation, patients are especially vulnerable to change in blood flow because of vascular anastomoses and liver function recovery after cold ischemia. Despite an increase in central venous and pulmonary capillary occluding pressure following 10 mbar of PEEP, there was fortunately no deterioration in Doppler flow velocities of portal and hepatic veins.[66]

Permissive hypercapnia has been observed to increase hepatic and splanchnic blood flow in a biphasic manner. Blood flow is initially reduced because of sympathetic stimulation and is then increased secondary to the direct vasodilator effect of CO_2.[67] The heterogeneity, however, observed in the individual changes of splanchnic perfusion secondary to decreased V_T supports the concept that the direct local vasodilation of an elevated tissue partial pressure of carbon dioxide (P_{CO_2}) is opposed by the increased release of catecholamines in the systemic circulation, with an end result of no significant change.[68]

PNEUMOPERITONEUM

An association between PPV and pneumoperitoneum has long been described.[69,70] The mechanism involves airflow dissection through overdistended alveoli into the pulmonic perivascular sheaths.[71] The pocket of air dissects to the mediastinum and migrates through the foramina of Morgagni and Bochdalek to cause free air in the peritoneal space.[72,73] Risk factors include high airway pressures, large V_T, noncompliant lungs, and preexisting pulmonary disease, including obstructive airway disease and acute respiratory distress syndrome. The diagnosis may be easily mistaken for a perforated viscus. In the absence of leukocytosis, abdominal pain, and peritoneal signs, perforation can be excluded by radiographic imaging with water-soluble contrast material administered via oral, rectal, or enterostomy tube.[74,75] Other approaches to define the etiology of pneumoperitoneum include aspiration and analysis of the partial pressure of oxygen (P_{O_2}) of the intraperitoneal free gas.[76,77] Spontaneous resolution usually occurs within a few days.[62,78] On rare occasions, "tension pneumoperitoneum" has been described, in which surgical decompression is necessary, even in the absence of peritoneal signs, to relieve vascular collapse.[79]

CARDIOVASCULAR COMPLICATIONS

Cardiovascular complications are associated with critical illness and mechanical ventilation, but are rarely a direct complication. The most common complications include arrhythmias, myocardial ischemia, usually a type II or demand non–ST-segment elevation myocardial infarction, although primary acute coronary syndrome (ST-segment elevation myocardial infarction) may also occur, as most patients have antecedent risk factors for coronary artery disease.

Arrhythmias

Most arrhythmias in medical ICU patients are tachyarrhythmia (90%), which are divided almost equally between supraventricular (atrial fibrillation 30%) and ventricular foci (monomorphic V_T 49%).[80] In surgical ICU patients, 61% of tachyarrhythmias were atrial fibrillation.[81] Although arrhythmias may occur as a result of underlying structural heart disease, physiologic alterations associated with the presenting illness and intrathoracic changes associated with PPV may also contribute. Ventilated patients often experience significant hypoxemia and hypercapnia, acidemia or alkalemia, hypokalemia, hypomagnesemia, and hypocalcemia that can all precipitate arrhythmias. Arrhythmias can also be precipitated by many drugs: vasopressors, inotropes, and inhaled β-agonists being the most common offenders. Clinicians must weigh the risk-to-benefit ratio of the drug relative to the degree of arrhythmia: specifically, is the arrhythmia more likely to have been triggered by the bronchospasm, hypoxemia or hypercapnia, or a β-agonist? Impaired electrical conduction of the normal cardiac impulse has obvious systemic effects, leading to decreased cardiac output and compounding the preexisting respiratory compromise. Identification and management of the inciting cause of the arrhythmia is important, as is appropriate management, as directed by advanced cardiac life support guidelines of the American Heart Association.[82]

Myocardial Ischemia

Myocardial ischemia in ventilated patients can be primary acute coronary syndrome (plaque rupture) or demand-related ischemia (non–ST-segment elevation myocardial infarction) in patients requiring mechanical ventilation for noncardiac indications. In patients presenting with acute coronary syndrome, the need for mechanical ventilation has been associated with increased mortality rates (as high as 50%).[83] Myocardial ischemia can occur at any time during the period of mechanical ventilation, and the increased systemic and myocardial oxygen demand during the time of weaning trials may precipitate acute ischemia.[84–88] Diagnosis is complicated by the lack of classical symptoms of chest pain and the low sensitivity of continuous electrocardiogram (ECG) monitoring.[89] The diagnosis should be considered in patients failing weaning trials. Diagnostic criteria should include clinical, ECG, and cardiac biomarkers, recognizing the limitations associated with biomarker use in the ICU (troponin elevation in clinical presentations of right-heart strain and elevated pulmonary vascular resistance, false elevations in renal failure). Treatment is based on advanced cardiac life support guidelines,[90] including interventional procedures.

RENAL COMPLICATIONS

The first report to show the impact of PPV on renal function was published in 1947.[91] Since then, several studies have documented an association between mechanical ventilation and development of renal failure in the ICU setting.[92–94] PPV increases the odds of developing renal failure threefold when PEEP is below 6 cm H_2O and more than 17-fold when PEEP is above 6 cm H_2O, despite volume replacement, maintenance of normal filling pressures, and adequate oxygen delivery.[92] Various mechanisms have been proposed to explain the alterations in renal function in patients receiving PPV, although three mechanisms are judged dominant: hemodynamic, neurohormonal, and biotrauma (Fig. 41-3).

The systemic hemodynamic effects of PPV originate in a complex interaction between intrathoracic pressure, intravascular volume, and cardiac output. The increase in intrathoracic pressure has been shown to correlate with a decrease in renal plasma flow, glomerular filtration rate, and urine output.[95,96] The reported effects, however, of PPV on glomerular filtration rate and renal blood flow are variable and may

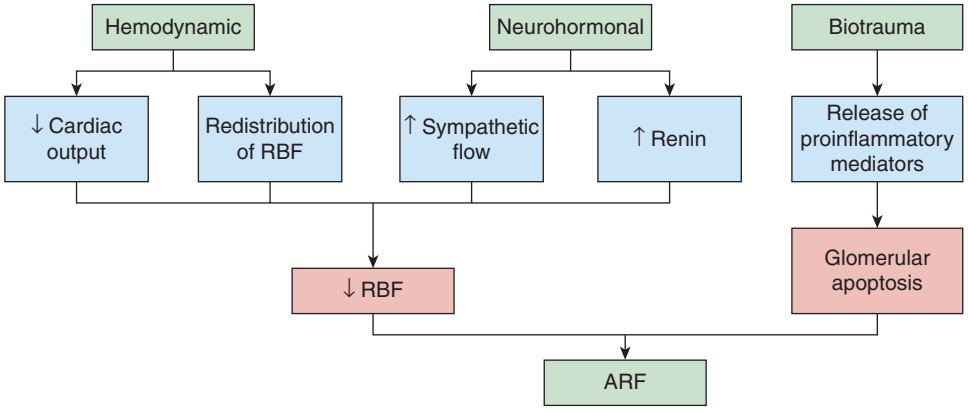

FIGURE 41-3 Mechanisms of acute renal failure during mechanical ventilation. *ARF*, acute renal failure; *RBF*, renal blood flow.

reflect differences in hydration status, underlying pulmonary and cardiac dysfunction, and use of vasoactive agents.[97] It has been suggested that redistribution of intrarenal blood flow from the cortical to juxtamedullary nephrons may play an important role in causing reduction of renal function during PEEP.[98] This may lead to decreased urinary output and creatinine clearance suggesting that small decreases in renal blood flow can seriously affect renal function.

PPV induces several neurohormonal changes in the sympathetic outflow, the renin–angiotensin axis, nonosmotic vasopressin release, and the atrial natriuretic peptide production. Thus far, no definite correlation between antidiuretic hormone levels[99,100] or atrial natriuretic factor,[101,102] and renal function during PPV has been confirmed. PPV, however, increases plasma renin levels by twofold,[96,102] driven by an increase in sympathetic tone. Consequently, renal blood flow and glomerular filtration are reduced, causing[103,104] a drop in distal tubule delivery of sodium. This, in turn, leads to further activation of the renin–angiotensin–aldosterone axis and increased sodium avidity. Clinically, these changes are manifested by a decrease in urine output as a result of decreased osmolar excretion. There are no definitive therapeutic trials for the treatment of PPV-induced renal hypoperfusion. Several small trials have shown that fluid administration and the use of vasoactive drugs (dopamine at 5 μg/kg/min or fenoldopam) may improve renal function,[101,105] but results are not conclusive. It is unlikely that approaches focused solely on the hemodynamic and neurohormonal mechanisms of PPV-induced renal dysfunction will be clinically effective in preventing or treating this multifactorial problem.

In addition to altering renal blood flow, PPV can impact renal function through the release of proinflammatory cytokines. These include IL-8, IL-6, and TNF-α, which promote glomerular and tubulointerstitial sequestration of neutrophils, upregulation of leukocyte adhesion molecules, and a decrease in filtration fraction associated with alterations in vascular tone.[106–111] Moreover, injurious ventilation strategies, such as high V_T and low PEEP, induces glomerular cell apoptosis via a soluble FasL-mediated pathway.[107] Regardless of the proposed mechanism, it is clear that derangements in the innate immune/inflammatory response, oxidative stress and cellular necrosis/apoptosis are important components of this organ cross talk in response to injury.

Several authors have described the effects of other ventilation techniques on renal function. Comparison of controlled mechanical ventilation plus PEEP with low-frequency ventilation and extracorporeal carbon dioxide removal resulted in an immediate increase in urinary flow, osmolar clearance, and creatinine clearance.[112] Spontaneous breathing during airway pressure release ventilation provides improved systemic blood flow and regional perfusion to the kidneys.[113] The effect of permissive hypercapnia on renal function is also well documented: Partial pressure of arterial carbon dioxide (Pa_{CO_2}) levels correlate inversely with renal blood flow.[114] Hypercapnia causes renal vasoconstriction directly[115] and stimulates noradrenaline release through activation of the sympathetic nervous system.[116] Indirectly, hypercapnia induces systemic vasodilation, which results in a drop of the systemic vascular resistance and subsequent activation of the renin–angiotensin–aldosterone system.[117] As a result, renal blood flow becomes compromised and worsen glomerular filtration rate. These hypocapnic changes occur independently of partial pressure of arterial oxygen (Pa_{O_2}),[118] suggesting that Pa_{CO_2} plays a pivotal role in determining the vascular response to changes in blood-gas pressures.

INFECTIOUS COMPLICATIONS

Most clinical investigations indicate that 25% to 50% of ICU patients experience one or more nosocomial infection.[119–121] Fever is the usual trigger for a set of diagnostic and therapeutic interventions. Although the source of fever is not always identified, ventilator-associated infection, sinusitis, catheter-related bacteremias, nosocomial diarrhea, and wound infections account for most infections.[122] Two of these complications (i.e., ventilator-associated pneumonia and sinusitis) are discussed in Chapters 46 and 47.

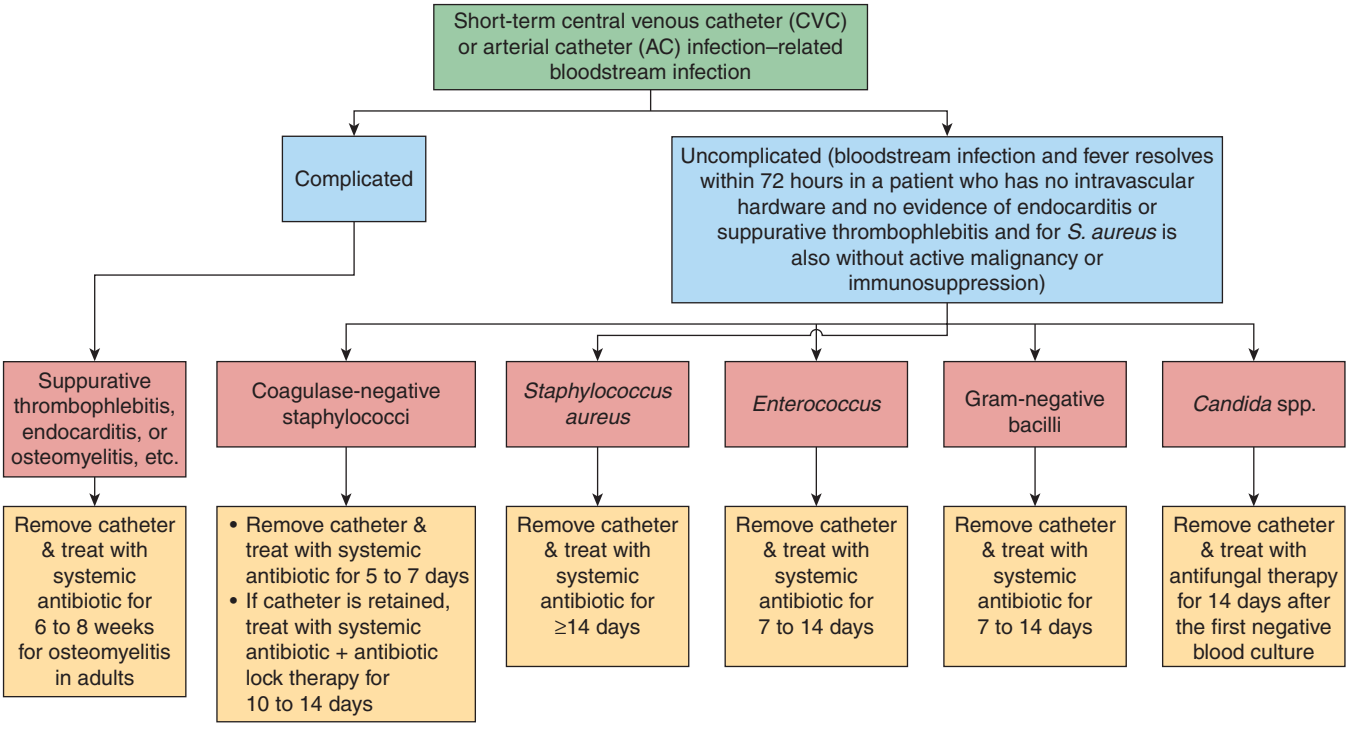

FIGURE 41-4 Approach to the management of patients with central venous catheter-related or arterial catheter-related bloodstream infection. (Reprinted with permission from Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2009;49:1–45 with permission of Oxford University Press.)

Infection of central venous catheters is a particular problem with a mortality of 10% to 35%.[123] The absolute number of catheter-related infections is rising annually because of increasing use, although incidence per catheter days has actually decreased.[124] The catheter insertion site itself provides the most direct route of entry for the pathogen and this is the most common cause of infection.[123] These infections are caused mainly by gram-positive bacteria, in particular *Staphylococcus aureus* and coagulase-negative staphylococci such as *Staphylococcus epidermidis.*[125] Infections, however, can be caused by a wide range of microorganisms including *Enterococci, Candida* spp., *Acinetobacter* spp., *Pseudomonas* spp., and *Klebsiella* spp.[126] Catheter management depends on the likely specific pathogens and the individual colonization profile of the patient (Fig. 41-4).[126]

Infectious causes of nosocomial diarrhea include *Pseudomonas aeruginosa, Escherichia coli,* and cryptosporidium, although *C. difficile* accounts for the majority of hospital-acquired diarrhea or colitis.[127] Prior antibiotics, advanced age, gastric acid suppression, and gastrointestinal surgery or manipulation are major risk factors for symptomatic infection. At least 20% of adults ventilated for more than 1 week are colonized with *C. difficile* and up to 4% develop infection.[128] A hypervirulent strain, the North American pulse-field gel electrophoresis type 1 (NAP1) strain, has been implicated as a cause of *C. difficile* infection of increasing severity.[129,130] A deletion in the toxin regulatory gene, *tcdC,* is thought to allow this strain to overproduce toxin A and toxin B by as much as 15- to 20-fold.[129] Outbreaks caused by this strain are strongly associated with use of fluoroquinolones, although other antibiotics are also implicated.[131] For *C. difficile* infection of every severity, cessation of the inciting antibiotic is the first step in management whenever possible. Metronidazole and vancomycin are the antibiotics most commonly used to treat *C. difficile* in patients with symptomatic infection. A novel macrocycle antibiotic, OPT-80, is currently in phase 3 trials. OPT-80 is minimally absorbed from the gastrointestinal tract and well tolerated in most subjects.[132] Although highly effective against *C. difficile,* OPT-80 leaves the majority of the gram-negative anaerobic flora of the gastrointestinal tract intact. Another commonly employed strategy is the administration of probiotics. In several randomized controlled trials,[133–135] however, the combination of *Saccharomyces* or *Lactobacillus* probiotics with conventional antibiotic therapy has failed to show significant benefit.

HEMATOLOGIC COMPLICATIONS

Anemia

Ninety-five percent of ventilated patients develop anemia after the third ICU day.[136] A significant part is attributed to frequent and excessive blood draws. ICU patients are phlebotomized 3.4 times a day (mean volume of 41.5 mL of blood) as compared to 1.1 times a day for patients on a general ward.[137] Occult gastrointestinal bleeding represents

another source of blood loss. The condition is aggravated by coagulation disorders that include platelet dysfunction, thrombocytopenia, loss of coagulation factors, and endothelium-related coagulation disorders.[138] Several investigations in the last decade, however, suggest that anemia in ICU patients bears many similarities to that associated with chronic disease. More than 90% of ICU patients have low serum iron, total iron-binding capacity, and iron-to-total-iron-binding-capacity ratio, but have a normal or, more usually an elevated, serum ferritin level.[139,140] At a time when the iron studies are abnormal, serum erythropoietin levels are only mildly elevated with little evidence of reticulocyte response to endogenous erythropoietin.[139] Various proinflammatory cytokines are implicated in this blunted response. Inhibition of renal erythropoietin-gene expression in rat kidneys has been demonstrated for IL-1 and TNF-α.[141] In some cases, a shorter erythrocyte life span may aggravate the anemia. There are strong indications that the mononuclear phagocytic system plays a key role, with enhanced iron entrapment and a temporary inhibition of iron release,[142] while the bone marrow is still capable of incorporating iron and of reacting to exogenous erythropoietin.

Critically ill patients respond to treatment with recombinant human erythropoietin and parenteral iron with increased erythropoiesis.[143] Despite early promising results,[144,145] two large placebo-controlled trials investigating the exogenous erythropoietin in critically ill patients failed to show improved 28-day mortality, shorter duration of mechanical ventilation, decreased ICU length of stay, or reduction in red-cell transfusions.[143,146] There was, however, an increased propensity for thrombotic vascular events in the erythropoietin arm.[146]

Thrombocytopenia

The incidence of thrombocytopenia in ICU patients varies from 23% to 41%, depending on the definition of thrombocytopenia and the ICU type.[147–149] Thrombocytopenia is often multifactorial (Table 41-2) and a marker of disease severity.[150] Nearly all studies have found an inverse correlation between platelet count and prolonged ICU stay or hospital mortality.[151–153] The magnitude of the drop in platelet count correlates more closely with adverse outcomes than the nadir in absolute count. The platelet count pattern over time provides important clues as to the cause of the thrombocytopenia. A gradual decrease in platelet counts over several days suggests worsening of the underlying disease and is often associated with multiorgan failure, whereas a new, rapid decrease in platelet count that begins after the fourth day is typical for immune-mediated causes. A classic example is heparin-induced thrombocytopenia, which is frequently considered as a cause of thrombocytopenia in ICU patients, although its incidence is only 0.3% to 0.5%.[154,155] It occurs in two forms. With the more common, type I, form, which occurs in 10% to 20% of patients receiving unfractionated heparin, nonimmune mechanisms produce a drop in platelet counts 1 to 4 days after the onset of therapy. The type I form is not associated with hemorrhagic or thrombotic sequelae, and management involves observation; platelet counts normalize in most patients despite heparin continuation.[156] With the type II form, in contrast, 30% to 80% of patients experience thrombotic sequelae. Venous thromboses outnumber arterial thromboses by 4:1, and life-threatening pulmonary embolism occurs in 25% of patients who have thrombosis.[156] The type II form occurs in 1% to 3% of patients who receive unfractionated heparin, and is induced by antibodies of the immunoglobulin G class against platelet factor 4-heparin complexes.[156] Heparin-induced thrombocytopenia is suspected when a platelet count falls by more than 50% after 4 days of treatment, and can present with new thrombosis, typically occurring 5 to 14 days after the start of prophylactic or therapeutic doses of heparin. To prevent new thrombosis, nonheparin anticoagulant therapy is required. Four drugs are approved for this purpose: (a) two direct thrombin inhibitors, lepirudin and argatroban; (b) a heparinoid, danaparoid; and (c) an antifactor Xa inhibitor, fondaparinux.

TABLE 41-2: ETIOLOGY OF THROMBOCYTOPENIA IN MECHANICALLY VENTILATED PATIENTS

Hemodilution	• Large volume of fluid infusion Excessive transfusion of packed red cells or plasma exchange
Increased platelet consumption	• Sepsis • Thrombotic thrombocytopenic purpura • Disseminated intravascular coagulopathy • Hyperfibrinolysis (metastatic prostate/ovarian cancer) • Intravascular devices
Decreased platelet production	• Myelodysplasia or leukemia • Drug-induced bone marrow depression • Radiation
Increased platelet destruction	• Autoimmune thrombocytopenia • Drug-induced thrombocytopenia • Posttransfusion purpura
Sequestration	• Hypersplenism • Hypothermia

NEUROMUSCULAR COMPLICATIONS

Critical illness polyneuropathy is an acute axonal sensory motor polyneuropathy, mainly affecting the lower limb nerves of critically ill patients including those receiving mechanical ventilation. Critical illness polyneuropathy is often associated with critical illness myopathy and differentiating between these entities may be difficult. For both, the clinical presentation is one of limb weakness or flaccidity, and respiratory muscle weakness or persistent respiratory failure, manifesting as unexplained difficulty in ventilator weaning. Most patients have an antecedent diagnosis of sepsis or septic shock, and the diagnosis should be considered in all patients with difficult weaning. Occurrence varies from

58% of patients with prolonged ICU stay,[157,158] to 70% to 80% of patients with sepsis, septic shock, or multisystem organ failure,[158–162] to 100% of patients with sepsis and coma.[158,163]

Etiology

The cause is believed to be microvascular damage, depletion of bioenergetic neuron reserves, altered sodium channel inactivation, and altered glycemic control, mediated by inflammatory cytokines,[158,162,164–170] and an association with use of glucocorticoids.[171] Although previous data ascribed increased risks with the use of depolarizing neuromuscular blockade and aminoglycoside administration, more recent data suggests that their association may be related to underlying severity of illness.[171–173] A multivariate analysis has identified four independent risk factors: female gender (odds ratio [OR] 4.66), number of days with dysfunction in equal to or greater than two organs (OR 1.28), duration of mechanical ventilation (OR 1.10), and corticosteroid administration (OR 14.9).[171]

Diagnosis

Electrophysiology is required to make the definitive diagnosis in distinguishing between polyneuropathy, myopathy, and neuromuscular blockade, as clinical neurologic examination is insensitive. These studies, however, can be difficult to obtain. Evaluation usually includes needle electromyography in upper and lower limbs. Phrenic nerve conduction studies and needle electromyography of the respiratory muscles may suggest critical illness polyneuropathy as a cause of difficult weaning. The classic electromyography pattern in critical illness polyneuropathy is one of primary axonal degeneration, and manifests as a reduction in the amplitude of the compound action potentials and sensor nerve action potentials. A decrease in the amplitude and prolonged duration of compound action potentials, which suggests an associated myopathy, may be one of the first signs of a developing polyneuropathy.[174,175] Additional features include inexcitability of the muscle on direct stimulation and abnormal spontaneous electromyographic activity. The decline in sensory nerve conduction may present after the above findings. Electrophysiologic studies may help to differentiate between generalized neuromuscular disorders associated with critical illness (Table 41-3); however, these studies require fully cooperative patients. Those afflicted do not necessarily have a fatal outcome as had previously been ascribed[163,176] to comatose patients with acute paralysis, because many patients make a full or near-full recovery.[158,162]

Prognosis

Patients with severe respiratory and limb weakness with electromyelogram evidence of predominant muscle involvement, minimal elevations of creatine phosphokinase and normal muscle biopsy may make a rapid recovery, whereas patients with significant enzyme elevation and evidence of muscle necrosis may have lasting deficit.[175]

NUTRITIONAL SUPPORT

Appropriate nutritional support in ventilated patients has emerged as an important variable in outcomes of ICU patients. The metabolic response to stress and injury is characterized by increased release of cytokines (IL-1, TNF-α, IL-6) with increased production of counterregulatory hormones (catecholamines, cortisol, glucagon, and growth hormones). Counterregulatory hormones induce catabolism and oppose the anabolic effects of insulin. The resultant effects are hypermetabolism and hypercatabolism with a loss of body energy stores through proteolysis, lipolysis, and glycogenolysis.[177–179]

Adverse Effects of Malnutrition

The adverse effects of malnutrition on ventilated patients include altered ventilatory drive; reduction in the ventilatory response to hypoxia; decreased mass; force contractility and endurance of the diaphragm; decreased respiratory muscle strength; hypercapnia; reduced synthesis of alveolar surfactant; and altered humoral and cellular immunity.[180] Despite the general consensus that nutritional support is important, and guidelines advocating provision of enteral nutrition within 24 to 48 hours of ICU admission,[181–184] observational studies reveal that up to 40% of critically ill patients receive no nutritional support during their ICU stay and 60% of patients in the ICU for at least 3 days remain without nutritional support for 48 hours or longer.[183,185–187] A recent meta-analysis of enteral nutrition in critically ill patients[186] demonstrated a reduction in mortality and pneumonia attributable to the inception of standard enteral nutrition within 24 hours of injury (trauma, burn) or ICU admission. Although five of the six trials were nonmedical critically ill patients,[188–192] the one medical trial focused on ventilated patients.[193] Earlier trials have demonstrated that failure to deliver adequate nutritional support or delaying nutritional support leads to cumulative energy deficit, which correlates with longer ICU stay, increased duration of mechanical ventilation, and more infectious complications.[194,195]

Recognition of the effects of undernutrition has led to the recent development of screening guidelines, as well as disease-specific nutritional guidelines.[196] Nutritional support studies have been challenged by major methodological problems in terms of defining the populations studied, standardization of severity of illness scoring, metabolic derangements, variability in enteral nutritional formulations, and outcome measures. The European Society for Clinical Nutrition and Metabolism generated the *ESPEN Guidelines on Enteral Nutrition* in 2006,[181,197–202] and the *ESPEN Guidelines on Parenteral Nutrition* in 2009;[184,203–206] the American Society

TABLE 41-3: GENERALIZED NEUROMUSCULAR CONDITIONS ENCOUNTERED IN MECHANICALLY VENTILATED PATIENTS

Condition	Clinical Findings	Electrophysiologic Findings	Creatine Phosphokinase	Muscle Biopsy	Prognosis
Polyneuropathy					
Critical illness polyneuropathy	Flaccid limbs, respiratory weakness	Axonal degeneration of motor and sensory fibers	Nearly normal	Denervation atrophy	variable
Neuromuscular Transmission Defect					
Transient neuromuscular blockade	Flaccid limbs, respiratory weakness	Abnormal repetitive nerve stimulation studies	Normal	Normal	good
Critical Illness Myopathy					
Thick filament myosin loss	Flaccid limbs, respiratory weakness	Abnormal spontaneous activity	Mildly elevated	Loss of thick (myosin) filaments	good
Rhabdomyolysis	Flaccid limbs	Nearly normal	Markedly elevated	Marked necrosis	good
Necrotizing myopathy of intensive care	Flaccid weakness, myoglobinuria	Severe myopathy	Markedly elevated (myoglobinuria)	Marked necrosis	poor
Disuse (cachectic) myopathy	Muscle wasting	Normal	Normal	Normal or type II fiber atrophy	good
Combined polyneuropathy and myopathy	Flaccid limbs, respiratory weakness	Indicate combined polyneuropathy and myopathy	Variable	Denervation atrophy and myopathy	variable

Source: Adapted, with permission, from Bolton.[175]

TABLE 41-4: GUIDELINES FOR ENTERAL NUTRITION IN CRITICALLY ILL PATIENTS

Population	Enteral Nutrition Summary Recommendations
Critically Ill (Nonsurgical)	1. All patients not expected to be on oral diet within 3 days should receive enteral nutrition (EN) 2. EN should be started within 24 hours of admission to ICU 3. 20 to 25 kcal/kg body weight (BW)/day replacement during the acute phase of illness 4. 25 to 30 kcal/kg BW/day replacement during anabolic recovery phase 5. No significant data to support immune-modulating EN formulas or supplements with the exception of: * Acute respiratory distress syndrome (ARDS)—consider EN enriched with omega-3 fatty acids 6. No significant difference in efficacy of jejunal as compared to gastric feeding 7. Parenteral nutrition should be avoided in patients who can tolerate EN and achieve target intake
Gastroenterology	
Liver Disease Alcoholic Steatohepatitis (excludes NASH)	1. Whole protein formulations are generally recommended. Oral nutritional supplements (ONS) are recommended to supplement oral intake 2. Tube feeding (TF) are recommended if oral intake remains inadequate (even if esophageal varices are present) 3. Use branched-chain amino acid EN formulations in patients in whom hepatic encephalopathy begins during EN 4. Consider the use of concentrated high-energy EN formulations in patients with ascites to avoid positive fluid balance 5. Percutaneous endoscopic gastrotomy (PEG) placement is associated with higher complication rates because of ascites and varices 6. There is no increased risk of bleeding with fine bore nasogastric tubes 7. Recommended energy intake: 35 to 40 kcal/kg BW/day 8. Recommended protein intake: 1.2 to 1.5 g/kg BW/day
Cirrhosis	All of the above and: 1. The use of branched-chain amino acid supplements may improve clinical outcome in advanced cirrhosis
Fulminant Liver Failure	1. Patients should receive enteral nutrition via nasoduodenal tube, with lose observation for hypoglycemia 2. No recommendations for specific EN formulations (absence of data) 3. Calorie recommendations as per critical illness (absence of data) 4. Glucose, lactate, triglyceride, and ammonia levels should be monitored as used as surrogate markers of substrate utilization
Renal Failure	
Acute renal failure	1. Standard critical care EN formulations are adequate, but patients should be assessed individually 2. If there are significant electrolyte abnormalities, EN formulations for chronic renal failure may be advantageous 3. Nonprotein nutritional requirements: 20 to 30 kcal/kg BW/day as carbohydrate 3 to 5 g/kg BW/day, fat 0.8 to 1.2 g/kg BW/day 4. Protein requirements differ depending on clinical status: a. conservative therapy 0.6 to 0.8 g/kg BW/day b. extracorporeal therapy 1.0 to 1.5 g/kg BW/day c. continuous renal replacement therapy (CCRT), hypercatabolism: up to maximum of 1.7 g/kg BW/day 5. Parenteral micronutrient supplementation in prolonged CRRT can be considered, with vitamin C 30 to 100 mg/day, folate, magnesium, calcium, selenium, and thiamine

for Parenteral and Enteral Nutrition generated the *ASPEN Clinical Guidelines* in 2009.[207] The guidelines are similar in their recommendations (Table 41-4), with some notable differences. The ASPEN guidelines advocate withholding enteral nutrition in patients with hemodynamic compromise or high-dose catecholamine requirements. This data is derived from mixed human and animal models and although splanchnic perfusion is increased with enteral nutrition,[208–216] multiple animal studies suggest differential splanchnic vasoconstriction with vasopressor agents (vasopressin > dopamine > phenylephrine). Of note, norepinephrine, the leading vasopressor for septic shock, and dobutamine are both associated with improved gut mucosal pH or perfusion.[217–219] Consequently, the decision to initiate enteral feedings in cases of hypotension is left to clinical judgment to weigh the risks of bowel ischemia against the benefits of enteral nutrition.

Complications of Nutritional Support

Complications of enteral nutrition in ventilated patients include improper tube placement, aspiration (more related to supine positioning because gastric residual volumes have not consistently correlated with aspiration risks[220,221]), vomiting, diarrhea, abdominal distension, and constipation. Most of these problems can be avoided or managed by altering the enteral formulation and with the use of promotility and stool-bulking agents.[53,222–231] The presence of gastric residual volumes of 250 to 500 mL in two consecutive measurements

over 8 hours should prompt the use of a prokinetic agent; if gastric residual volume consistently exceeds 500 mL, interruption of enteral nutrition should be stopped and jejunal feedings considered.[232]

Parenteral Nutrition

Parenteral nutrition should be reserved for patients unable to tolerate or attain their targeted energy requirements within 2 days of enteral feeding, and patients not expected to be on normal nutrition within 3 days.[184] In some meta-analyses,[233,234] parenteral nutrition has been associated with increased rates of infectious complications, which may be associated with the hyperglycemia that is seen more often with parenteral than with enteral nutrition. Parenteral nutrition is administered through a dedicated central venous device, given the osmolarity. Low-osmolarity (<850 mOsm/L) mixtures, designed to cover only a portion of the nutritional needs (usually supplementing enteral nutrition), can be infused through peripheral venous access devices.[184] Lipid emulsion is required as a source of energy as well as essential fatty acids (linoleic [omega-6] and α-linolenic [omega-3] fatty acids). The meta-analysis that suggested an increased complication rate with the use of lipid emulsion was thought to have suboptimal control for total calories and carbohydrates, as per the ESPEN committee on parenteral nutrition, which may have negatively affected outcome. The evidence for a detrimental effect of lipids was not strong.[184] More recent data suggest that delaying the use of lipids does not change complication rates.[235] The choice of long-chain triglycerides from soybean oil or mixtures of long-chain and medium-chain triglycerides from coconut oil is at a practitioner's discretion. Evidence supports tolerance of the mixed emulsions and several small studies have demonstrated clinical advantages (less immunosuppression and fewer infections,[236–238] and lower rates of oxygen consumption in ventilated patients) than with long-chain triglycerides alone, although prospective controlled studies are lacking. Olive oil-based formulations are also available and thought to be safe and well tolerated in other patient populations (burn, home total-parenteral nutrition for intestinal failure), but only one small retrospective observational trial has been done in critically ill patients. There is conflicting data on the addition of eicosapentaenoic acid and docosahexaenoic acid infusions to lipid emulsion, but may decrease length of stay in critically ill patients.

VENOUS THROMBOEMBOLISM

Incidence and Risk Factors

The clinical manifestations of venous thromboembolism (VTE) are protean, ranging from asymptomatic tachycardia and mild dyspnea to hemodynamic collapse. Given this range of presentation, the wide case fatality rate (1% to 60%) is not surprising.[239] Deep venous thrombosis (DVT) is the leading risk factor for the development of VTE, and proximal DVT is found in up to 60% of critically ill patients with venous thrombosis; more proximal thromboses are associated with a 40% to 95% incidence of pulmonary embolism (PE).[240–243] DVT can be clinically silent, and 10% to 100% of ultrasonographically detected thromboses were not detected on clinical examination.[241,244–246] There are differences in incidence of DVT in different ICU settings: medical and surgical ICU patients not receiving thromboprophylaxis have an incidence of approximately 30% within 2 weeks, trauma patients 60%, orthopedic surgery patients 40% to 60%, general neurosurgical patients 20% to 50%, and spinal cord injury patients 50% to 80%.[240,247,248] Risk factors for the development of venous thrombosis include malignancy, duration of mechanical ventilation, immobility (associated with use of sedatives and paralytic agents), severity of illness, emergent surgery, vascular injury from central venous catheterization (femoral), prior VTE, female gender, obesity, cardiac failure, acute myocardial infarction, and inadequate implementation of thromboprophylaxis.[244,249–251]

Diagnosis

PE should be suspected in all ventilated patients with new or unexplained hypoxemia, tachypnea, or sustained hypotension without an obvious alternative diagnosis. It should be considered in the evaluation of unexplained fever and progressive right heart failure.

The diagnostic approach varies with the severity of illness and is tailored to a patient's hemodynamic stability. The ultimate goal is to objectively define the presence or absence of VTE (Fig. 41-5). In ventilated patients who are hemodynamically stable, the diagnostic approach includes pretest probability evaluation and multidetector CT scanning. D-dimer is excluded from this evaluation. Unlike in the evaluation of outpatients, D-dimer is of little value in hospitalized patients, as it lacks specificity in oncology patients, hospitalized patients, pregnant women, the elderly, and in situations where the pretest probability of VTE is high.[252] Most probability scoring systems (Wells Score, Modified Wells Score, Geneva Score, revised Geneva Score, Christopher Study, PERC [Pulmonary Embolism Rule-out Criteria], and PISA-PED [Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis]) are designed for outpatient use or have been evaluated in only small populations of noncritically ill inpatients.[253–257] If the pretest probability of PE is anything but low, a patient should proceed to CT-angiography, which has been well validated with respect to pulmonary angiography[258–260] and has an accepted negative predictive value of 95%. Ventilation–perfusion scanning has limited utility in ventilated patients.

The diagnostic approach for hemodynamically unstable patients is not as clearly defined. The focus here is to rapidly exclude embolism-associated obstructive shock from the differential diagnosis. A recently published algorithm divides the hemodynamically unstable group into critically ill and

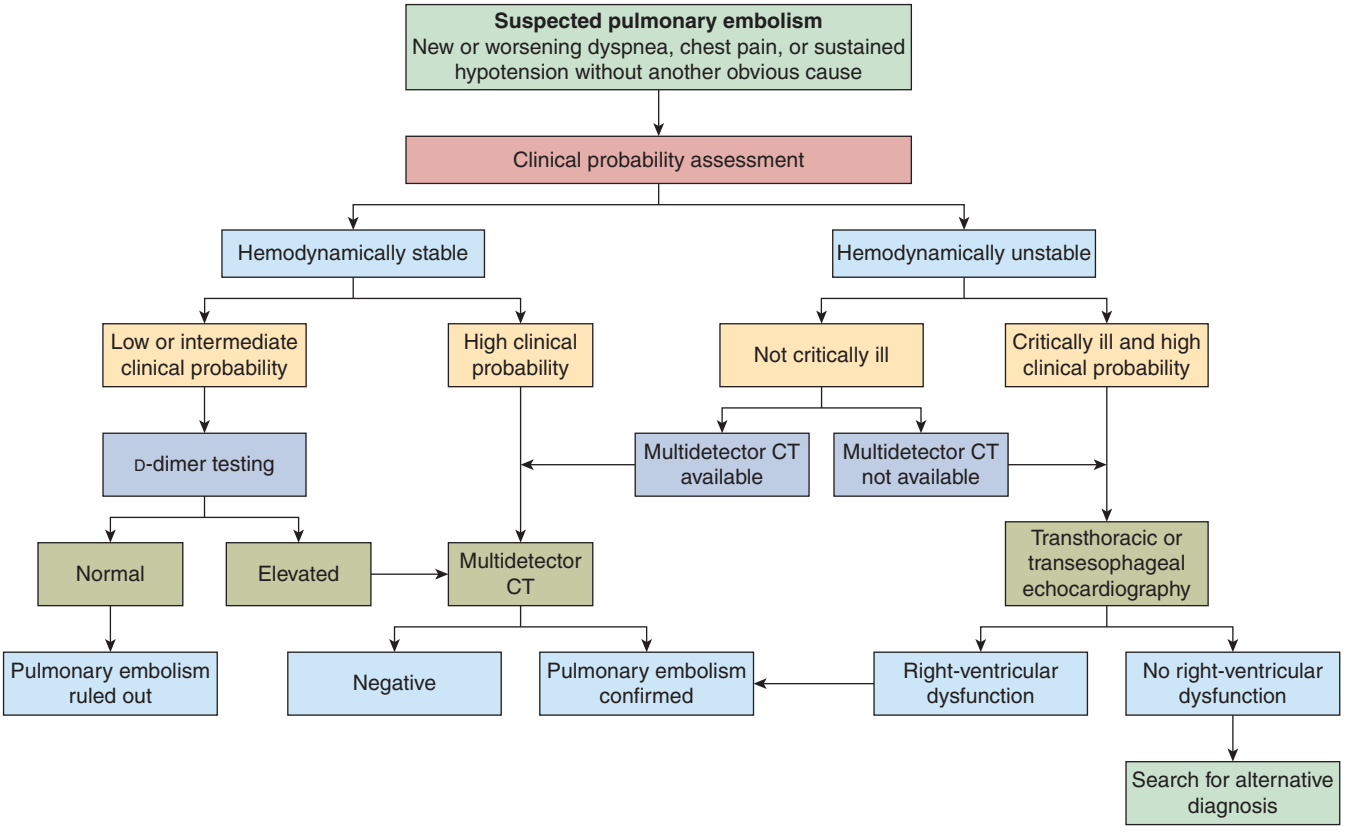

FIGURE 41-5 Diagnostic work-up for suspected pulmonary embolism. (Used, with permission, from Agnelli.[260])

not critically ill, but this can be a difficult distinction.[261] If the patients can be transported for CT-angiography, they should undergo this procedure, which has a 97% sensitivity for detecting emboli in the main pulmonary arteries.[253] If they are too unstable for transport and they have a high pretest probability of PE, they can undergo either transthoracic echocardiography or transesophageal echocardiography, with the goal of detecting right-ventricular dysfunction (defined as a ratio of right-ventricular-to-left-ventricular end-diastolic diameter of greater than 1 in the apical four-chamber view), right-ventricular end-diastolic diameter greater than 30 mm, or paradoxical septal motion. The absence of right-ventricular dysfunction indicates a low likelihood of obstructive shock secondary to PE as the cause of hemodynamic compromise and an alternate source should be identified. The use of the natriuretic peptides and troponin values has a more defined role in the risk stratification and prognostication of patients with an established diagnosis of PE than in initial diagnostic evaluation.

Risk Stratification

Most of the risk stratification tools apply more to the patients on their initial admission and evaluation, and not specifically to ventilated patients who have been in the hospital for some time.

Early mortality rates from PE range from 5% in patients who are hemodynamically stable, to 58% in patients with hemodynamic collapse.[239,262,263] Clinical variables include prognostication scores in the Pulmonary Embolism Severity Index (PESI)[264,265] and Simplified PESI[266] and were designed to identify patients with low risk for death who could be managed safely as outpatients or candidates for early hospital discharge.

More pertinent to ICU population is the use of troponin, natriuretic peptide and right-ventricle-to-left-ventricle (RV/LV) ratio in identifying patients at risk for adverse outcomes. Previous studies have demonstrated increased short-term mortality associated individually with right-ventricular dysfunction in hemodynamically stable PE ("submassive PE") (defined by RV/LV ratio, pooled from CT angiography and echocardiographic studies) elevated brain natriuretic peptide (BNP) or N-terminal pro brain natriuretic peptide and myocardial injury as detected by elevated troponin.[267–273] The PREP study,[263] a prospective cohort study of 570 patients demonstrated combining the individual variables into a prognostic scoring system could further assist in identifying high-risk and low-risk patients. When pooled with the biomarker data, the multivariate model independently associated the highest risk of 30-day adverse events were altered mental status, cardiogenic shock, malignancy, BNP, and RV/LV ratio. The risk factors were used to calculate a prognostic score and based on this score, assigned to three risk classes

(low, intermediate, and high risk). In the group as whole, the risk of adverse of events for Class I (low risk), Class II (intermediate risk), and Class III (high risk) were 2.5%, 11.6%, and 43.2%, respectively. In the hemodynamically stable subgroup, the risks were 1.8%, 11.7% and 22.2%, respectively.

Prevention

Prevention of VTE is important in ventilated patients although the optimal method of thromboprophylaxis is difficult to ascertain. The first difficulty is the lack of studies of routine surveillance screening and the lack of a reference standard for the diagnosis of DVT. Ultrasonography is less sensitive as a screening tool, but venography is not uniformly utilized for many reasons. Studies utilizing ultrasound to determine the incidence of DVT in two treatment arms may underestimate the true incidence. Recognizing the variability in the reported studies, chemoprophylaxis, in general, is uniformly superior to mechanical prophylaxis in all critically ill populations, with the exception of neurosurgical patients (in whom chemoprophylaxis is routinely avoided, despite a lack of sound evidence of increased risk of bleeding).[240,241,247] Recent evidence-based guidelines have been published by the American College of Chest Physicians and by the International Union of Angiology. Despite accumulating evidence of significant reductions in the incidence and mortality of DVT and PE with the use of thromboprophylaxis, and at least three consensus statements guiding appropriate thromboprophylaxis,[248,274,275] three recent reports point out that only 40% to 60% of at-risk medical patients and 53% to 86% of surgical patients received American College of Chest Physicians recommended prophylaxis.[276–278]

Studies demonstrate that appropriate chemoprophylaxis with unfractionated heparin, low-molecular-weight heparin, or direct antithrombin III inhibitors (fondaparinux) can reduce the incidence of VTE by approximately 50%, without a significant increase in bleeding.[240,247,248,274,279–286] The recommendations listed below are from the 2008 *American College of Physicians Clinical Guidelines.* For patients with a moderate risk (medical ICU or postoperative patients), low-molecular-weight heparin or low-dose unfractionated heparin should be used for thromboprophylaxis. For high-risk (trauma or orthopedic surgery) patients, low-molecular-weight heparin should be given. For critical care patients at high risk for bleeding, optimal use of mechanical thromboprophylaxis with graduated compression stockings and/or intermittent pneumatic compression devices should be prescribed at least until the bleeding risk decreases. At that point, pharmacologic thromboprophylaxis should be substituted for or added to the mechanoprophylaxis.

SUMMARY AND CONCLUSIONS

Critically ill patients are at risk of succumbing to their primary disease or the undesired sequelae associated with their therapy. Although frequently lifesaving, the use of positive airway pressure therapy can have deleterious physiologic consequences. Alterations in renal, hepatic, and gastrointestinal functions have been described. Many of these derangements appear to be a direct result of increased intrathoracic pressure, sympathetic stimulation, and neurohormonal changes. Other indirect complications pertain to therapeutic interventions designed to optimize gas exchange and to alleviate the discomfort of mechanical ventilation. Among these complications are neuromuscular dysfunction, malnutrition, and venous thromboembolism. As ventilators become more complex and offer more options, the potential of unintended consequences increase in tandem. While preventing these untoward events may not be always feasible, recognizing their manifestations may be lifesaving.

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VENTILATOR-INDUCED LUNG INJURY

Didier Dreyfuss
Nicolas de Prost
Jean-Damien Ricard
Georges Saumon

The deleterious effects of mechanical ventilation on the lungs have long been referred to as *barotrauma*. For many years, clinicians defined barotrauma as the occurrence of air leaks resulting in the accumulation of extraalveolar air responsible for a number of manifestations, of which the most threatening is tension pneumothorax. In addition to these "macroscopic" events whose adverse consequences are usually immediately obvious, mechanical ventilation may produce more subtle physiologic and morphologic alterations, especially when it results in high airway pressures. Our knowledge of such alterations has stemmed mainly from experimental studies and has expanded considerably over recent years. Indeed, alterations in alveolar–capillary barrier integrity and release of both inflammatory and antiinflammatory mediators have been reported in animals ventilated with modalities resulting in high lung stretching. Tissue damage also may occur during mechanical ventilation when distal airways close and open repeatedly because of the movement of foam in the airway lumen or rupture of liquid menisci. The clinical relevance of these experimental findings received resounding confirmation with the results of the ARDS Network study, which showed a 22% reduction in mortality in patients with the acute respiratory distress syndrome through a simple reduction in tidal volume.[1]

The first comprehensive work demonstrating that mechanical ventilation may be unsafe in intact animals was performed by Webb and Tierney.[2] Rats ventilated with a peak inspiratory pressure (PIP) of 30 or 45 cm H_2O displayed pulmonary edema within 20 minutes to 1 hour, depending on the pressure level. Microscopic examination of the lungs disclosed moderate interstitial edema in animals ventilated with the lower peak pressure, contrasting with profuse edema and alveolar flooding in animals ventilated with the highest PIP. Other studies subsequently documented the occurrence of pulmonary edema and lung ultrastructural abnormalities[3,4] after even very short periods of intermittent positive-inspiratory pressure with high PIP. Kolobow et al[5] reported progressive lung injury in sheep ventilated with 50 cm H_2O PIP over 48 hours, manifested as decreased pulmonary compliance and deterioration in blood oxygenation. Some of the animals died before the 48-hour end point. At autopsy, lungs exhibited congestion and severe atelectasis.

The mechanisms underlying this ventilator-induced lung injury (VILI) have been for the most part elucidated. Two main factors explain its development: the magnitude of lung overdistension and its duration. Ventilation with very high peak transalveolar pressure results in acute, rapidly fatal, permeability pulmonary edema, whereas more protracted ventilation involving alveolar distension of lesser magnitude produces a lung injury in which inflammatory phenomena may play a role. This chapter presents the current knowledge on VILI. A Medline research employing "ventilator-induced lung injury" as keywords and limited to English articles yielded approximately 1900 results up to January 2005 (when the chapter in the second edition of this book was written). A Medline search employing the same keywords yielded 3860 results when updated to December 2010, reflecting the huge scientific productivity in this field over the past 6 years. To provide the most recent findings to readers, we have condensed material that was presented in greater detail in the second edition of this book.

MECHANISMS OF VENTILATOR-INDUCED LUNG INJURY

Ventilation modalities with very high distending pressures (typically >30 cm H_2O, depending on the species) result in pulmonary edema. Both increased filtration and alteration in capillary permeability participate in edema formation. The reasons for these abnormalities have been partly elucidated.

Evidence in Support of Increased Filtration

The first hypothesis put forward to account for ventilator-induced edema involved hydrostatic alterations.[2,6] Parker et al[6] calculated that mean lung microvascular pressure increased by 12.5 cm H_2O during ventilation of open-chest dogs at 64 cm H_2O PIP. Increased filtration may result from an increase of pulmonary capillary pressure, a decrease in lung interstitial pressure, or both. Surfactant inactivation and increased lung volume participate in the decrease in lung interstitial pressure.

The increase in alveolar surface tension resulting from surfactant inactivation would be expected to further decrease the negative pressures surrounding alveolar vessels, thereby increasing vascular transmural pressure and enhancing fluid filtration. Faridy et al[7] showed that ventilating excised dog lungs altered pulmonary pressure–volume curves and increased surface tension of lung extracts commensurately with the magnitude of tidal volume and duration of ventilation. Comparable findings were reported in excised rat lungs.[8,9] These anomalies were ascribed to depletion or inactivation of surfactant. Of note, surfactant alterations failed to occur when positive end-expiratory pressure (PEEP) was used.[7,8,10,11]

Pattle[12] and Clements[13] suggested that an increase in alveolar surface tension might increase filtration. Albert et al[14] found that the isogravimetric pressure (the vascular pressure at which net fluid flux from pulmonary vessels is zero) decreased when alveolar surface tension was increased by cooling and ventilating lungs at a low resting volume in open chest dogs. The authors interpreted this fall in isogravimetric pressure as indicative of a fall in perimicrovascular pressure.

Aerosolized ^{99m}Tc-DTPA (technetium-99m diethylenetriamine pentaacetic acid) clearance was found to increase following detergent aerosolization in rabbits[15] and dogs.[16] This finding was ascribed to regional overexpansion secondary to uneven lung inflation during mechanical ventilation of alveoli with altered surface tension rather than to elimination of peculiar barrier properties of surfactant.[16]

Increased filtration during mechanical ventilation probably also occurs at the extraalveolar level. During lung inflation, because of "pulmonary interdependence," the pressure in the perivascular space surrounding extraalveolar vessels decreases, which, in turn, increases transmural pressure. This effect of lung volume on pulmonary vessels is well documented.[17] Inflating the lungs dilates the extraalveolar vessels.[18] During inflation from a low transpulmonary pressure, the increase in vessel diameter is such that an effective outward-acting pressure in excess of pleural pressure (1 to 2 cm H_2O for each centimeter of water increase in transpulmonary pressure) expands the vessels.[19] The potential importance of fluid leakage through extraalveolar vessels has been established in both excised lungs[20] and in situ lungs of open-chest animals.[21] Moreover, inflation of in situ lobes under zone 1 conditions (i.e., where alveolar pressure exceeds pulmonary arterial and venous pressures) was found to precipitate hydrostatic pulmonary edema in dogs.[22] Because there is no flow in capillaries under zone 1 conditions, it is likely that the edema fluid leaked from distended extraalveolar vessels. The rate of edema formation was significantly correlated with the level of alveolar pressure and, therefore, the magnitude of distension (Fig. 42-1).

The effects of decreased perimicrovascular pressure and surfactant alterations probably combine with increased intravascular pressure to augment transmural microvascular pressure during overinflation. Although the magnitude

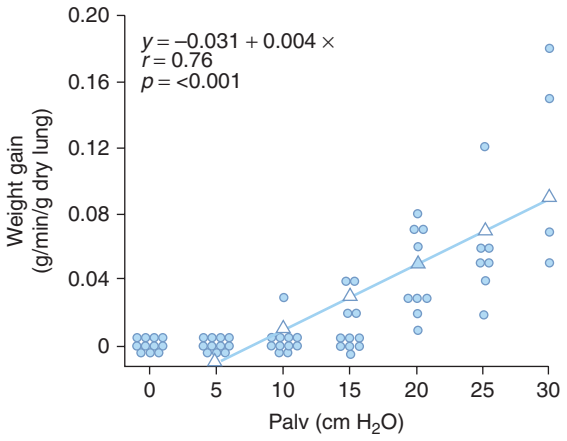


FIGURE 42-1 Relationship between alveolar pressure (Palv) and rate of hydrostatic edema formation in in situ lobes of open-chest dogs. Pulmonary arterial and venous pressures were kept at 1 cm H_2O. When lung volume was low (Palv = 10 cm H_2O), no edema occurred, whereas greater distensions produced a linear increase in lung weight gain, indicating edema formation. (Used, with permission, from Albert et al.[22])

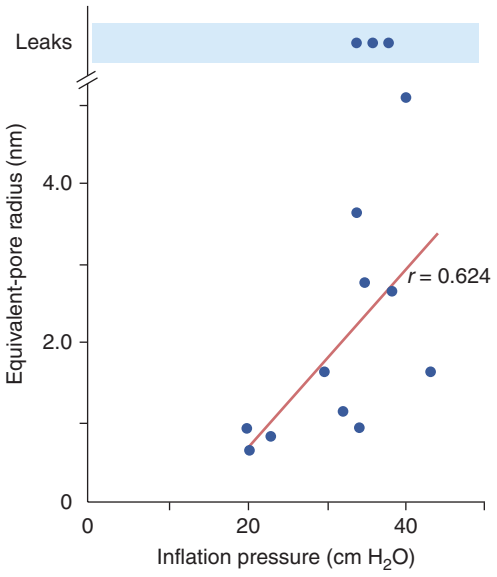


FIGURE 42-2 Effect of inflation pressure on the epithelial permeability of fluid-filled in situ lobes of sheep lung. Permeability is characterized by an equivalent-pore radius. A linear relationship was observed between inflation pressure and pore radius. At the highest levels of inflation, free diffusion of albumin was sometimes observed, indicating the presence of large leaks. (Used, with permission, from Egan et al.[25])

of these changes is difficult to evaluate with precision, the increase in vascular pressure seems relatively modest and is unlikely to explain per se the rapid development of profuse edema (especially in small animals) observed after high PIP ventilation.

Evidence in Support of Permeability Alterations

Many experimental studies in isolated lungs, as well as in open-chest or intact animals, have demonstrated permeability alterations (in response to high airway pressures) in the epithelium and, more unexpectedly, the endothelium.

Epithelial Permeability Changes in Response to High Airway Pressure

The increase in alveolar epithelial permeability to small hydrophilic solutes observed when lung volume increases is a physiologic phenomenon. Elevation of functional residual capacity (FRC), in sheep, obtained by increasing the level of PEEP during mechanical ventilation[23] or spontaneous ventilation,[24] was associated with an increase in aerosolized diethylenetriamine pentaacetic acid (DTPA) clearance. Clearance augmentation was larger than expected from the changes in alveolar exchange surface area.

Effects of overinflation on epithelial permeability were studied extensively by Egan during static inflation of fluid filled in situ lobes.[25,26] The equivalent-pore approach was used to describe the permeability of the epithelium to hydrophilic solutes of various sizes. Equivalent-pore radii increased from about 1 nm at 20 cm H_2O inflating pressure to 5 nm at 40 cm H_2O alveolar pressure. In some instances, free diffusion of albumin across the epithelium was observed, indicating the presence of large leaks (Fig. 42-2). Permeability alterations persisted or even increased after cessation of inflation, suggesting irreversible epithelial injury. High airway pressures applied to in situ lobes, however, resulted in supraphysiologic overinflation because of the compression of adjacent parenchyma. Egan[27] performed experiments under less extreme conditions in rabbits, in which both in situ lobes and entire lungs were distended with 40 cm H_2O airway pressure. Static segmental inflation resulted in a sixfold to 12-fold increase in lung volume from FRC and in an epithelium permeable to solutes such as albumin, cytochrome c, and cyanocobalamin. In contrast, whole-lung inflation resulted in only a threefold to fourfold increase in lung volume and a lesser rate of escape of the smaller solutes from the alveolar spaces. The increase in albumin permeability resulting from whole-lung overinflation was negligible. Hence, only major increases in lung volume produce significant changes in permeability to large molecules.

Although less-well-documented on a quantitative basis, epithelial alveolar permeability alterations are probably present in varying degrees during ventilator-induced pulmonary edema. During positive pressure-ventilation with 41 cm H_2O PIP, increases in alveolar permeability to small (DTPA), but not large (albumin), solutes were observed after 8 hours by Ramanathan et al in lambs.[28] After 2 minutes of high-pressure ventilation, epithelial lining fluid (ELF) volume calculated from bronchoalveolar lavage increased by 180%[4] (Fig. 42-3). ELF protein concentration decreased (Fig. 42-4A) even though protein content increased by 76% (Fig. 42-4B), suggesting that most of the excess fluid

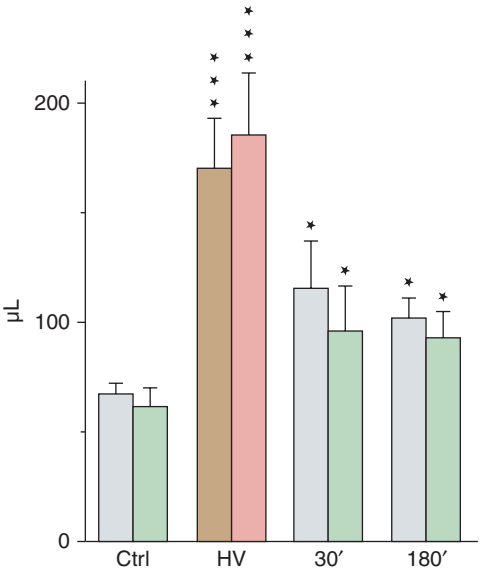


FIGURE 42-3 Estimates of epithelial lining fluid (ELF) volume by bronchoalveolar lavage after ventilation with 45 cm H_2O peak airway pressure for 2 minutes (*HV*) and recovery. Two successive lavages were performed (*grey and brown bars,* first lavage; *green and pink bars,* second lavage). ELF volume increased significantly after HV and then decreased during recovery but remained higher than in control subjects (*Ctrl*). * = $p < 0.05$; *** = $p < 0.001$, as compared to controls. (Used, with permission, from Dreyfuss et al.[4])

entered the alveolar-airway lumen through increased convection. In contrast to the severely altered sieving properties of microvessels after only 2 minutes of overinflation, epithelial permeability appears to be better preserved. This speculation is consistent with the scarcity of epithelial cell alterations on electron microscopic examination, contrasting with the widespread endothelial abnormalities.[4] The presence of blood cells in the alveoli, however, suggested a few large endothelial and epithelial tears. During longer (2 hours) ventilation periods with a lower tidal volume (V_T) (19 mL/kg in rats, resulting in a PIP of 19 cm H_2O), the presence of secretory Clara-cell protein (a protein found in airway lumen) in the vasculature contrasting with a decrease in its concentration in bronchoalveolar lavage fluid further suggests an increase in alveolar barrier permeability.[29] Secretory Clara-cell protein was also found in the plasma of mice ventilated with 35 cm H_2O PIP for 2 hours and even earlier (30 minutes) when PIP was 55 cm H_2O.[30] Resorption of alveolar liquid by distal airway epithelium is decreased during VILI because of depressed sodium transport mechanisms.[31] It can be restored by β-adrenergic stimulation that recruits ion-transporting proteins to the plasma membrane of alveolar epithelial cells or by β_1-sodium-potassium adenosine triphosphatase (ATPase) subunit gene transfer.[32,33]

Microvascular Permeability Alterations during Mechanical Ventilation-Induced Pulmonary Edema

In a study in isolated blood-perfused lobes from dogs, Parker et al[34] demonstrated that ventilation for 20 minutes with graded increases in PIP did not affect microvascular permeability up to 30 cm H_2O. Higher PIP (45 to 65 cm H_2O) was associated with increases in the capillary filtration coefficient (Fig. 42-5) and decreases in isogravimetric capillary pressure, suggesting the existence of an airway pressure threshold. Similarly, the estimated protein reflection coefficient was decreased only at the highest airway pressures. Of note, at an airway pressure above the threshold, the increase in capillary filtration coefficient occurred

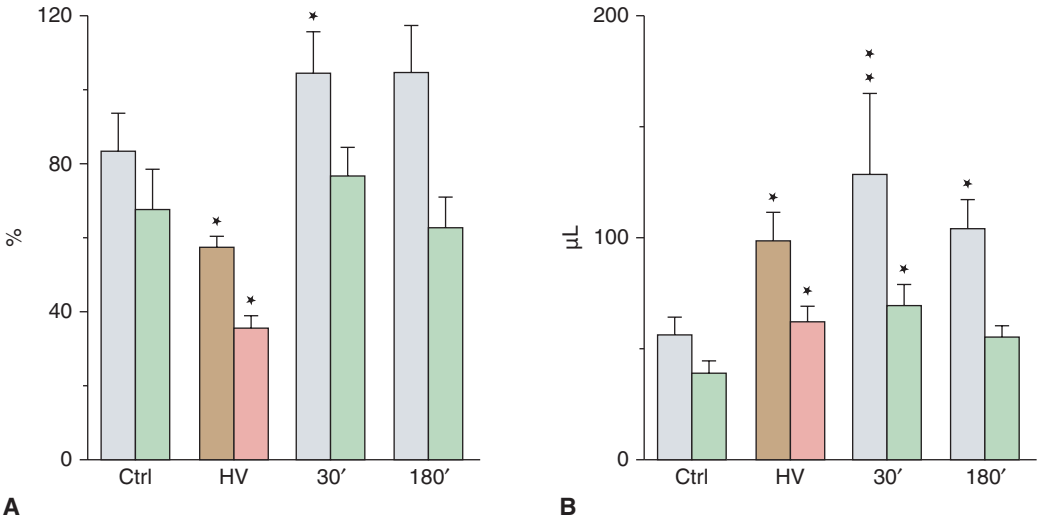


FIGURE 42-4 **A.** Protein concentration and (**B**) protein content in epithelial lining fluid (see Fig. 42-3 for details on the lavages). Protein content (expressed as the equivalent plasma volume) increased after high-pressure ventilation (*HV*) and then remained unchanged during recovery. Protein concentration (as a percentage of plasma protein concentration) decreased after HV and returned to normal during recovery (see text for details). * = $p < 0.05$; ** = $p < 0.01$, as compared to controls. (Used, with permission, from Dreyfuss et al.[4])

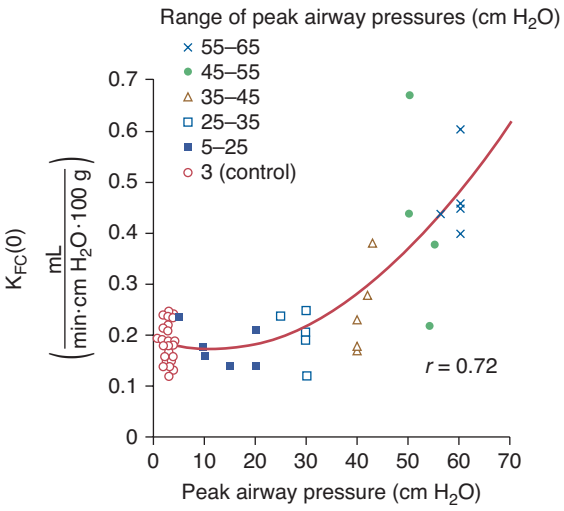


FIGURE 42-5 Effect of peak airway pressure on the capillary filtration coefficient (K_{FC}) of isolated, blood-perfused lobes of dog lungs receiving 20 minutes of intermittent positive-pressure ventilation. Moderate (up to 30 cm H_2O) increases in peak pressure did not affect K_{FC}, whereas higher levels of peak pressure resulted in a very steep increase in K_{FC}. (Used, with permission, from Parker et al.[34])

immediately and continued in some lobes after cessation of distension.

To evaluate permeability alterations in intact animals, extravascular lung water and bloodless dry-lung weight and the distribution space in lungs of ^{125}I-labeled albumin injected in the systemic circulation were measured in intact rats subjected to 45 cm H_2O PIP ventilation.[3] Pulmonary edema developed very rapidly and was easily demonstrable after only 5 to 10 minutes of high-pressure ventilation (Fig. 42-6). Light microscopic examination revealed that, at this stage, edema fluid remained confined to interstitial spaces, where it accumulated in the large peribronchovascular cuffs. No alveolar flooding was apparent. The presence of permeability alterations was indicated by a significant increase in dry-lung weight and of albumin distribution space (Fig. 42-6). After 10 minutes of high PIP ventilation, pulmonary edema was more abundant but still involved only the interstitial spaces. After 20 minutes of ventilation, findings were strikingly different, with tracheal flooding in all animals. Widespread alveolar flooding was obvious upon light microscopic examination. The severity of the permeability alterations was such that the ratio of ^{125}I-albumin activity in tracheal fluid versus plasma was close to unity, indicating the loss of permselectivity of the capillary barrier. The severity of the permeability defect was indicated by the relationship between dry-lung weight and extravascular lung water (Fig. 42-7), which indicated that the concentration of protein in extravasated fluid was high, suggesting the presence of numerous large capillary leaks. Similar findings relating the duration of high-PIP ventilation and alterations in capillary permeability have been made in mice.[30] This increase in endothelium permeability occurs both at the alveolar and extraalveolar level.[35]

The time course of edema development depends on the size of the species: in rats, high PIP ventilation for as little as 2 minutes is sufficient to produce permeability edema,[4] although alterations are minor and result in fairly mild edema. The increase in the ratio of extravascular lung water to blood-free dry-lung weight was increased by only 17%

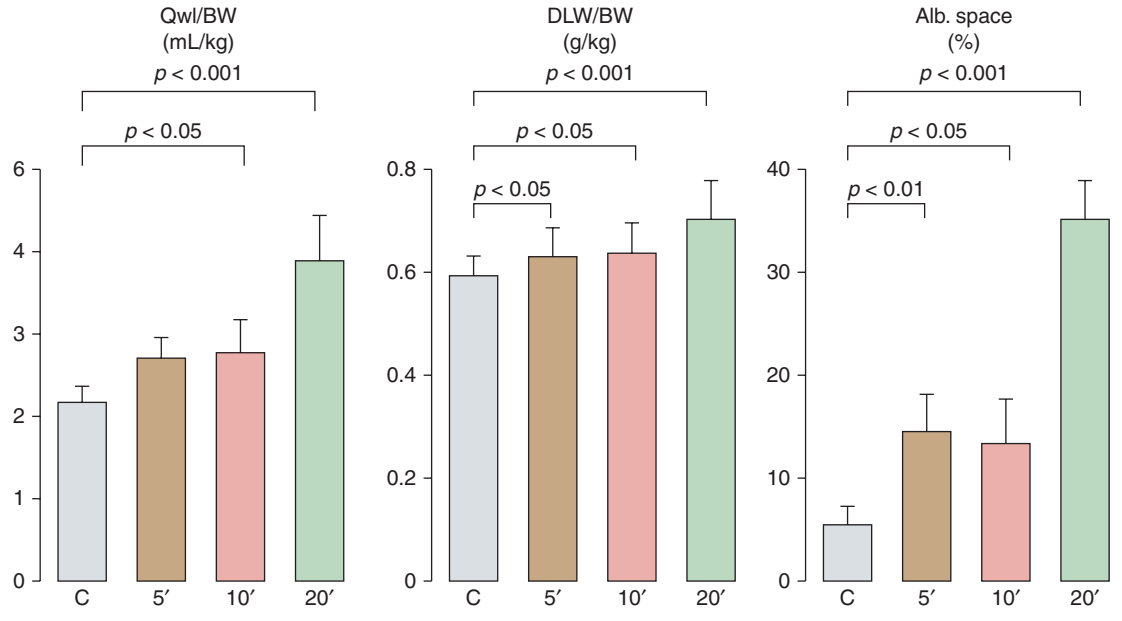


FIGURE 42-6 Effect of 45-cm H_2O peak airway pressure ventilation in intact rats. Pulmonary edema was assessed by the determination of extravascular lung water content (*Qwl/BW*) and permeability alterations by the determination of bloodless dry lung weight (*DLW/BW*) and of the distribution space in the lungs of ^{125}I-labeled albumin (*Alb. Space*). Permeability pulmonary edema developed rapidly (5 minutes). After 20 minutes of mechanical ventilation, there was a dramatic increase in all indexes ($p < 0.01$ versus other groups). (Adapted, with permission, from Dreyfuss et al.[3])

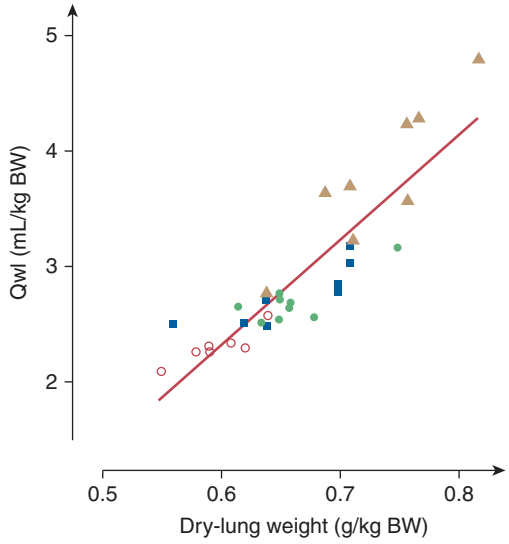


FIGURE 42-7 Relationship between extravascular lung water content (*Qwl/BW*) and dry lung weight during mechanical ventilation with peak airway pressure 45 cm H_2O. The concentration of proteins in the edema fluid estimated from this relationship was consistent with the outpouring of protein-rich edema fluid reflecting severe permeability alterations. *Open circles*, control conditions; *closed circles*, 5 minutes of ventilation; *closed squares*, 10 minutes of ventilation; *closed triangles*, 20 minutes of ventilation. (Used, with permission, from Dreyfuss et al.[3])

after 2 minutes[4] versus 90% when the duration of the challenge was increased up to 20 minutes.[36] In larger animals, considerably longer durations of high PIP ventilation are required to produce significant alterations. For instance, in lambs mechanically ventilated at 58 cm H_2O PIP for 6 hours, Carlton et al[37] found an increase in the ratio of extravascular lung water to dry-lung weight of only 19%. Results of histologic lung studies were either normal or showed only mild perivascular edema with no alveolar edema. In a study by Borelli et al,[38] sheep mechanically ventilated for 18 hours with a PIP of 50 cm H_2O developed both interstitial and alveolar edema.

Wet-lung weight normalized for body weight increased by 89% compared to normal lungs.[39] After 27 hours of ventilation, pathologic abnormalities were much more marked, and lung weight was increased by 136% compared to normal lungs. Clearly, the ventilation time needed to produce severe edema is less than 1 hour in small species but more than 24 hours in large animals. Blood-gas barrier thickness is an important component of capillary resistance to mechanical stretch, and is more important in larger animals.[40] Thus, one reason why permeability alterations were not consistently found is that they may become detectable only after longer ventilation times, in contrast to the immediate occurrence of microvascular pressure anomalies.

In summary, increased microvascular filtration pressure and altered microvascular permeability probably compound their effects to produce high PIP pulmonary edema. Although the hydrostatic component seems to be moderate on a quantitative basis, at least in closed-chest animals, it may nevertheless have a substantial impact. Indeed, in the face of a microvascular barrier with altered sieving properties, any increase in driving pressure will have a dramatic effect on edema formation.[41–43]

Mechanisms of Acute Increase in Alveolo-Capillary Permeability during Lung Overinflation

Interest has increasingly focused on the cellular response to mechanical strain and this subject has been comprehensively reviewed.[44] Tschumperlin and Margulies[45] observed increased cell death when alveolar epithelial cells were submitted in vitro to deformation. Cyclic deformation led to significantly greater cell death than did static deformation. The percentage of dead cells after 1 day ranged from 0.5% to 72% depending on the changes in surface area (up to 50%). In cyclically deformed cells, injury occurred rapidly, with most of cell death occurring during the first 5 minutes of deformation.[46] These authors showed that basement membrane surface area increased approximately 40% when lung volume was varied from FRC to total lung capacity.[47] These increases suggest that epithelial cells undergo significant stretch during large inflations. Vlahakis et al[48,49] labeled membrane lipids to study deformation-induced lipid trafficking and studied in a direct manner (laser confocal microscopy) the response of epithelial cells of the alveolar basement membrane response to forces. A 25% stretch deformation resulted in lipid transport to the plasma membrane that allowed maintenance of its integrity and an increase in epithelial cell surface area. Such lipid trafficking occurred in all cells, whereas plasma breaks were seen in only a small percentage of cells. The authors concluded that deformation-induced lipid trafficking serves, in part, to repair plasma breaks so as to maintain plasma membrane integrity and cell viability, and that this could be viewed as a cytoprotective mechanism against the plasma membrane stress failure seen during VILI.[36,50]

Overinflating the lungs results in the increase in epithelial[25] and endothelial[3,34] permeability, both occurring after inflating the lung above the same end-inspiratory pressure threshold.[51] Using an isolated perfused rat model, Parker et al showed that gadolinium (which blocks stretch-activated nonselective cation channels) annulled the increase in microvascular permeability induced by high PIP.[52] This suggests that entry through stretch-activated channels and an increase in intracellular calcium ion (Ca^{2+}) concentration might initiate the increase in permeability. This increase results in the activation of tyrosine kinases,[53] activation of the Ca^{2+}–calmodulin pathway and phosphorylation of myosin light chain kinase.[54] Taken together, these results suggest that the increase in microvascular permeability below the cell rupture point, which occurs under extreme stretch conditions ("stress failure"[50,55]), is not simply a passive physical phenomenon, but the result of biochemical reactions. In vitro studies show that cell plasticity and deformation-induced

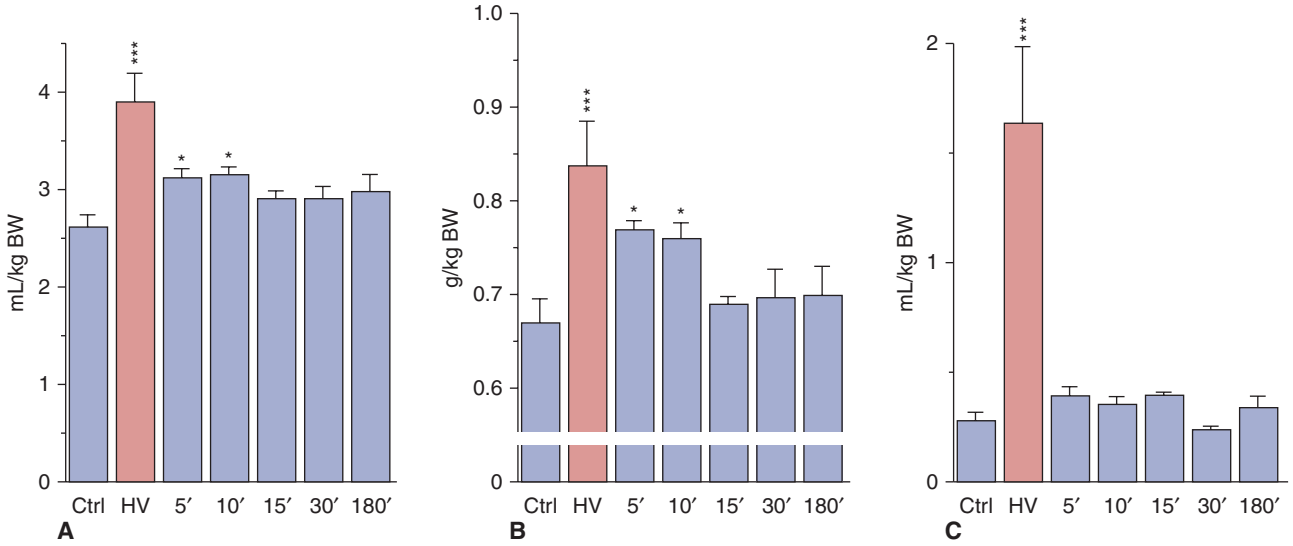


FIGURE 42-8 Effect of 45 cm H_2O peak airway pressure ventilation for 2 minutes (*HV*) and followed by recovery for various lengths of time in intact rats. **A.** Extravascular lung water. **B.** Dry lung weight. **C.** Albumin distribution space. Permeability edema already present after 2 minutes cleared rapidly after cessation of ventilation. * = $p < 0.05$; *** = $p < 0.001$, as compared to controls. (Used, with permission, from Dreyfuss et al.[4])

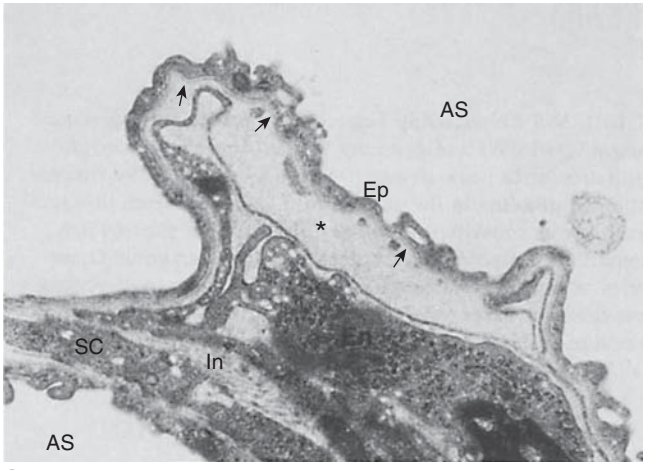
lipid trafficking protect against strain injury. Interventions that impair deformation-induced lipid trafficking reduce the likelihood of plasma membrane resealing[49,56] and increase cell death. It may help explain why the breaks seen across endothelial cells, after short periods of high transmural capillary pressure[57] or overinflation[4] are transient. In this latter study, rats were subjected to mechanical ventilation with 35 mm Hg PIP for only 2 minutes and allowed to recover for graded periods of up to 3 hours. The animals that were killed immediately after the challenge exhibited mild pulmonary edema with severe permeability alterations, as attested by increases in dry-lung weight and albumin space (Fig. 42-8). The very rapid occurrence of microvascular injury was ascertained by the ultrastructural study, which disclosed changes identical with those previously described after longer periods of ventilation.

These data strongly suggest that, at least in small animals, vascular leakage after overinflation is almost immediate and extensive. During recovery, both extravascular lung water and dry lung weight promptly returned to normal (see Fig. 42-8A and B), indicating that resorption of edema can be very rapid. Edema resorption does not necessarily indicate restoration of the alveolo–capillary barrier. The 30-minute distribution space of ^{125}I-albumin in lungs, however, was found to be normal, indicating that no albumin permeability defect was present after the time of tracer injection (see Fig. 42-8C). Because the tracer was injected during the recovery period (i.e., after cessation of overinflation), this finding demonstrated reversal of the alterations in permeability. ELF volume decreased after cessation of overinflation (see Fig. 42-3), reflecting resorption of the excess alveolar fluid concomitantly with the decrease in extravascular lung water. Even after 3 hours of recovery, however, ELF volume remained higher than in control animals. No marked changes in epithelial fluid protein content were observed (see Fig. 42-4B), reflecting the slower-than-water clearance of protein in alveolar edema fluid.[58] The absence of notable protein resorption explains why the protein concentration in ELF increased during recovery (see Fig. 42-4A).

ULTRASTRUCTURAL FINDINGS OF VENTILATOR-INDUCED LUNG INJURY

Electron microscopic studies have confirmed that permeability alterations are prominent in the genesis of ventilator-associated pulmonary edema. Both endothelial and epithelial alterations have been observed.[3,4,30,36]

After short durations (5 to 10 minutes) of 45 cm H_2O PIP mechanical ventilation in rats, striking capillary abnormalities consistent with pulmonary edema of the nonhydrostatic type were observed. Some endothelial cells were detached from their basement membrane, resulting in the formation of intracapillary blebs filled with plasma-like material (Fig. 42-9A). Endothelial cells exhibited focal disruptions (Fig. 42-9B). Bleb formation has been reported in experimental high-permeability edema, regardless of the nature of the causative agent, and in acute respiratory distress syndrome (ARDS),[59–62] but not in experimental hydrostatic pulmonary edema.[59,60,63] Longer durations (20 minutes) of high PIP ventilation in rats resulted in alveolar flooding and obvious permeability alterations. Pathologic studies showed that this severe edema was accompanied with diffuse damage to the alveolar–capillary barrier. In addition to the capillary lesions, ultrastructural studies disclosed profound alterations in the epithelial layer. The severity of alterations varied. In some sites, the epithelial lining appeared intact. In many areas, however, findings included discontinuities (Fig. 42-10A and B) and sometimes



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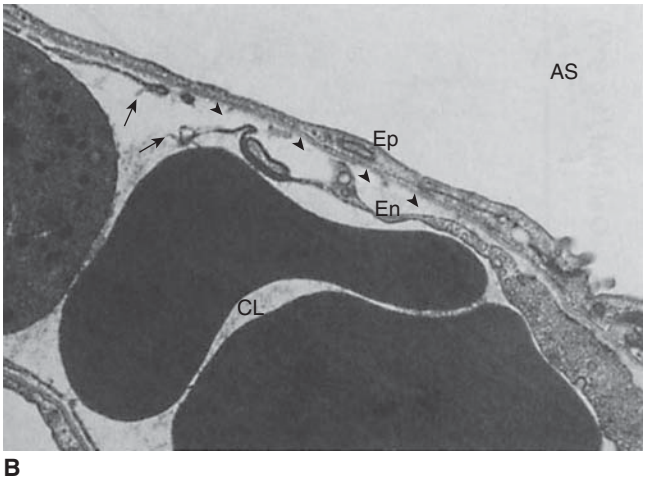

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FIGURE 42-9 Ultrastructural features of the blood–air barrier after 5 minutes of 45 cm H_2O peak airway pressure in a closed chest rat. **A.** The most striking change is the formation of an endothelial bleb secondary to detachment of the thin part of the endothelial cell (*En*) from the basement membrane (*arrows*). This bleb is filled with electron-dense material (*) of the same density as plasma. At this stage, epithelial type I cells (*Ep*) are intact. Note interstitial edema (*In*). *AS*, alveolar space; *SC*, septal cell. (Used, with permission, from Dreyfuss et al.[3]) **B.** *Arrows* indicate a disruption of the thin part of the endothelial cell detached from the basement membrane (*arrowheads*). *CL*, capillary lumen. (Courtesy Paul Soler, Ph.D.)

almost complete destruction of type I cells, leaving a denuded basement membrane (Fig. 42-10B and C). In contrast, type II cells appeared preserved. Hyaline membranes filled the alveolar spaces in many of the sections examined (Fig. 42-10C). Similar to the endothelial abnormalities, these lesions are not specific and occur in toxic injuries as well as in ARDS.[59–62] In contrast, when pressures remain in the 30- to 40-mm Hg range, hydrostatic edema does not affect epithelial integrity.[59,60,64]

Studies using both transmission and scanning electron microscopy have demonstrated ultrastructural breaks in endothelial and epithelial cells when capillary transmural pressure was raised to 40 mm Hg or more.[55,65,66] These breaks are the morphologic correlates of the increased microvascular permeability reported with very high microvascular pressures[67,68] and described as the stretched-pore phenomenon.[69,70] The similarities between capillary stress failure and VILI are quite remarkable. First, the electron microscopic appearance of endothelial and epithelial cell lesions exhibit similarities (Fig. 42-11).[55,65] Second, both types of damage are partly reversible. Albumin leakage from capillaries during high-volume ventilation ceased almost immediately after discontinuation of ventilation.[4] When capillary pressures were lowered to normal after elevation to a level causing stress failure, the number of endothelial and epithelial breaks fell compared with control experiments in which pressure remained elevated.[57] More importantly, capillary stress failure is influenced by lung inflation: At a capillary transmural pressure of 32.5 cm H_2O, increasing lung volume from a transpulmonary pressure of 5 to 20 cm H_2O resulted in a significant increase in the number of capillary endothelium and alveolar epithelium breaks (Fig. 42-12).[50] Thus, vascular pressures that are too low to affect microvascular permeability when lung volume is normal may produce permeability alterations when combined with a sufficiently marked increase in lung volume.

EFFECTS OF ACTIVATION OF INFLAMMATION BY PROTRACTED HIGH-VOLUME VENTILATION

The endothelial cell disruptions that have been observed during overinflation edema in small animals may allow direct contact between polymorphonuclear cells and basement membrane (see Fig. 42-10B) and promote leukocyte activation. Proinflammatory mediators may also be released by cells undergoing necrosis. Infiltration of inflammatory cells into the interstitial and alveolar spaces is not seen before several hours of injurious ventilation. In mice subjected to high PIP ventilation, leukocyte sequestration in lungs progressively increased with time.[71] Woo and Hedley-White[72] observed that overinflation produced edema in open-chest dogs, and that leukocytes accumulated in the vasculature and macrophages in the alveoli. Further studies confirmed these results[73] and showed that high transpulmonary pressure increased the transit time of leukocytes in the lungs of rabbits.[74] Conversely, high-volume pulmonary edema was less severe in neutrophil-depleted animals. Kawano et al[75] observed that neutrophil-depleted rabbits had preserved gas exchange, little lung albumin leakage, and no hyaline membranes after 4 hours of mechanical ventilation in contrast to nondepleted animals in a saline-lavage model. Whereas it is predictable that healing of wounded tissue would involve inflammation, several authors have suggested that lung tissue stretching might result in lung damage solely through the release of inflammatory mediators and leukocyte recruitment, the so-called biotrauma hypothesis.[76]

The term *biotrauma* encompasses all molecular and cell-mediated mechanisms involved in VILI, such as the production of lung-borne cytokines.[76,77] Although the causative role of those mediators on VILI has been debated,[78] as

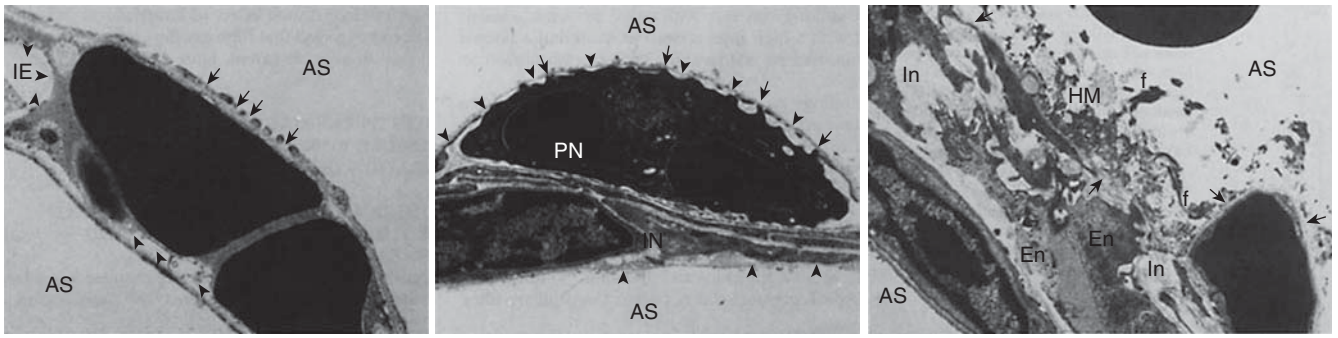


FIGURE 42-10 Ultrastructural features of the blood–air barrier after 20 minutes of 45 cm H_2O peak airway pressure in a closed chest rat. **A.** Type I cells show numerous gaps (*arrows*). *Arrowheads* point at the basement membrane from which the endothelial cell is detached. *AS*, alveolar space; *IE*, interstitial edema. (Courtesy Dr. Paul Soler.) **B.** Epithelial and endothelial cells are almost completely destroyed, resulting in denuded basement membranes (*arrowheads*). A polymorphonuclear neutrophil (*PN*) inside the capillary lumen exhibits cytoplasmic processes, protruding through gaps in the capillary endothelium. *IN*, interstitium. (Courtesy Dr. Paul Soler.) **C.** Very severe alteration of the alveolar capillary barrier. Complete lysis of the epithelial layer (*upper right quadrant*) results in denudation of the basement membrane (*arrows*). Alveolar space is occupied by hyaline membranes (*HM*) composed of cell debris and fibrin (*f*). *En*, endothelial cells; *In*, interstitial edema. (Used, with permission, from Dreyfuss et al.[3])

comprehensively discussed in Chapter 42 of the second edition of this book and in "Pharmacologic Interventions" below, several investigators have tested the effect of cytokine modulators on lung dysfunction in experimental models of VILI.

PHYSIOLOGIC DETERMINANTS OF VENTILATOR-INDUCED INJURY

Respective Roles of Increased Airway Pressure and Increased Lung Volume

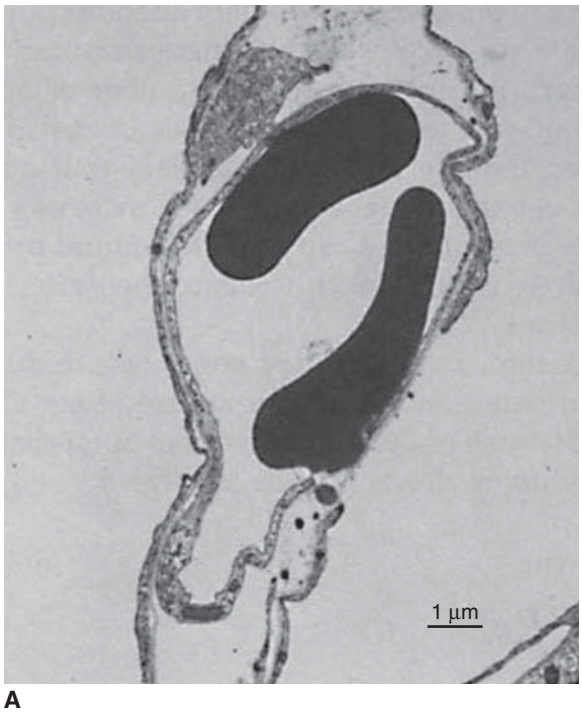
High inspiratory pressures consistently result in high lung volumes in normal animals. They induce well-documented hemodynamic changes in the systemic circulation,[79] and may potentially affect blood-flow distribution in the lungs because parts of the lungs are placed under zone 1 condition over the ventilatory cycle. Another possibility is that high pressures per se produce regional distortions that may result in specific deleterious effects. Several studies have been conducted to determine the relative roles of intrathoracic pressure increases and lung distension in the genesis of pulmonary edema.

High-volume ventilation with low airway pressure was obtained by ventilating closed-chest rats with intermittent negative perithoracic pressures (using an iron lung). Ventilation with high airway pressures but low tidal volumes was obtained with thoracoabdominal strapping to limit thoracic movements. The effects of high PIP plus high tidal-volume ventilation were compared with those of intermittent negative airway pressure plus high tidal-volume ventilation and intermittently positive high PIP plus low tidal-volume ventilation.[36] Pulmonary edema of the permeability type occurred in both groups of rats that received high tidal-volume ventilation, irrespective of inspiratory pressure (i.e., positive or negative; Fig. 42-13). In both groups, electron microscopic examination disclosed the same abnormalities as described above. In striking contrast with these findings, animals ventilated with a high PIP but a normal tidal volume had no edema (Fig. 42-13) and no ultrastructural changes. These findings have been replicated in rabbits[80] and lambs.[37]

Roles of the Magnitude of Pressure–Volume Changes and of Duration of the Challenge

IS THERE A PRESSURE–VOLUME THRESHOLD FOR THE OCCURRENCE OF EDEMA AND PERMEABILITY ALTERATIONS?

A threshold volume for permeability changes as the lung is overexpanded was suggested by Carlton et al.[37] These authors studied the effects of graded increases in tidal volume on lymph flow and protein concentrations in lambs. Peak inspiratory pressure (and therefore tidal volume) was increased in three successive steps (each lasting 4 hours) from baseline (16 cm H_2O to 61 cm H_2O). During the first two steps (33 and 43 cm H_2O PIP), no changes in lymph flow or protein composition were observed. In contrast, when the highest PIP was reached (corresponding to a tidal volume of 57 mL/kg), lung lymph flow increased fourfold to sixfold compared with baseline. Similarly, the lymph-to-plasma-protein-concentration ratio did not change until the highest PIP was reached, at which time it increased significantly compared with controls. The investigators concluded that microvascular alterations in response to overinflation occurred beyond a pressure threshold rather than gradually as pressure increased. They pointed out, however, that the albumin-to-globulin ratio in lymph versus plasma decreased before maximum PIP was reached, suggesting altered protein sieving and probably abnormal microvascular permeability. Indeed, Tsuno et al[39] demonstrated that ventilation of sheep with a moderately



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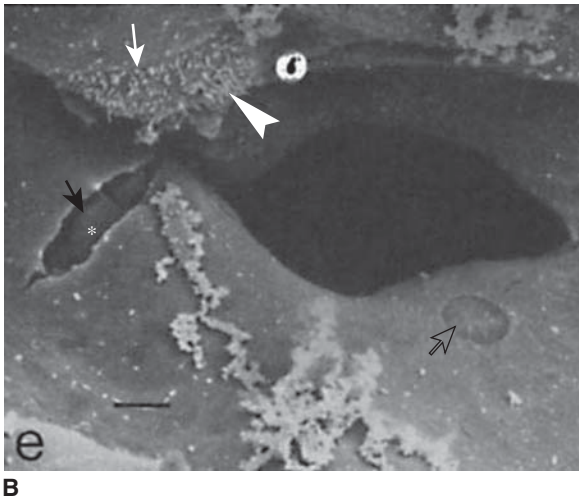

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FIGURE 42-11 Examples of disruptions of the blood-gas barrier in in situ rabbit lungs perfused at 72.5 cm H_2O capillary transmural pressure. **A.** Transmission electron microscopy. The alveolar epithelium and capillary endothelium are disrupted, but the basement membrane is intact. **B.** Scanning electron microscopy. Circular rupture involving only the epithelial layer (*open arrow*) and complete disruption of the blood-gas barrier (*closed arrow*) showing red blood cells in the opening (*asterisk*). A large amount of proteinaceous material is present in the alveolar lumen. The *arrowhead* indicates a type II cell with an intercellular junction (*white arrow*). (Used, with permission, from West et al.[55] and Costello et al.[66])

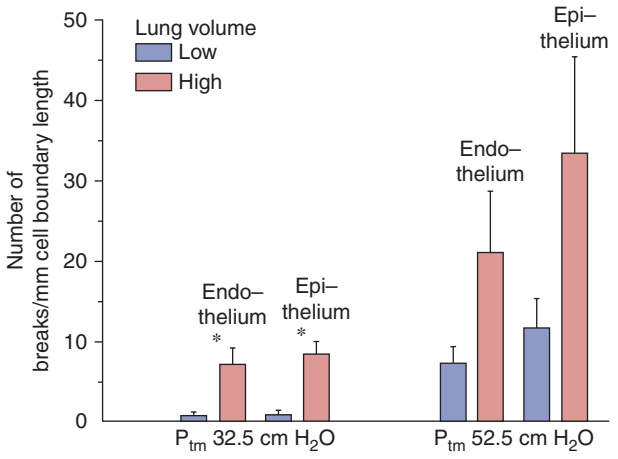

FIGURE 42-12 Effect of lung inflation on capillary stress failure. In situ rabbit lungs subjected to a capillary transmural pressure of 32.5 cm H_2O had more endothelial and epithelial breaks at high lung volume (transpulmonary pressure of 20 cm H_2O) than at low lung volume (transpulmonary pressure of 5 cm H_2O). (Used, with permission, from Fu et al.[50])

elevated PIP of 30 cm H_2O (corresponding to a tidal volume of 30 mL/kg) for more than 40 hours invariably resulted in gross pathologic alterations and an increase in wet-lung weight. Ventilating healthy sheep with tidal volumes ranging from 9 to 51 mL/kg for 54 hours, Protti et al demonstrated that ventilator-induced lung edema developed only when a strain (i.e., the ratio between tidal volume and FRC[81]) greater than 1.5 to 2.0 was applied to the lungs.[82] Interestingly, systemic inflammation and organ dysfunction also developed in pigs ventilated above this strain threshold.[82] In smaller species, such as rats, in which VILI occurs more rapidly, edema was demonstrated with a PIP as low as 30 cm H_2O, provided ventilation was sufficiently prolonged.[2] Recently, scintigraphic methods allowing for real-time imaging of two-way protein fluxes across the alveolo-capillary barrier were used to measure simultaneous changes in alveolar and microvascular permeability during lung inflation in rats.[51] The same end-inspiratory pressure threshold (between 20 and 25 cm H_2O, corresponding to tidal volumes of 13.7 ± 4.69 and 22.2 ± 2.12 mL/kg) was observed for epithelial and endothelial permeability changes (Fig. 42-14). Of note, this threshold corresponds approximately to the pressure at which a decrease is observed in the slope of the respiratory system pressure–volume curve (the so-called upper inflection point) in rats.[83]

These studies emphasize that both the degree and the duration of lung overexpansion are crucial in determining the severity of pulmonary edema. Interestingly, the possibility of a potential pressure–volume threshold for additional lung injury during mechanical ventilation of patients with acute lung injury is also debated. This is discussed in "Clinical Relevance" below.

Respective Contributions of Sustained Inflation (Positive End-Expiratory Pressure) and Large Pressure–Volume Swings

For the same level of overall lung inflation, increasing FRC by PEEP results in less-severe alterations, the reasons for

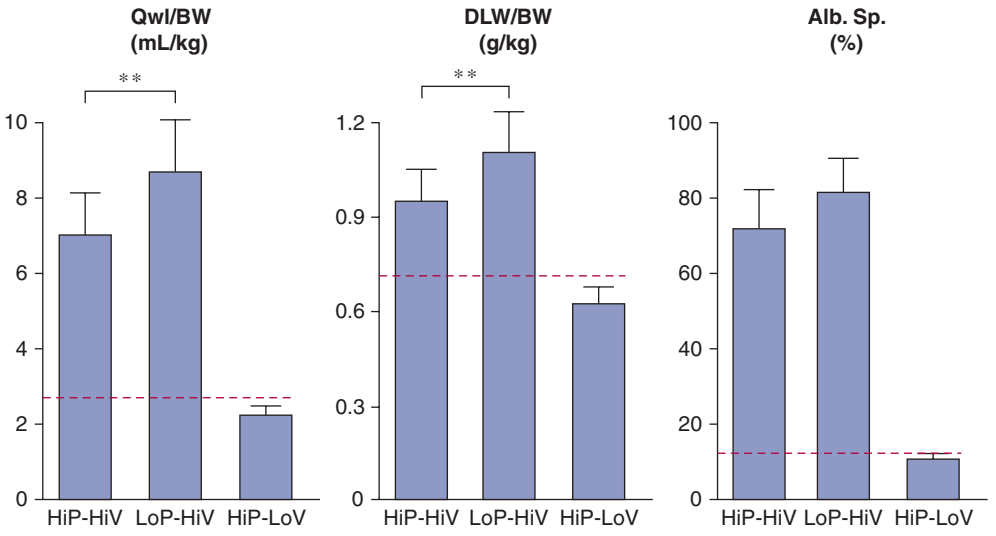

FIGURE 42-13 Comparison of the effects of high peak (45 cm H_2O) positive inspiratory pressure plus high tidal-volume ventilation (*HiP-HiV*) with the effects of negative inspiratory airway pressure plus high tidal-volume ventilation (iron lung ventilation = *LoP-HiV*) and of high peak (45 cm H_2O) positive inspiratory pressure plus low tidal-volume ventilation (thoracoabdominal strapping = *HiP-LoV*). *Dotted lines* represent the upper 95% confidence limit for control values. See Figure 42-6 for details on edema indexes. Permeability edema occurred in both groups receiving high tidal-volume ventilation. Animals ventilated with a high peak pressure and a normal tidal volume had no edema. ** = $p < 0.01$. (Used, with permission, from Dreyfuss et al.[36])

which may be reduction of V_T at the same respiratory rate, and hence of peak inspiratory flow, or stabilization of terminal units.

Several studies assessing the deleterious effects of high gas flow rates on lung function, a minor determinant of VILI, are discussed in detail in Chapter 42 of the second edition of this book. Webb and Tierney showed that, for a given level of teleinspiratory pressure, edema was less severe when a 10-cm H_2O PEEP was applied.[2] It was subsequently shown[36] that, although the amount of edema fluid was smaller with PEEP (Fig. 42-15), permeability alterations were similar to those observed with zero end-expiratory pressure. When rats were ventilated with PEEP, however, less edema occurred and, in particular, no alveolar flooding was observed on light microscopy.[2,36] More strikingly, whereas diffuse alveolar damage was present in the animals ventilated with zero end-expiratory pressure, no epithelial-cell lining alterations were observed on electron microscopic examination of the lungs of animals ventilated with PEEP. The only ultrastructural alterations consisted of endothelial blebbing. It is worth noting that PEEP decreases lung-capillary blood volume,[84] which, in turn, may lessen the capillary permeability alterations caused by high PIP ventilation.[85]

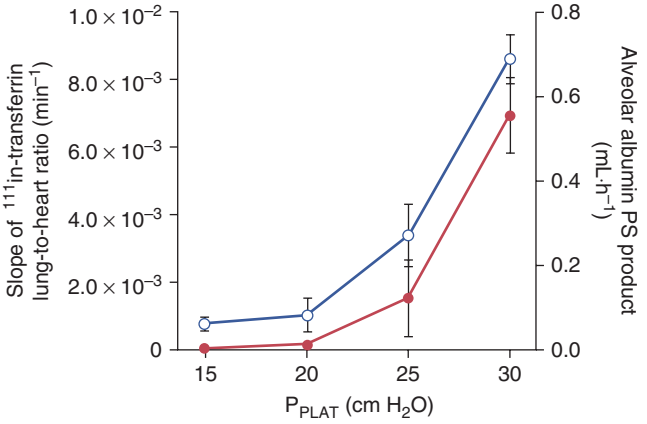

FIGURE 42-14 Relationship between plateau pressure (P_{PLAT}) and ^{111}In-transferrin lung-to-heart ratio slopes (*left axis, open circles*), reflecting lung-endothelial permeability, and alveolar ^{99m}Tc-albumin permeability-surface area product (*right axis, full circles*), reflecting lung-epithelial permeability. There is an increase in the permeability to proteins in both layers of the alveolo-capillary membrane above the same P_{PLAT} threshold, between 20 and 25 cm H_2O. (Used, with permission, from de Prost et al.[51])

This preservation of the alveolar–epithelial layer has received no satisfactory explanation. It may be that PEEP eliminated repetitive opening and closing of terminal airways, thereby decreasing shear stress and the development of surface-tension-induced epithelial cell damage at this level.[86] Alternatively, avoidance of alveolar flooding by PEEP[87,88] may have protected the epithelial lining from injury through the effects of yet unidentified humoral mediators.

One effect of PEEP is to reduce tidal volume for a given end-inspiratory pressure. It is interesting to note that studies using in situ perfused canine lobes[89] found that, for equivalent perfusion-flow rates and microvascular hydrostatic pressures, the rate of hydrostatic edema formation increased with tidal volume. When an identical increase in mean airway pressure was achieved either by applying PEEP or by increasing tidal volume, edema was less marked under the former condition, suggesting that large cyclic changes in lung volume promote the development of edema. This explanation was also put forward by Corbridge et al,[90] who

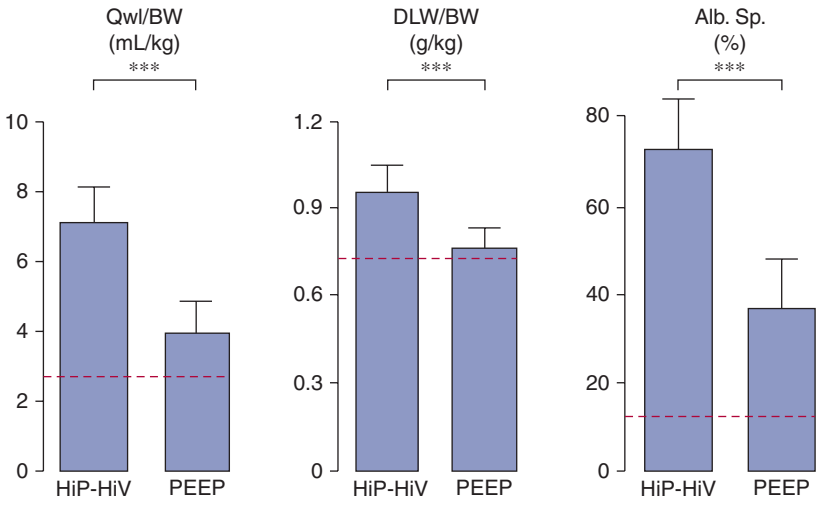

FIGURE 42-15 Effect of 10 cm H_2O PEEP during high peak (45 cm H_2O) positive inspiratory pressure plus high tidal-volume ventilation. *Dotted lines* represent the upper 95% confidence limits for control values. See Figure 42-6 for details on edema indexes. With PEEP, edema was less marked. ** = $p < 0.001$. (Used, with permission, from Dreyfuss et al.[36])

observed in hydrochloric acid-injured dog lungs that ventilation with a large tidal volume and a low PEEP resulted in more severe edema than did ventilation with a small tidal volume and a high PEEP. The effect of the amplitude of tidal volume on alveolar epithelium protein permeability was confirmed in rats using noninvasive scintigraphic techniques.[91] The alveolar albumin permeability-surface area product, measured from the clearance of an intratracheally instilled ^{99m}Tc-labeled albumin solution, dramatically increased, and in a dose-dependent manner, when V_T was increased from 8 to 24 and 29 mL/kg.[91]

Finally, the potential role of hemodynamic alterations during PEEP ventilation should also be considered. For instance, rats ventilated with 45 cm H_2O PIP and 10 cm H_2O PEEP had more edema when PEEP-induced hemodynamic alterations were corrected by dopamine administration (Fig. 42-16).[92] Moreover, arterial blood pressure was found to be significantly correlated with the amount of pulmonary edema under such conditions. The reason why use of PEEP during ventilation with high PIP is associated with reductions in both the amount of edema and the severity of cell damage may be a combination of hemodynamic alterations, shear stress reduction, and surfactant modifications. It should be borne in mind that this beneficial effect of PEEP during overinflation edema contrasts with the usual lack of reduction or even increase in edema reported with PEEP in most forms of experimental pulmonary edema.[93,94]

It would be inappropriate to conclude from the data summarized above that tidal volume, which governs opening and closing of terminal units, is the sole determinant of VILI. On the contrary, the overall degree of lung distension (i.e., teleinspiratory volume) is probably the crucial factor. Hence, rats ventilated with a tidal volume within the physiologic range at two levels of PEEP (10 and 15 cm H_2O) developed pulmonary edema only at the higher level of PEEP (Fig. 42-17).[92] Similarly, doubling tidal volume had no effect in animals ventilated with zero end-expiratory pressure, but resulted in pulmonary edema when 10 cm H_2O PEEP was used (Fig. 42-17).[92] Thus, the safety of small tidal volumes

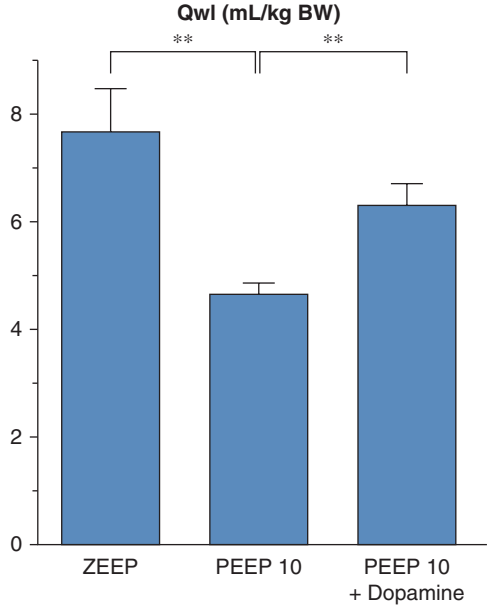

FIGURE 42-16 Effect of hemodynamic support with dopamine during 45 cm H_2O peak pressure ventilation with 10 cm H_2O PEEP on the amount of edema as evaluated by extravascular lung water. Compared with animals ventilated with 45 cm H_2O peak pressure and zero end-expiratory pressure (ZEEP), animals ventilated with 45 cm H_2O peak pressure ventilation with 10 cm H_2O PEEP had less edema. This reduction of edema associated with PEEP was partly abolished when dopamine was administered. ** = $p < .01$. (Adapted, with permission, from Dreyfuss and Saumon.[92])

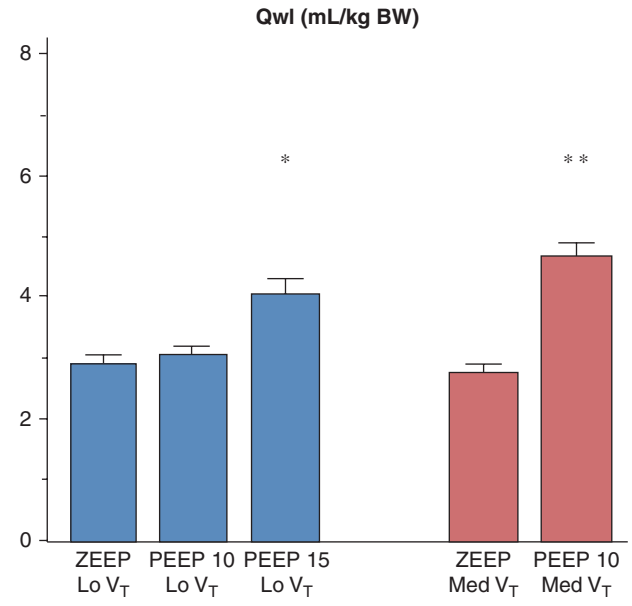

FIGURE 42-17 Effect of increasing PEEP from 0 to 15 cm H_2O during ventilation with two levels of tidal volume (V_T, 7 mL/kg of body weight [BW] = *Lo* V_T; 14 mL/kg BW = *Med* V_T). When PEEP was increased, pulmonary edema (as evaluated by extravascular lung water increases) occurred. The level of PEEP required to produce edema varied with tidal volume: 15 cm H_2O PEEP during ventilation with a low tidal volume versus 10 cm H_2O PEEP during ventilation with a moderately increased V_T. * = $p < .05$; ** = $p < .01$ versus zero end-expiratory pressure (*ZEEP*) and the same V_T. (Used, with permission, from Dreyfuss and Saumon.[92])

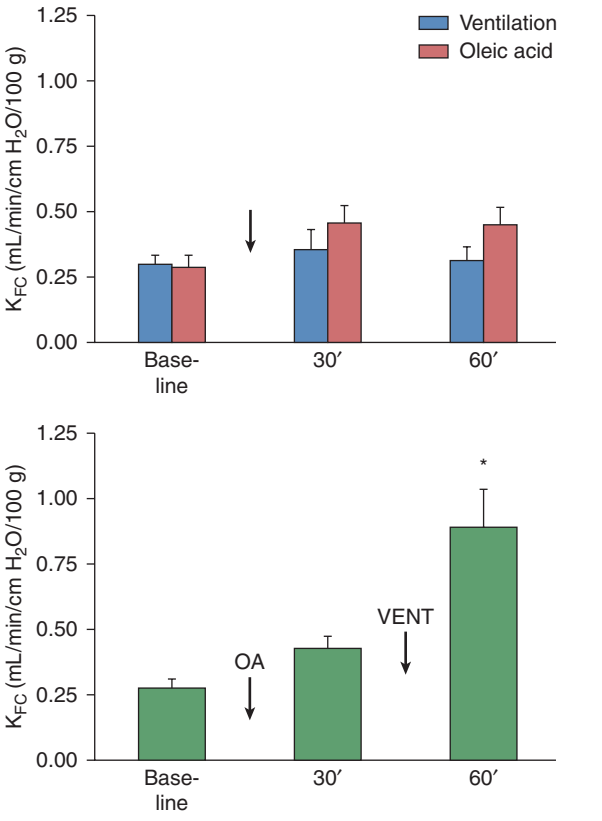

FIGURE 42-18 Effect of single and combined insults on the filtration coefficient of isolated rabbit lungs. A low dose of oleic acid (*OA*) or a moderately high peak pressure (24 cm H_2O) alone failed to induce K_{FC} (capillary filtration coefficient) changes, whereas the combination of both insults was responsible for a significant increase in K_{FC}. (Used, with permission, from Hernandez et al.[97])

depends on whether or not FRC is increased, and raising end-inspiratory volume by increasing FRC may cause lung injury independently of tidal volume.[92]

It is now clear that VILI occurs whenever a certain degree of lung overinflation is reached, by whatever means. For a given level of teleinspiratory pressure (and volume), adjunction of PEEP seems to slow the development or diminish the severity of alterations[95] but does not prevent the occurrence of permeability pulmonary edema.[36,92]

EFFECTS OF VENTILATION ON PREVIOUSLY INJURED LUNGS

This chapter does not consider the problems associated with lung prematurity, which is discussed in Chapter 23.

Combination of High-Volume–High-Pressure Ventilation and Previous Injury

ROLE OF LUNG MECHANICAL PROPERTIES ON SUSCEPTIBILITY TO VILI

The aforementioned studies were conducted on animals with healthy lungs. It is conceivable, however, that diseased lungs may be more susceptible than healthy lungs to the deleterious effects of mechanical ventilation. Diseased lungs with a patchy distribution of lesions may be subjected to considerably greater regional stress than homogeneously inflated lungs. As stressed by Mead et al, the pressure tending to expand an atelectatic region surrounded by a fully expanded lung is approximately 140 cm H_2O at a transpulmonary pressure of 30 cm H_2O.[96]

Hernandez et al[97] showed that whereas low doses of oleic acid or mechanical ventilation with PIP 25 cm H_2O did not affect filtration coefficient and wet-to-dry ratio, the combination of the two did (Fig. 42-18). The same group also reported that the filtration coefficient increase observed during high PIP (30 to 45 cm H_2O) ventilation of isolated perfused rabbit lungs was more marked following inactivation of surfactant by dioctyl succinate instillation.[98] Moreover, whereas light microscopic examination showed only mild abnormalities (minimal hemorrhage and vascular congestion) in the animals subjected to ventilation only or surfactant inactivation only, the combination of both injuries caused severe damage (extensive hemorrhage, pulmonary edema, and hyaline membranes). Thus, ventilator-induced lung edema seems to develop at lower airway pressures in

lungs with preexisting injury. Lung injury is usually inhomogeneous. The more compliant zones will thus receive the bulk of ventilation, which may favor their overinflation, a localized "baby lung effect." Analysis of the pressure–volume curve may help understand how preexisting lung injury may interact with ventilator-induced injury. Before examining this interaction, it is important to understand how lung mechanical properties are modified by lung injury.

The upper inflection point (UIP) often seen on the inspiratory pressure–volume curve of the respiratory system in patients with ARDS has been interpreted as reflecting the beginning of overinflation,[99,100] or the end of recruitment.[101,102] Whether ventilation, however, that results in pressure and/or volume excursions above the UIP is deleterious is unsettled. Better understanding of the UIP significance is required before it can be used to set tidal volume in patients. An experimental study examined the hypothesis that pulmonary edema development alters the pressure–volume curve of respiratory system mainly because of distal airway obstruction,[83] and this reduction in ventilatable lung volume (the baby lung effect) may not only decrease compliance[103,104] but also affects UIP position. When the distal airways of rats were obstructed by instilling a viscous liquid, the changes in the shape of the pressure–volume curve (gradual decrease in compliance, the volume at which UIP was seen and progressive increase in end-inspiratory pressure) were similar to the changes seen during the development of pulmonary edema. The higher the compliance and volume of the UIP, the lesser was the edema observed after high PIP ventilation (Fig. 42-19). Taken together, these results suggest that the position of the UIP is a marker of the amount of ventilatable lung volume, and it is both influenced by, and predictive of, the development of edema during mechanical ventilation.

The effect of high PIP ventilation on injured lungs in intact animals was investigated by comparing different degrees of lung distension in rats whose lungs had been injured by α-naphthylthiourea (ANTU).[105] ANTU infusion alone caused moderate interstitial pulmonary edema of the permeability type. Mechanical ventilation resulted in a permeability edema, the severity of which depended on the tidal-volume amplitude. It was possible to calculate the extent that mechanical ventilation theoretically injures lungs diseased by ANTU by adding the separate effect of mechanical ventilation alone or ANTU alone on edema severity (Fig. 42-20). The lungs of the animals injured by ANTU ventilated at high PIP (45 mL/kg body weight [BW]) had more severe permeability edema than predicted (Fig. 42-20), indicating synergy between the two insults. Even minor alterations, such as those produced by spontaneous ventilation during prolonged anesthesia (which degrades surfactant activity and promotes focal atelectasis), were sufficient to synergistically increase the harmful effects of high-volume ventilation.[105] The extent to which lung mechanical properties deteriorate before ventilation is a key factor in this synergy. The amount of pulmonary edema produced by high-volume ventilation in animals given ANTU, or that had undergone prolonged

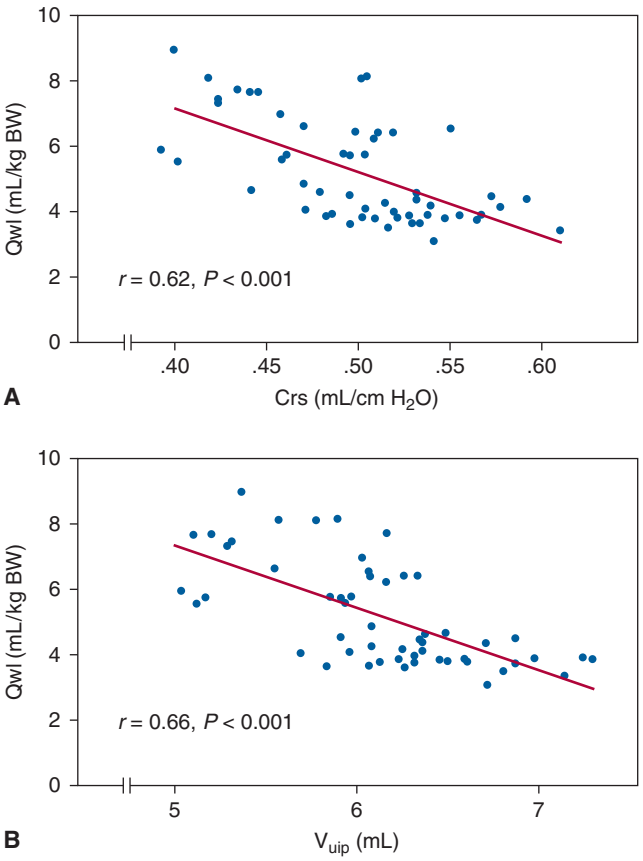

FIGURE 42-19 **A.** Correlation between the amount of edema (extravascular lung water, *Qwl*) produced by high-volume ventilation and the respiratory system compliance (*Crs*) measured before high-volume ventilation. **B.** Correlation between *Qwl* and the volume at the upper inflection point on the pressure–volume curve (V_{uip}) measured before high-volume ventilation. (Used, with permission, from Martin-Lefèvre et al.[83])

anesthesia, was inversely proportional to the respiratory system compliance measured at the very beginning of mechanical ventilation.[83,105] The same conclusions were reached about the volume of UIP.[83]

The reason for this synergy requires clarification. Local alveolar flooding in animals subjected to the most harmful ventilation protocol was the most striking difference from animals ventilated with lower, less harmful, tidal volumes.[105] It is conceivable that edema foam in airways reduced the number of alveoli that received the tidal volume, exposing them to overinflation and rendering them more susceptible to injury, further reducing the aerated lung volume. The result is a positive feedback loop. To explore this possibility, alveolar flooding was produced by instilling saline into the trachea of rats that were immediately ventilated with tidal volumes of up to 33 mL/kg.[106] Flooding with saline did not significantly affect microvascular permeability when tidal volume was low. As tidal volume was increased, capillary permeability alterations were larger in flooded than in intact animals, reflecting further impairment of their endothelial

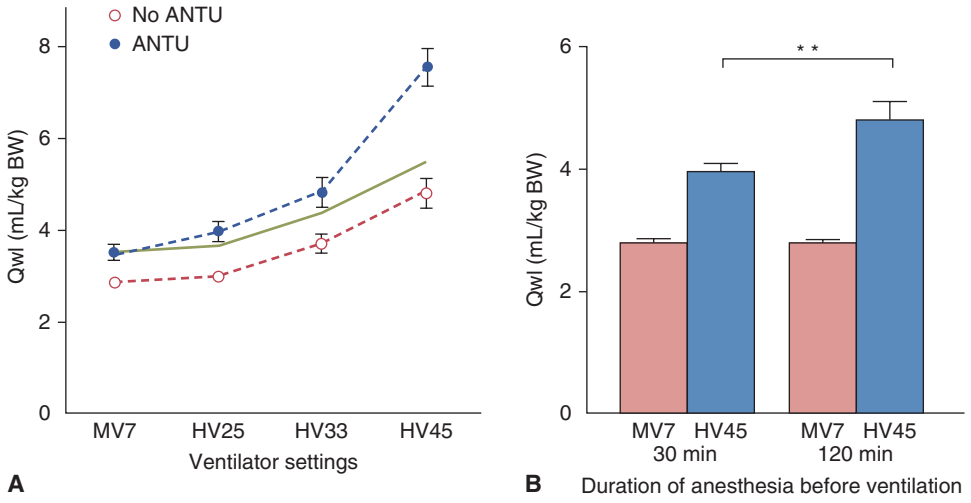

FIGURE 42-20 Interaction between previous lung alterations and mechanical ventilation on pulmonary edema. **A.** Effect of previous toxic lung injury. Extravascular lung water (*Qwl*) after mechanical ventilation in normal rats (*open circles*) and in rats with mild lung injury produced by α-naphthylthiourea (*ANTU*) (*closed circles*). Tidal volume (V_T) varied from 7 to 45 mL/kg BW. The *solid line* represents the Qwl value expected for the aggravating effect of ANTU on edema caused by ventilation, assuming additivity. ANTU did not potentiate the effect of ventilation with V_T up to 33 mL/kg BW. In contrast, V_T 45 mL/kg BW produced an increase in edema that greatly exceeded additivity, indicating synergy between the two insults. **B.** Effect of lung functional alteration by prolonged anesthesia. Intact rats were anesthetized and breathed spontaneously for 30 to 120 minutes before ventilation with V_T 7 mL/kg BW (*pink open bars*) or 45 mL/kg BW (*blue shaded bars*). Qwl of animals ventilated with a high V_T was significantly higher than in animals ventilated with a normal V_T. Qwl was not affected by the duration of anesthesia in animals ventilated with a normal V_T. In contrast, 120 minutes of anesthesia before high V_T ventilation resulted in a larger increase in Qwl than did 30 minutes of anesthesia. ** = $p < 0.01$. (Used, with permission, from Dreyfuss et al.[105])

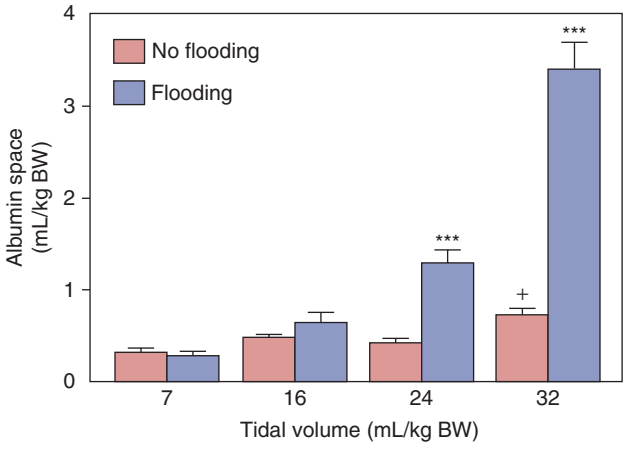

FIGURE 42-21 Effect of increasing tidal volume (V_T) during mechanical ventilation for 10 minutes on lung capillary permeability (i.e., extravascular albumin distribution space in lungs) of rats with intact lungs (*pink open bars*) or with alveolar flooding (*purple closed bars*) produced by saline instillation. There was a moderate increase in albumin space in intact rats at the larger V_T. Lung flooding did not produce significant increases of albumin space when V_T was normal or moderately increased. Albumin space was significantly increased with a V_T of 24 and 32 mL/kg BW. The increase in albumin space greatly exceeded additivity, indicating a positive interaction between the two insults. *** = $p < 0.001$ as compared with intact animals. + = $p < 0.05$, as compared to animals of the "no flooding" group ventilated with V_T 7 mL/kg. (Used, with permission, from Dreyfuss et al.[106])

barrier (Fig. 42-21). There was also a correlation between end-inspiratory airway pressure and capillary permeability alterations in flooded animals ventilated with a high tidal volume. Thus, the less compliant and recruitable the lung was after saline flooding, the more severe were the changes in permeability caused by lung distension.

These studies support the conclusion that the risk of overinflation is more important in diseased than in healthy lungs. Strategies to prevent VILI should oppose the synergy between ventilation and previous lung injury.

Does Ventilation without Overinflation Aggravate Previous Lung Injury?

EFFECT OF POSITIVE END-EXPIRATORY PRESSURE

It has been suggested that mechanical ventilation may worsen lung injury because of increased shear stress in distal airspaces secondary to their repeated closing, either because of obstruction by liquid menisci or collapse and reopening. Coker et al[98] reported that the capillary filtration coefficient of isolated perfused rabbit lungs was not modified by either ventilation at 15 cm H_2O PIP (which results in much larger tidal volumes in isolated lungs than in intact animals) or surfactant inactivation, but doubled the coefficient when the two insults were combined. Several studies have investigated the effects of conventional ventilation on acutely

injured lungs by using sufficiently high PEEP levels to keep the small airways open throughout the entire ventilatory cycle, thereby avoiding repeated closure and reopening.

Sykes et al[107,108] studied the effect of ventilation in rabbits with surfactant-depleted lungs. The animals were ventilated with a PIP ranging from 15 mm Hg at the beginning of the experiment to 25 mm Hg at the end (5 hours later) because of the fall in lung compliance (tidal volume was not stated); PEEP adjusted to position the FRC either above or below the lower inflection point (LIP). Mortality rate was not influenced by PEEP level, although arterial oxygen tension (Pa_{O2}) was better-preserved in the high-PEEP group.[107,108] There was less hyaline membrane formation in animals ventilated with a high PEEP than in those ventilated with low PEEP. This lessening of pathologic alterations was observed even with ventilator settings that achieved identical mean airway pressures in the low and high PEEP groups.[108] Comparable results were reported in isolated, nonperfused, lavaged rabbit lungs ventilated with a low tidal volume and with a PEEP level set either below or above the LIP.[109] The same findings could not be replicated in hydrochloric acid-injured rabbit lungs using similar ventilator settings.[110] Thus, it is conceivable that the protective effect of PEEP, when set above the LIP of the pressure–volume curve, is observed only in the very special setting of surfactant deficiency and not during severe alveolar edema, because lung instability and airspace collapse is observed only during the former.

Using in vivo videomicroscopy, Nieman et al[111–115] directly observed and quantified the dynamic changes in alveolar size throughout the ventilatory cycle during tidal ventilation, in normal lungs and in lungs in which surfactant had been deactivated by generic. Injuries occurred independently of the presence of neutrophils.[111] In normal lungs, alveoli never collapsed. These findings agree with the previous findings of Bachofen and Wilson, who showed that alveoli do not change volume appreciably during ventilation.[116] Collapse and reopening and increase in the alveolar size at end-inspiration were observed in surfactant-deactivated lungs. In a subsequent study, the same authors documented the effect of increasing end-expiratory pressure.[115] The application of PEEP to a surfactant-deactivated lung reversed the observed increase in alveolar size, returning it to control levels.

The reality of the repetitive opening and closure of terminal units and the significance of the LIP on the pressure–volume curve have been challenged by Martynowicz et al,[117] who studied the regional expansion of oleic acid-injured lungs using a parenchymal marker technique. The gravitational distribution of volume at FRC was not affected by oleic acid injury, and the injury was not associated with decreased parenchymal volume of dependent regions. In addition, temporal inhomogeneity of regional tidal expansion did not increase with oleic acid injury. These findings do not support the hypothesis that a superimposed gravitational pressure gradient during VILI produces compression atelectasis of dependent lung, which in turn produces shear injury from cyclic recruitment and collapse.[117] The authors propose that the occurrence of a LIP on the pressure–volume curve represents the transition from the liquid-filled state to the air-filled state, when the lung is initially filled with a liquid with constant surface tension properties.[118] Thus, abrupt expansion of distal lung units is unlikely to occur at the LIP.

The protective effect of PEEP, however, is not restricted to the particular setting of surfactant depletion.[2,3,95] Distal airspace damage during tidal ventilation may occur because of repeated airway opening and closing secondary to the movement of foam with increased surface tension[86] or the rupture of liquid menisci. PEEP may prevent diffuse lung damage during prolonged ventilation by stabilizing these units.[119] The beneficial effect of PEEP, however, is variable in different models of lung injury.[120] The difficulty in proving whether or not PEEP exerts a protective effect on VILI may be explained by taking into account the distinction between atelectatic and fluid-filled distal airways when interpreting LIP. In the case of diffuse filling of distal airways with liquid, VILI may be caused by overdistension of already aerated zones rather than by shear stress secondary to opening of collapsed zones.[121] With this scenario, it would be difficult to expect any reduction of injury by PEEP.

This uncertainty about the actual occurrence of injury at low lung volumes contrasts with the unambiguous demonstration of high-volume (overdistension) injury. This uncertainty has a clinical counterpart that is discussed in "Clinical Relevance" below.

EFFECT ON REMOTE ORGANS AND NORMAL LUNG REGIONS

As further discussed in "Pharmacologic Interventions" below, neutrophilic infiltration and increased levels of proinflammatory cytokines have been found in the lungs of animals that were subjected to long-lasting injurious ventilation.[73,76] These observations led to the hypothesis that mechanical ventilation might promote or aggravate a systemic inflammatory state.[122] In addition to increasing the amount of cytokines in the lung, it has been suspected that overinflation may promote the release of cytokines[123,124] or bacteria[125–127] into the blood, thus suggesting that mechanical ventilation plays a causative role in multiorgan dysfunction.[122,128] Higher levels of proinflammatory cytokines (tumor necrosis factor [TNF]-α, interleukin [IL]-1β and macrophage inflammatory protein [MIP]-2) were found in lung homogenates of rats ventilated for 2 hours with high PIP when they were previously subjected to mesenteric ischemia–reperfusion[129] or hemorrhagic shock and resuscitation[130] (Fig. 42-22). This suggests the validity of the "two-hit" hypothesis, that a preexisting inflammatory state augments cytokine release during VILI.

A few experimental studies have evaluated the consequences of injurious ventilation on peripheral organs. Choi et al[131] found that rats ventilated with high PIP for 2 hours had increased endothelial nitric oxide synthase expression in lung and kidney tissue and increased microvascular permeability in both organs. Nitric oxide was probably involved in these abnormalities, because *N*-nitro-L-arginine

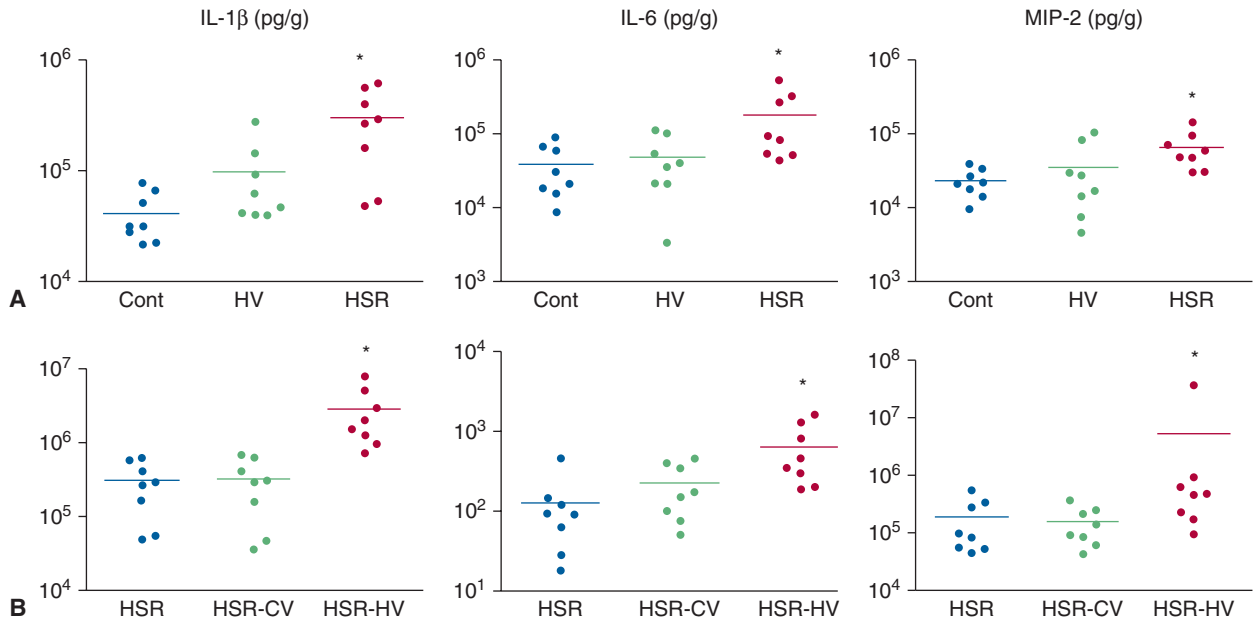

FIGURE 42-22 **A.** Comparison of lung cytokine levels in nonventilated rats (controls [*Cont*]) and in rats subjected to an injurious mechanical ventilation strategy (30 mL/kg tidal volume and zero end-expiratory pressure) alone (*HV*) or to hemorrhagic shock-reperfusion injury alone (*HSR*). Compared with controls, lung cytokine concentrations were higher after HSR but not after HV. **B.** Comparison of lung cytokine levels in rats subjected to HSR alone, HSR combined with conventional ventilation (*HSR-CV*) and HSR followed by HV (*HSR-HV*). Injurious ventilation (HV) after HSR significantly increased mediator release above the levels observed after HSR alone or in combination with conventional ventilation. Results are expressed in pg/g. * = $p < 0.05$ as compared to controls (*A*) or to HSR (*B*). The same observations were made in bronchoalveolar lavage fluid and in plasma. (Adapted, with permission, from Bouadma et al.[130])

methyl ester administration attenuated the microvascular leak of lung and kidney. An increase in gut permeability was also observed during a similarly long-lasting ventilation, albeit with larger tidal volume (30 instead of 20 mL/kg), which was attenuated by anti–TNF-α antibody administration.[132] Injurious ventilation of rabbits with hydrochloric acid-induced lung injury resulted in increased rates of epithelial cell apoptosis in the kidney and small intestine villi.[133]

There is also growing evidence that ventilator settings may localize or disperse proteinaceous lung edema or bacteria. In a model of unilateral *Pseudomonas aeruginosa* pneumonia in rats, Schortgen et al showed that high-volume ventilation with no PEEP promoted contralateral bacterial seeding.[127] Interestingly, ventilation at the same end-inspiratory pressure but with high PEEP, and thus a lower V_T, prevented contralateral lung dissemination. To better understand these observations, the potential effect of adverse ventilator patterns on the dispersal of localized radiolabeled alveolar edema to the opposite lung was studied.[91] A ^{99m}Tc-labeled albumin solution was instilled into the distal airways and it produced a zone of alveolar flooding that remained localized during conventional ventilation. High end-inspiratory pressure ventilation dispersed alveolar liquid in the lungs. This dispersion was prevented by PEEP even when V_T was the same and thus end-inspiratory pressure even higher (Fig. 42-23). Interestingly, contralateral liquid dispersion began almost immediately after high-volume ventilation was started, suggesting that this dispersion might be the consequence of a convective movement induced by the ventilation. High-inspiratory and high-expiratory flows favored fluid transport back and forth toward the alveoli and the airways. In the heterogeneous lung, fluid transfer may be propelled toward regions of normal compliance. PEEP may have prevented dispersion by avoiding lung collapse and stabilizing edema fluid in the distal airways. The clinical relevance of the movement of such noxious biofluids in the airways has been discussed elsewhere.[134]

PROTECTION FROM VENTILATION-INDUCED LUNG INJURY

Strategies That Aim at Improving Lung Mechanics

USE OF PRESSURE–VOLUME CURVES

Taking the presence and value of a LIP on the pressure–volume curve into account when setting the level of PEEP may lessen VILI in some,[107–109] but not all, instances.[110] The concept on lung protection against VILI with the setting of a PEEP above the LIP, however, relies on a putative stabilizing effect of PEEP that would abolish the tendency of distal airways to collapse at end-expiration and reopen during the next inspiration. As discussed above, serious criticisms have been raised against this opening-and-closing theory,[121]

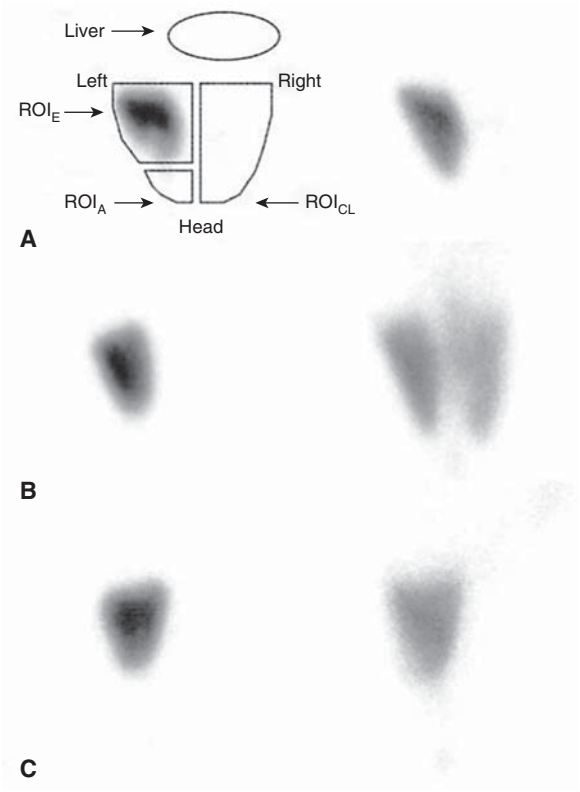

FIGURE 42-23 Scintigraphy images integrated over 15 minutes after instillation (t0 to t15; *left panels*) and the last 15 minutes of the experiment (t195 to t210; *right panels*). Regions of interest (*ROIs*) were drawn around initial focus of edema (ROI_E), the apex of the same lung (ROI_A), the contralateral lung (ROI_{CL}), and over the thorax. At baseline (*left panels*), all animals were ventilated with tidal volume 8 mL/kg and PEEP 2 cm H_2O and exhibited focalized localization of the tracer in the left lung. When the same ventilator settings were maintained during the experiment (**A**), the tracer remained remarkably confined in the initial zone; there was no contralateral and only slight homolateral dissemination. High-volume ventilation (pressure plateau [P_{PLAT}] = 30 cm H_2O) with no PEEP (**B**) induced strong homolateral and contralateral dispersion of the tracer and systemic leakage as attested by the decrease in overall activity. High-volume ventilation with 6 cm H_2O PEEP (**C**) induced systemic, but not contralateral, dissemination of the tracer. (Used, with permission, from de Prost et al.[91])

casting doubt on the usefulness of measuring LIP in order to prevent VILI.

The overall degree of lung distension resulting from the settings of both PEEP and tidal volume is a fundamental determinant of VILI. Although the exact physiologic significance of UIP is debated, it may indicate lung overstretching. Ventilation that takes place above UIP was found to be markedly deleterious (see Fig. 42-19).[83] Thus, determination of the volume at which the UIP is observed may help reduce the risk of VILI, because it indicates the maximum stretch that the lung can sustain without noticeable damage.[83] Analysis of the airway pressure–time curve during mechanical ventilation with constant flow has also proven useful in determining the stress applied to lungs. Indeed, an upward concavity of the pressure–time curve suggests that compliance decreases as tidal volume is delivered, with resulting high-volume stress.[135] Such a ventilation pattern was associated with histologic lung injury in an isolated, nonperfused, lavage model of acute lung injury[135] and with overdistension, as attested by computed tomography scan analysis, of the lungs of intact animals with saline lavage-induced lung injury.[136]

SURFACTANT

Numerous studies have been conducted on the effect of surfactant administration on gas exchange in experimental models of lung injury. In contrast, few experimental studies have specifically addressed the effect of surfactant administration during VILI. Verbrugge et al studied the effect of surfactant administration on lung function and alveolar permeability during 45 cm H_2O PIP ventilation in rats.[137] Alveolar permeability was significantly reduced in animals receiving 200 mg/kg of surfactant.[137] Exogenous surfactant prevented high-volume (20 mL/kg) lung injury in isolated rat lungs, but it did not affect the release of inflammatory cytokines by these lungs during ventilation.[138] In rats receiving lipopolysaccharide by tracheal instillation, however, surfactant pretreatment reduced decompartmentalization of TNF-α from the lungs to the systemic circulation during injurious mechanical ventilation.[139]

PERFLUOROCARBONS

Partial liquid ventilation[140] with perfluorocarbons was developed during the last decade as an alternative to conventional gas ventilation for the treatment of acute respiratory failure. Several investigators using different models of acute respiratory failure (surfactant depletion, oleic acid, hydrochloric acid, prematurity) have reported improvement in gas exchange, lung mechanics, and lung histology.[141] Although some investigators have shown a dose-dependent improvement in gas exchange with perflubron (LiquiVent) in a rabbit model of surfactant depletion,[142] others have highlighted the risk of barotrauma (namely pneumothorax) with the use of large volumes of perfluorocarbon combined with high PEEP or increased tidal volume.[143] Until recently, the effect of partial liquid ventilation on VILI has received little attention. Mechanical nonuniformity of diseased lungs may predispose lungs to VILI by overinflation of the more compliant (ventilatable), aerated zones.[105] Perfluorocarbon may reduce this nonuniformity by suppressing air–liquid interfaces and allowing reopening of collapsed or liquid-filled areas.

The effect of perfluorocarbon instillation on hyperinflation-induced lung injury during alveolar flooding was investigated in rats.[106] Saline was instilled into the trachea to mimic alveolar edema and reduce aerated lung volume. Alveolar flooding significantly aggravated VILI, as attested by an increase in capillary permeability alterations. Tracheal instillation of a low dose (3.3 mL/kg) of perflubron in these flooded lungs considerably reduced VILI and decreased permeability alterations (Fig. 42-24). Whereas instillation of saline alone raised LIP pressure to values as

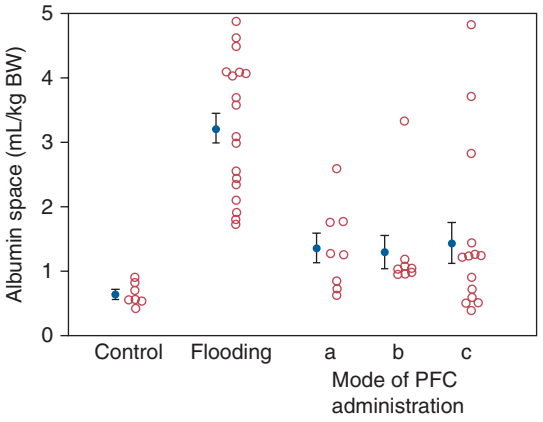

FIGURE 42-24 Effect of perflubron (LiquiVent) instillation on permeability pulmonary edema as assessed by the extravascular albumin distribution space in the lungs of rats ventilated with a tidal volume of 33 mL/kg BW. Flooding significantly increased albumin space ($p < 0.001$). Perflubron given as a bolus (*a*), by slow infusion before flooding (*b*), or as a bolus dose after flooding (*c*) resulted in a significant decrease in albumin space, the values of which remained higher than in controls ($p < 0.05$). *Closed circles with error bar* indicate means ± standard error of mean (SEM). *PFC*, perfluorocarbon. (Used, with permission, from Dreyfuss et al.[106])

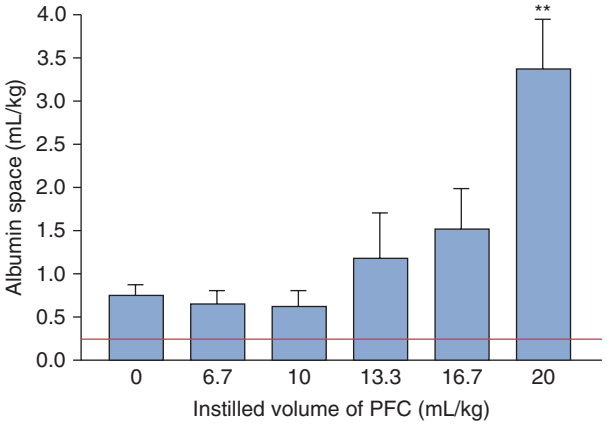

FIGURE 42-25 Dose–response effect of perflubron instillation on microvascular permeability assessed by the distribution space of albumin in the lung. Rats were ventilated with a tidal volume of 33 mL/kg BW. The albumin space value of control rats ventilated with a tidal volume of 7 mL/kg BW is represented by the *horizontal line*. Albumin space was three times higher after high-volume ventilation, in the absence of perflubron instillation. Lung injury was not aggravated by the instillation of 6.7 and 10 mL/kg perflubron, tended to increase with doses of 13.3 and 16.7 mL/kg, and increased significantly with 20 mL/kg perflubron. ** = $p < 0.01$; *PFC*, perfluorocarbon. (Used, with permission, from Ricard et al.[144])

high as 25 cm H_2O, and produced a significant increase in the end-inspiratory pressure, administration of perflubron significantly reduced LIP pressure and normalized end-inspiratory pressure.

To further investigate the effect of partial liquid ventilation on VILI with respect to the dosage of perfluorocarbon, intact animals ventilated with a high tidal volume (33 mL/kg BW) received increasing doses of perflubron (from 6 to 20 mL/kg).[144] Hyperinflation-induced pulmonary edema tended to decrease with doses of perflubron lower than 10 mL/kg as compared with animals not given perflubron. By contrast, ventilator-induced pulmonary edema was aggravated in animals given 13 and 16 mL/kg, and even more in animals given 20 mL/kg perflubron (Fig. 42-25). Large doses worsened volutrauma because they increased FRC, thus increasing end-inspiratory volume for the same tidal volume, and because they favored gas trapping in the distal lung, as demonstrated by computed tomography imaging.[144] Consistently, in rats with preinjured lungs (after ANTU administration) and subjected to ventilation with a high tidal volume (33 mL/kg BW), low and moderate doses of perflubron, but not larger doses (approximately 20 mL/kg), improved respiratory mechanics and ventilator-induced permeability alterations (Fig. 42-26).[145] These observations suggest that monitoring of end-inspiratory pressure might help detect the risk of volutrauma during partial liquid ventilation.

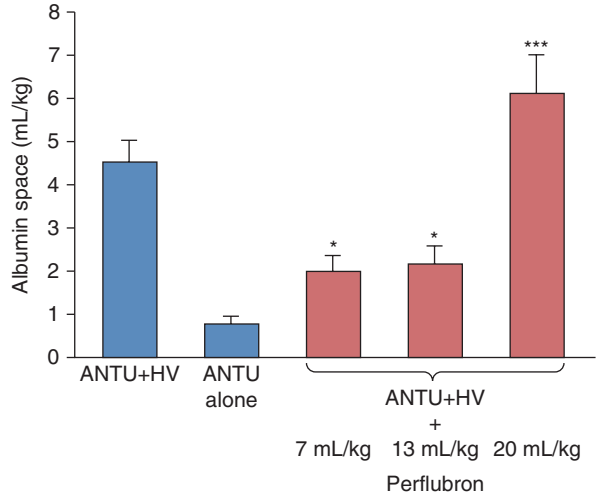

FIGURE 42-26 Dose–response effect of perflubron instillation on microvascular permeability assessed by the distribution space of albumin in lungs injured either by α-naphthylthiourea (*ANTU*) alone or combined with high tidal-volume ventilation (tidal volume 33 mL/kg BW; *ANTU+HV*). ANTU alone produced a mild permeability defect, which was considerably increased when combined with HV. This dramatic change in microvascular permeability was significantly reduced by doses of 7 and 13 mL/kg perflubron (* = $p < 0.05$). In contrast, animals that received 20 mL/kg perflubron had a further significant increase in microvascular permeability, as compared with animals that received ANTU+HV without perflubron instillation (*** = $p < 0.001$). (Used, with permission, from Ricard et al.[145])

PRONE POSITION

Prone position lessened the deleterious effect of high PIP ventilation with PEEP in dogs with previous oleic acid lung

injury;[146] similar benefit was shown in rabbits[147] and rats.[148] Prone position resulted in a more homogenous distribution of lung injury,[149] an observation that was not confirmed in other studies in rabbits or rats. These differences are probably a result of difference in lung size, with a larger lung increasing the influence of gravity. Indeed, computed tomography scans in rats did not disclose a gradient of lung inflation at end-expiration as in humans.[148] In rats, the beneficial effect of prone position was ascribed to a more homogenous distribution of tidal volume and thus of strain, because of the downward displacement of the diaphragm.[148] In a rat model of paraquat-induced acute lung injury, the prone position was consistently associated with a more homogeneous lung expression of type III procollagen than observed in the supine position.[150]

NOISY VENTILATION

Spontaneously breathing subjects show an intrinsic variability in tidal volume and respiratory frequency during normal ventilation.[151] It has been theorized that the respiratory system may work as a stochastic resonance system where the variability of input parameters leads to an increase in the surface area for gas exchange in the lungs, thus improving lung function.[152] In a model of endotoxin-induced acute lung injury in guinea pigs, variability of tidal volumes of some 10% to 60% above and below the mean combined with a respiratory frequency that kept minute ventilation constant significantly decreased lung elastance and improved oxygenation as compared to conventional ventilation.[153] After oleic acid-induced lung injury, pigs ventilated with a comparable strategy exhibited lower concentrations of IL-8 in tracheal aspirates than did pigs ventilated with a conventional strategy.[154] Recently, Spieth et al[155] studied the effects of variability of tidal volume (within 40% of mean) in a surfactant-depletion model of acute lung injury in pigs. Animals were ventilated with two different strategies for setting PEEP: the ARDS Network protocol and an open-lung approach where PEEP was set according to the minimal elastance of the respiratory system. Adding noisy ventilation to these settings not only improved oxygenation, but also decreased histologic damage.[155] Depending on the strategy with which it was combined, noisy ventilation likely improved VILI by distinct mechanisms. When combined with the ARDS Network protocol, noisy ventilation stabilized distal lung units and likely reduced their repetitive opening and closing. When combined with an open-lung approach, noisy ventilation generated lower peak airway pressures, thereby limiting the overdistension of nondependent lung regions. Further experimental studies are required to determine whether similar results would be obtained in less recruitable models of acute lung injury and after longer periods of mechanical ventilation.

Pharmacologic Interventions

The following observations show that a tremendous number of cell-signaling pathways are involved in the pathophysiology of VILI. Although it is probably illusory to believe that a single pharmacologic intervention might be beneficial in patients, the description of those pathways illustrates the complexity of the cellular mechanisms involved in VILI.[78]

MODULATION OF MICROVASCULAR PERMEABILITY

Blocking stretch-activated cation channels[52] and inhibiting phosphotyrosine kinase,[54] phosphodiesterase,[54] and calcium-dependent phospholipase A_2[71] reduced the pulmonary capillary permeability alterations caused by high PIP ventilation. Reducing myosin light-chain phosphorylation with adrenomedullin, an endogenous peptide belonging to the calcitonin gene-related peptide family, decreased lung vascular permeability and the accumulation of neutrophils in the lungs of mice subjected to high PIP ventilation.[156] These inhibitions suggest that stretch-induced calcium entry in lung cells and intracellular calcium signaling play an important role in the early response to high PIP ventilation. Indeed, the phosphorylation of myosin light chains by Ca^{2+}/calmodulin-dependent myosin light chain kinase leads to endothelial cell contraction, a key mechanism of VILI-induced endothelial barrier dysfunction.[157] Intravenous delivery of a myosin light-chain kinase inhibitor in a mouse model of VILI reduced lung microvascular permeability and neutrophilic infiltration.[158]

β-adrenergic agonist infusion reduced accumulation of plasma protein in the lungs of patient who survived an episode of ARDS,[159] suggesting that it might have lessened their microvascular permeability alterations. In a model of high PIP ventilation in rats, terbutaline administered intratracheally lessened both the increase in lung epithelial and endothelial permeability caused by VILI, whereas terbutaline administered intraperitoneally lessened only lung endothelial permeability (Fig. 42-27).[160] These results help

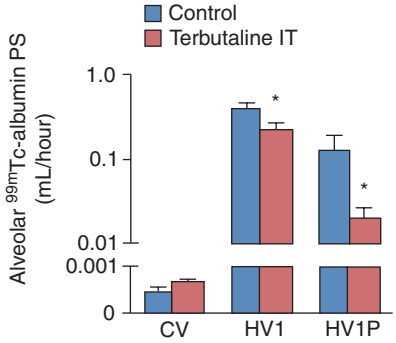

FIGURE 42-27 Alveolar ^{99m}Tc-albumin permeability surface-area product (*PS*), reflecting lung-epithelial permeability. PS was dramatically increased during high-volume ventilation using 30 cm H_2O PIP (*HV1*), as compared to conventional ventilation (*CV*). This effect was present even when positive end-expiratory pressure was applied (*HV1P*) and was decreased when terbutaline was administered intratracheally (*IT*). * = $p < 0.05$ when compared with the same ventilation modality. (Adapted, with permission, from de Prost et al.[160])

us understand the disappointing results of a trial that compared the intravenous administration of β-adrenergic agonists versus placebo in patients with ARDS.[161] In that study, gas exchanges and lung injury score remained unchanged despite a decrease in extravascular lung water, as measured by thermodilution. The findings suggest that airway delivery might be more efficient in preventing the increase in alveolocapillary barrier permeability during mechanical ventilation.

Inhibition of nitric oxide synthase[131,162] lessened ventilator-induced capillary permeability abnormalities. Inhibition of the endothelial isoform mitigated VILI via a decrease in the production of superoxide.[163] Recently, phosphoinositide 3-kinase-γ of resident lung cells was consistently shown to mediate alveolar edema induced by high-stress ventilation in part through an increase in nitric oxide production by endothelial cells.[164] Surprisingly, transgenic mice that overexpressed endothelial nitric oxide synthase exhibited less lung damage, lung water content, and neutrophil infiltration as compared to wild-type mice, suggesting that this isoform might also be protective from VILI in different conditions.[165] These discrepant results suggest that the mechanisms of VILI are equivocal and that more work is needed to determine the involvement of the nitric oxide pathway despite the fact that the ultrastructural abnormalities observed after high-volume ventilation[3] resemble those seen during increased endothelial nitric oxide production.[166]

MODULATION OF INFLAMMATION

Tremblay et al[76] examined the effects of different ventilator strategies on the level of several cytokines in bronchoalveolar lavage fluid of ex vivo, unperfused rat lungs ventilated with different end-expiratory pressures and tidal volumes. High tidal volume ventilation (40 mL/kg BW) with zero end-expiratory pressure resulted in the release of considerable amounts of TNF-α, IL-1β, IL-6, and MIP-2, a potent neutrophil chemoattractant and the rodent functional homolog of human IL-8 (Fig. 42-28). These results have not, however, been replicated by other groups using either the same ex vivo lung model.[78,167] In vivo studies of intact animals showed that high-volume mechanical ventilation, which produces a very severe pulmonary edema, does not induce lung release of TNF-α in rats.[167,168] Similarly, TNF-α release was not found in mice ventilated with a high PIP in vivo, although it was found in the perfusate of isolated lungs from the same strain.[30] Studies on TNF-α messenger RNA (mRNA) also yielded conflicting results. Takata et al[169] showed large increases in TNF-α mRNA in the intraalveolar

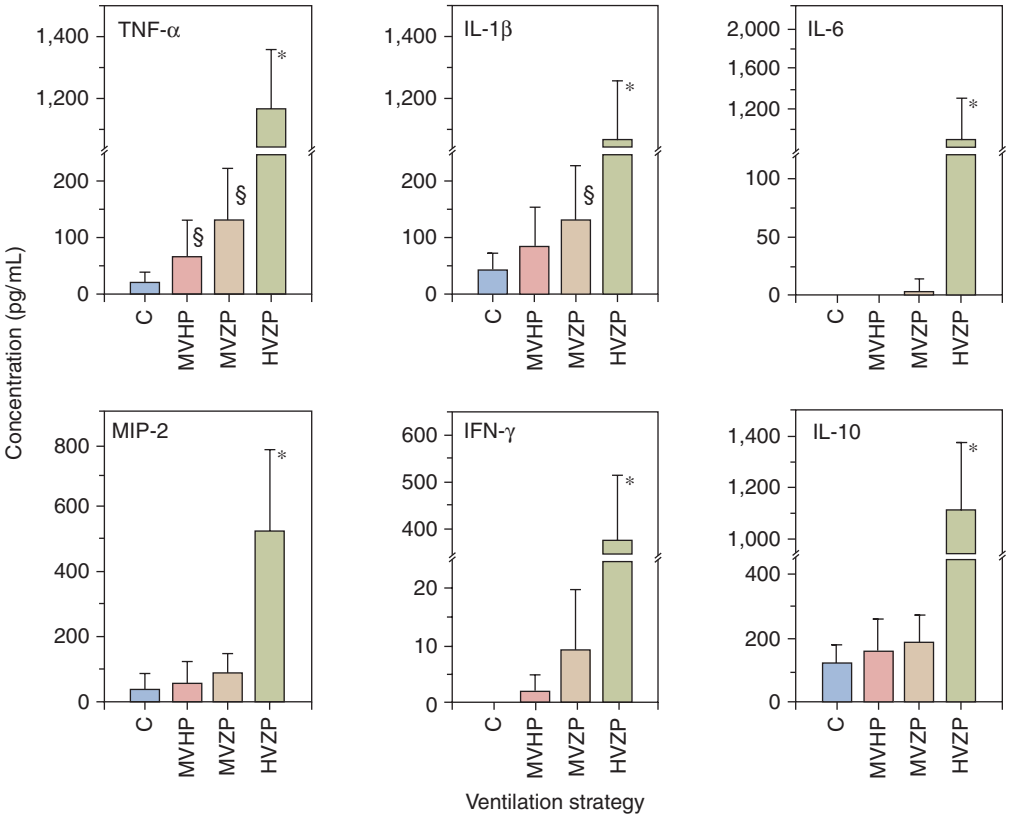

FIGURE 42-28 Effect of different ventilator strategies on cytokine concentrations in lung lavage of isolated unperfused rat lungs. Four ventilator settings were used: controls (*C* = normal tidal volume), moderate tidal volume + high PEEP (*MVHP*), moderate tidal volume + zero PEEP (*MVZP*), high tidal volume + zero PEEP (*HVZP*) resulting in the same end-inspiratory distension as MVHP. Major increases in cytokine concentrations were observed with HVZP. * = $p < 0.05$ vs all other groups; § = $p < 0.05$ vs controls. (Used, with permission, from Tremblay et al.[76])

cells of surfactant-depleted rabbits after 1 hour of conventional mechanical ventilation with peak inspiratory and end-expiratory pressures of 28 and 5 cm H_2O. Conversely, Imanaka et al found no increase in lung tissue TNF-α mRNA of rats ventilated with 45 cm H_2O PIP.[170] Administration of an anti–TNF-α antibody via the trachea, but not via the systemic circulation, lessened inflammation in lungs of mice subjected to high PIP ventilation.[132,171,172] Mice with knockout of the TNF receptor had less lung inflammation, but no less release of CXC chemokines, in bronchoalveolar lavage fluid.[30]

The only mediator that was consistently released by lungs subjected to high-volume ventilation[30,76,123,167,173] or in vitro in stretched lung cells, such as human alveolar macrophages[174] or cell lines such as A549 epithelial cells,[175] was the chemokine IL-8 or its rodent equivalent MIP-2. The release of MIP-2 may explain the recruitment of neutrophils that occurs during subacute VILI.[73,176,177] Leukocyte sequestration during injurious ventilation strategies seems to be the result of polymorphonuclear stiffening and mediated by L-selectin–dependent but CD18 (β_2-integrin)-independent mechanisms.[178] Belperio et al[173] showed that inhibition of the chemokine interaction with the CXCR2 receptor attenuates neutrophil sequestration and lung injury after 6 hours of high-volume ventilation in mice. Whether neutrophil recruitment alone is sufficient to produce VILI or merely accompanies mechanical injury continues to be debated.[78] Inhibition of MIP-2 activity by specific antibodies[179] of the MIP-2 receptor[173] reduced neutrophil infiltration and lung injury caused by high PIP ventilation.

Leukocyte activation, however, is an unlikely explanation for the major vascular leakage observed during high-inflation edema because the speed with which permeability and ultrastructural alterations develop[4] is not consistent with such a mechanism. Besides, the potent proinflammatory mediators, TNF-α and MIP-2, are unlikely to be involved in the acute lung injury consequent to high-volume ventilation[30] for two reasons. First, there was no correlation between the flux of albumin in alveolar spaces (as reflected by its concentration in bronchoalveolar lavage fluid) and MIP-2 (or IL-6) concentration in this fluid. Second, the authors did not detect TNF-α in bronchoalveolar fluid in any intact mouse model that developed pulmonary edema after lung overinflation and the absence of TNF-α receptors did not preclude the development of acute VILI.[30] These observations confirm that two different types of VILI exist: acute VILI that follows marked overexpansion, and subacute VILI in which inflammatory phenomena prevail. Recently, the use of genomic-intensive approaches allowed for the identification of VILI susceptibility candidate genes[180] and revealed that pre–B-cell colony-enhancing factor is a direct neutrophil chemotaxin and potentially a key pharmacologic target in VILI.[181]

The concept of biotrauma (i.e., the release of proinflammatory cytokines and mediators by lung parenchymal cells, alveolar macrophages, and neutrophils) led to the publication of a tremendous number of studies that tested the effect of modulating the imbalance between proinflammatory and antiinflammatory mediators in the lung. For instance, ventilation with high tidal volume of isolated mouse lungs for 1 hour resulted in nuclear factor-κB (NF-κB) activation, which was inhibited by dexamethasone.[182] Pretreatment of rats with NF-κB antibodies resulted in less permeability pulmonary edema, pathologic changes, and IL-1 expression in an isolated rat lung model of VILI.[183] Administration of an IL-1 receptor antagonist reduced lung albumin, elastase, and neutrophil counts in surfactant-depleted rabbits ventilated with hyperoxia and a high tidal volume[184] and decreased pulmonary edema, airspace neutrophils, and expression of nitric oxide synthase 2 and intercellular adhesion molecule 1 mRNA in rats ventilated with 30 mL/kg tidal volume.[185] In a rat model of VILI, Hoegl et al showed that the prophylactic inhalation of IL-22 before initiation of 45 cm H_2O PIP ventilation protected the lung against lung edema and improved survival.[186] This beneficial effect might be related to an increase in STAT3/SOCS3 expression in alveolar epithelial cells. In a rat model of VILI, prophylactic IL-10 inhalation mitigated the increase in MIP-2 and IL-1β in bronchoalveolar fluid and plasma, and increased animal survival time.[187]

Finally, other kinds of antiinflammatory interventions, such as the stimulation of the endogenous cholinergic pathway,[188] the administration of adenosine A_{2A} receptors agonists,[189] the inhalation of carbon monoxide,[190] and the inhibition of the cyclooxygenase[191] or lipooxygenase[192] showed beneficial effects in animal VILI models.

MODULATION OF HORMONAL AND METABOLIC PATHWAYS

The renin–angiotensin system is involved in lung inflammation during VILI, as attested by increased angiotensin II levels and angiotensinogen mRNA levels in bronchoalveolar lavage fluid of rats subjected to 4 hours of high PIP ventilation.[193] Angiotensin-converting enzyme II, which inactivates angiotensin II and is thus a negative regulator of the renin–angiotensin system, protects mice from acute lung injury related to acid aspiration or sepsis.[194] Moreover, pretreatment of animals with captopril attenuated lung injury and inflammation.[193,195] These protective effects might be related to a reduction in the angiotensin II-induced production of plasminogen activator inhibitor-1.[196]

Pretreatment with atorvastatin decreased alveolar capillary permeability and improved hemodynamics in an isolated rabbit lung model of VILI.[197] Muller et al confirmed these findings in an in vivo model of VILI in mice, showing that treatment with simvastatin limited lung endothelial injury and hyperpermeability, decreased lung neutrophilic infiltration, and improved oxygenation.[198] It remains unknown, however, whether these effects are related to the lipid-lowering properties of statins or to antiinflammatory, antioxidative, or nitric oxide synthesis regulatory properties.[196]

Lung-soluble mediators are pathogenic in VILI.[199] Indeed, isolated perfused mouse lungs ventilated with low tidal volumes but perfused with a perfusate derived from lungs previously ventilated with high tidal volumes develop a similar

decrease in compliance and an increase in lung water.[199] Several lipid-derived mediators have been identified as candidate mediators in VILI.[200] For instance, inhibition of cytosolic phospholipase A_2 mitigates the increase in capillary permeability induced by high PIP ventilation.[201] Finally, ceramides and other sphingolipids are essential constituents of plasma membranes and have been recognized as potential pharmacologic targets in the treatment of acute lung injury.[202] Whether this also applies to prevention or treatment of VILI is unknown.

Reversible induction of a suspended animation-like state (i.e., a hypometabolic state characterized by decreased heart rate, body temperature, and exhaled amounts of CO_2) obtained by the intravenous infusion of a hydrogen sulfide donor, reduced pulmonary inflammation and improved oxygenation in rodent models of VILI.[203,204]

Hypercapnia

Ventilator strategies consisting of a low tidal volume to lower the risk of VILI have a positive impact on survival in ARDS.[1] It has been proposed that the hypercapnic acidosis that accompanies a tidal volume reduction may reduce VILI.[205]

Extreme hypoventilation (with partial pressure of arterial carbon dioxide [Pa_{CO_2}] between 150 and 250 mm Hg) lessened lung injury in surfactant-depleted rabbits, suggesting a therapeutic role for high Pa_{CO_2}.[206] Studies on isolated rabbit lungs[205] found that hypercapnia lessened the acute (within 30 minutes) increase in endothelial permeability produced by high PIP ventilation. Other studies in rabbits ventilated for 4 hours showed that hypercapnic acidosis lessened neutrophil infiltration and lung injury when tidal volume was high,[207] and also reduced the increases in alveolar–arterial oxygen gradient and airway pressure at a clinically relevant tidal volume.[208] Two other in vivo studies, however, were unable to demonstrate a reduction by hypercapnia of the acute capillary permeability alterations caused by high tidal-volume ventilation in a rabbit model of surfactant depletion[209] or in intact rats.[210] The latter investigation concluded that hypercapnia probably has a greater influence on late inflammation-dependent phenomena than on acute stress failure.

Studies in isolated rat lungs, however, have shown that hypercapnia lessened lung weight gain and the decrease in compliance during high tidal-volume ventilation,[211] but the number of subpleural damaged cells, evaluated by confocal microscopy with a membrane impermeant fluorescent tracer, did not differ between normocapnic and hypercapnic lungs. Furthermore, compared to normocapnia, hypercapnia significantly reduced the probability of wound repair in A549 cell cultures.[211] These observations suggest that there is no strong correspondence between the occurrence of cell lesions and the physiologic response of the lung to stretch. They also suggest that the benefit from hypercapnia, if any, may be offset by alterations in the cellular reparation process.[49] This hypothesis was further confirmed by Caples et al in an isolated-perfused rat-lung model of VILI.[212] The buffering of hypercapnic acidosis decreased the rate of cell membrane wounding when lungs were exposed to an injurious ventilation strategy, which suggested the importance of pH-dependent mechanisms.

CLINICAL RELEVANCE

It is clear that microvascular lung injury and pulmonary edema during mechanical ventilation are not the consequences of "barotrauma," but rather of "volutrauma."[36] The main determinant of volutrauma seems to be end-inspiratory volume (the overall lung distension) rather than tidal volume or FRC (which is dependent on the level of PEEP).[92]

It is fascinating to see how the experimental concept of VILI was rapidly translated into a preoccupation of clinicians, as exemplified by the term *ventilator-associated lung injury*.[213] Although the validity of this concept could not be directly demonstrated in patients, it formed the rationale beneath all lung-protective strategies that aimed to reduce the risk of lung overinflation during ventilation of patients with ARDS. That the lungs in ARDS exhibit significant heterogeneity is well documented,[103,214] and ARDS is a condition that results in uneven distribution of ventilation. Gattinoni et al[103] demonstrated that ARDS lungs include healthy tissue, recruitable tissue, and diseased tissue unresponsive to pressure changes. Healthy units represent as little as 20% to 30% of total units.[103] These units can be viewed as "baby lung," another term for the "shrunken lung" described by Gibson and Pride in patients with lung fibrosis.[104] Thus, during conventional ventilator treatment in ARDS, the bulk of ventilation may be directed to healthy units, resulting in regional overdistension, especially when high PIP is required.

Ventilator strategies aimed at reducing the risk of overinflation, such as extracorporeal membrane oxygenation,[215] extracorporeal CO_2 removal,[216] and high-frequency oscillation[217] were proposed (see Chapters 19 to 21). These techniques are merely experimental (at least in adults) and require special devices and highly trained physicians and nurses. In addition, the lack of demonstrable benefit with extracorporeal CO_2 removal,[218] and the scarcity of data on high-frequency oscillation in adults,[219] preclude their acceptance in many centers. Emerging data, however, have generated renewed interest in these techniques.[220,221] It is beyond the scope of this chapter to discuss this issue extensively. Nevertheless, the complexity of these techniques is in striking contrast with the extraordinary simple lung-protective strategies that accompany permissive hypercapnia.[222] Although caution should be exercised when extrapolating experimental data to clinical situations as complex as infant respiratory distress syndrome or ARDS, the clinical relevance of available experimental data received resounding support with the publication of the ARDS Network study.[1] This study showed that simply reducing tidal volume from 12 mL/kg to 6 mL/kg resulted in a 22% reduction in mortality. The effectiveness of this strategy was attributed to a reduction of lung stress, as attested by markedly decreased airway plateau pressure.[223]

The demonstration, however, of a technique to prevent overdistension is difficult. Airway pressure monitoring is easy to perform but cannot completely eliminate the risk of VILI. For instance, application of a continuous distending pressure during high-frequency oscillation or extracorporeal CO_2 removal may be associated with a gradual increase in lung volume. If the increase in volume is the result of recruitment of previously closed lung units, it is likely to be beneficial, at least in terms of gas exchange, and will probably not cause additional lung damage. On the contrary, failure to recruit closed alveoli may result in overdistension of open alveoli.[224]

Because of the study protocol, the same reduction in tidal volume was employed in all patients allocated to the low tidal volume group in the ARDS Network trial.[1] It has, however, repeatedly been shown that the pressure and volume considered safe for some patients with ARDS may cause lung overdistension in others.[99,100,103,225] Conversely, arbitrary settings may result in an unnecessary reduction in tidal volume.[226] As discussed above, information from the inspiratory pressure–volume curve of the respiratory system may be used to tailor ventilator settings, especially when the significance of its particular characteristics (LIP, UIP) are better understood.[83]

Another question that cannot be answered at present is whether or not a threshold tidal volume exists below which experimental VILI or ventilator-associated lung injury in patients does not occur in previously injured lungs. If such a threshold exists, it is unnecessary to drastically reduce tidal volume in all patients as was done in the ARDS Network study,[1] especially in view of possible adverse effects that occur with too great a reduction in tidal volume.[226] In such conditions, staying within the so-called safe limits of plateau pressure[213,223] will be sufficient. In contrast, the absence of such a safe threshold was suggested in the ARDS Network study:[1] Mortality was lower in patients with reduced tidal volume independently of static compliance of the respiratory system at baseline. This observation suggests that low tidal volume was advantageous regardless of lung compliance.[1] Notwithstanding, the reduction of mortality by simply reducing end-inspiratory lung stress lends credence to the possibility that end-inspiratory lung volume is the main determinant of volutrauma (as contended at the beginning of this section). Indeed, it was recently suggested that higher tidal volume may be associated with the onset of acute lung injury[227] or ARDS[228] in patients ventilated for other causes of respiratory failure.

In contrast with the experimental and clinical demonstration of the importance of reducing lung stretch by reducing tidal volume, the clinical relevance of the concept of low lung-volume injury (discussed above) is less obvious. This is a crucial issue as it governs the level of PEEP that should be applied to reduce ventilator-associated lung injury. It is beyond the scope of this chapter to discuss in detail the clinical studies that evaluated this issue. It is worth noting, however, that three randomized, controlled trials did not show any difference in survival of patients with ARDS ventilated with higher or lower levels of PEEP.[229–231] Despite the conclusion of a meta-analysis of these three studies[232] that higher PEEP levels were associated with better survival in the patient with the most severe diseases, the best level of PEEP to apply when ventilating patients with ARDS is still unknown,[233,234] given the fact that ventilator protocols were markedly different between the three studies, with considerable heterogeneity in the values for plateau pressure in the high PEEP groups.

A recent study measuring lung metabolic activity (a surrogate of lung inflammation), using positron emission tomography with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) in patients with ARDS showed that lung regions undergoing cyclic recruitment–derecruitment did not exhibit higher ^{18}F-FDG uptake than did regions that remained collapsed throughout the respiratory cycle.[235] Instead, ^{18}F-FDG uptake in normally aerated regions correlated with plateau pressure and regional volume expansion. Although these results should be interpreted cautiously because of the small number of patients involved and because pulmonary infection, a major confounding factor for the interpretation of lung inflammation, was often the cause of ARDS, they suggest that "volutrauma" rather than "atelectrauma" is a more significant contributor to lung inflammation in ventilated patients with ARDS.[235]

Improving lung mechanical properties so as to decrease the risk of ventilator-associated lung injury is another option that may combine with protective lung strategies. Two treatments were tested during clinical trials: surfactant administration and partial liquid ventilation. The failure of both strategies could have been predicted on physiologic and experimental grounds.

Administration of surfactant by aerosol[236] or tracheal instillation[237] was not associated with any survival advantage in the treatment of adult patients with ARDS. These treatments failed to improve oxygenation in one study[236] and achieved only mild improvement in another study[237] and were not associated with changes in lung mechanics.[237] It has been suggested that the treatments were not effective in preventing damage caused by lung overstretching or oxygen toxicity, either because the mode of administration was not optimal or because the particular type of surfactant was not physiologically effective in diseased lungs. In contrast, administration of a natural surfactant containing high levels of surfactant-specific protein B in a pediatric population with acute lung injury (premature infants were not included) was associated with increased survival.[238] Moreover, the oxygenation index (which takes into account both lung mechanical properties and oxygenation) was markedly improved.

The recent failure of a multicenter clinical trial of partial liquid ventilation with perflubron (a perfluorocarbon) during mechanical ventilation of adult patients with acute lung injury illustrates the clinical relevance of VILI.[239] The amount of administered perflubron was high and was associated with a high level of PEEP (>13 cm H_2O). Consequently, inspiratory pressure was higher in the patients who received perflubron than in controls. Not only was mortality higher (although not significantly) in patients receiving liquid ventilation, but the incidence of macroscopic barotrauma was also particularly high, more than double that in the controls

(17% vs. 6%). All these results were predictable from careful analysis of experimental studies, which showed increased incidence of barotrauma[143] and worsening of VILI[106,144,145] when both the amount of instilled perfluorocarbon and the pressures delivered by the respirator were high.

As already discussed, the literature on possible cytokine involvement during VILI contains many contradictions and inconsistencies.[78] Indeed, it is not surprising that the clinical correlate of such experimental findings is very vague. Ranieri et al[77] reported significant decreases in bronchoalveolar fluid and plasma concentrations of many inflammatory and antiinflammatory mediators in patients ventilated with a so-called lung-protective strategy (low tidal volume plus high PEEP). They suggested that nonprotective ventilation (high tidal volume plus low PEEP) was responsible for the inflammatory state. In contrast, Stuber et al[240] reported the release of mainly antiinflammatory mediators in the bronchoalveolar fluid and plasma of patients ventilated with a nonprotective modality.[241] Finally, very modest although significant decreases of plasma inflammatory cytokines were reported in patients of the low tidal-volume arm of ARDS Network study[1] compared with patients of the high tidal-volume arm.[242] The decrease, however, was trivial and very unlikely to have any clinical consequence. Thus, developing possible antiinflammatory therapy to prevent ventilator-associated lung injury based on these findings is speculative at best.

CONCLUSION

Considerable clinical progress has accrued from the extensive physiologic experimental research on VILI since its initial description by Webb and Tierney in 1974.[2] There is now widespread consensus on the need to ease the stress on diseased lungs during mechanical ventilation. The extent, however, to which tidal volume should be decreased, the level of PEEP that should be used, and how to identify lung overdistension in an individual patient remain largely unknown. A tremendous number of experimental studies aimed at exploring the pathophysiology of VILI and at identifying pharmacological targets for its prevention and treatment have been performed. None of those pharmacologic interventions, however, has proven beneficial in patients. The multiplicity of the pathways involved in VILI suggests that a single pharmacologic intervention is unlikely to impact on the outcome of patients.

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43

VENTILATOR-INDUCED DIAPHRAGMATIC DYSFUNCTION

Theodoros Vassilakopoulos

Controlled mechanical ventilation (CMV) is a ventilator mode where the respiratory muscles are not contracting, and the ventilator takes full responsibility for inflating the respiratory system. Evidence accumulating over the past two decades has shown that CMV can induce dysfunction of the diaphragm, mainly consisting of atrophy, oxidative stress, and ultrastructural injury, resulting in decreased diaphragmatic contractility. This is called *ventilator-induced diaphragmatic dysfunction (VIDD)*.[1]

The frequency with which CMV is used cannot be determined with certainty. An international survey revealed that 13% of mechanically ventilated patients receive a neuromuscular blocker for 8% of the total days of ventilator support.[2] In these patients, full ventilator support is mandatory. Moreover, it was recently shown that the use of neuromuscular blockers during the first 2 days of ventilator support improves the survival of patients with severe acute respiratory distress syndrome,[3] a finding that may lead to increased use of CMV. Other patient groups not receiving neuromuscular blockers also receive full ventilator support, such as patients with traumatic brain injury, postoperative neurosurgical patients, comatose patients, patients with status epilepticus on barbiturate coma to suppress seizure activity, and so on. Thus, a considerable percentage of ventilated patients are at risk of developing VIDD.

The mechanisms of this dysfunction and the clinical relevance for mechanically ventilated patients is the subject of this chapter.

EVIDENCE FOR VENTILATOR-INDUCED DIAPHRAGM DYSFUNCTION IN HUMANS

The first human evidence for the existence of VIDD came from retrospective analysis of postmortem data obtained in neonates who received ventilatory assistance for 12 days or more immediately before death. This study revealed diffuse diaphragmatic myofiber atrophy (small myofibers with rounded outlines), not present in extradiaphragmatic muscles or diaphragms of infants ventilated for 7 days or less.[4]

Recently, direct evidence came from studies of brain-dead organ donors (with an intact circulation) who underwent CMV and who developed biopsy-proven atrophy[5,6] and decline in the contractility of their diaphragm.[6]

THE COMPONENTS OF VENTILATOR-INDUCED DIAPHRAGM DYSFUNCTION

Atrophy

Ventilator-induced atrophy[7] is usually measured by the reduction of the cross-sectional area of myocytes in histologic sections. Atrophy has been observed in both slow-twitch and fast-twitch human diaphragmatic fibers and is

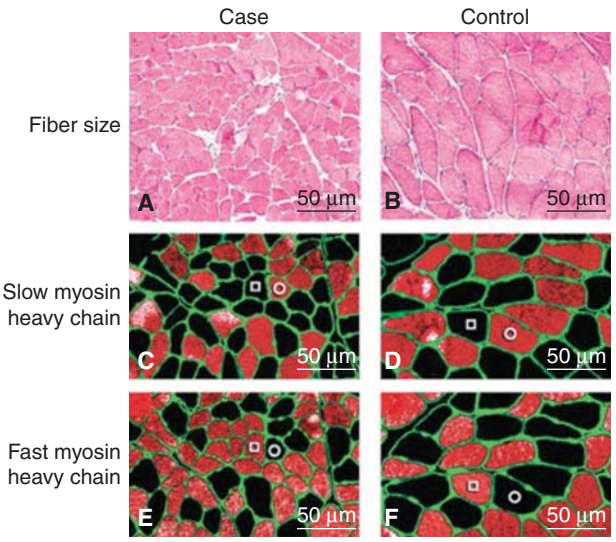

FIGURE 43-1 Atrophy in the human diaphragm after CMV. The slow-twitch and fast-twitch fibers in the case specimens (Panels **A, C,** and **E**) are smaller than those in the control diaphragms (Panels **B, D,** and **F**). Panels A and B (hematoxylin and eosin) show that neither inflammatory infiltrate nor necrosis is present in case or control specimens. The sections in Panels C and D were preincubated with NOQ7.5.4D antibody, which is specific for the slow myosin heavy chain, whereas sections in Panels E and F were preincubated with the MY-32 antibody, which reacts with all fast myosin heavy chains. In addition, in each section, all fibers are outlined by an antibody reactive to laminin. In each of the sections, fibers reacting with the antibody appear *orange-red*, whereas fibers not reacting with the antibody appear *black*. In Panels C, D, E, and F, a representative slow-twitch fiber is indicated by an *open circle* and a fast-twitch fiber by an *open square*. (Used, with permission, from Levine et al.[5])

quite significant (Fig. 43-1), its magnitude amounting to 40% to 50% after quite variable periods of CMV (range: 15 to 276 hours.)[5,6,8] Atrophy preferentially affects the diaphragm because it was not observed in the pectoralis major muscle of the same patients.[5] The longer the duration of CMV, the greater the observed atrophy (Fig. 43-2).[6]

Animal studies also suggest that atrophy is more pronounced in the diaphragm, which atrophies earlier than the peripheral skeletal muscles, which are also inactive during CMV.[9–11] Two days of CMV with positive end-expiratory pressure (PEEP) (2 cm H_2O) induced atrophy in rabbits,[12] whereas 3 days of CMV without PEEP were inadequate to

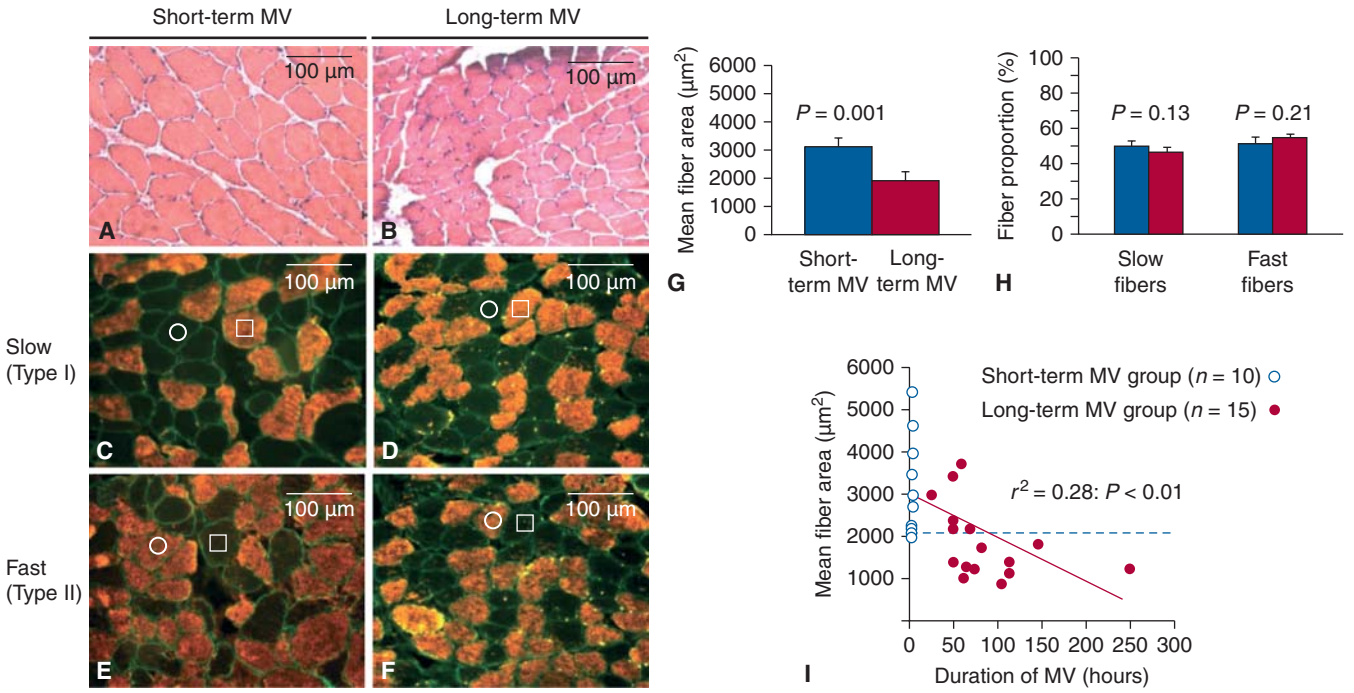

FIGURE 43-2 Relationship between duration of mechanical ventilation (MV) and diaphragmatic atrophy. Representative images of transverse frozen sections obtained from the diaphragms of the short-term MV (**A, C, E**) and long-term MV (**B, D, F**) groups are shown. The diaphragmatic sections are stained with hematoxylin and eosin (A, B) or with antibodies directed against slow (C, D) or fast (E, F) isoforms of myosin heavy chain. **C** to **F**. Serial sections, individual representative slow-twitch and fast-twitch fibers are marked by an *open square* and *circle*, respectively. **G** and **H.** Quantitative analyses of diaphragmatic fiber size (mean cross-sectional area) and fiber-type proportions in the two patient groups, respectively. **I.** The significant correlation between the degree of diaphragmatic atrophy and the duration of MV (*horizontal dashed line* indicates lowest value of fiber size measured in short-term MV group). (Used, with permission, from Jaber et al.[6])

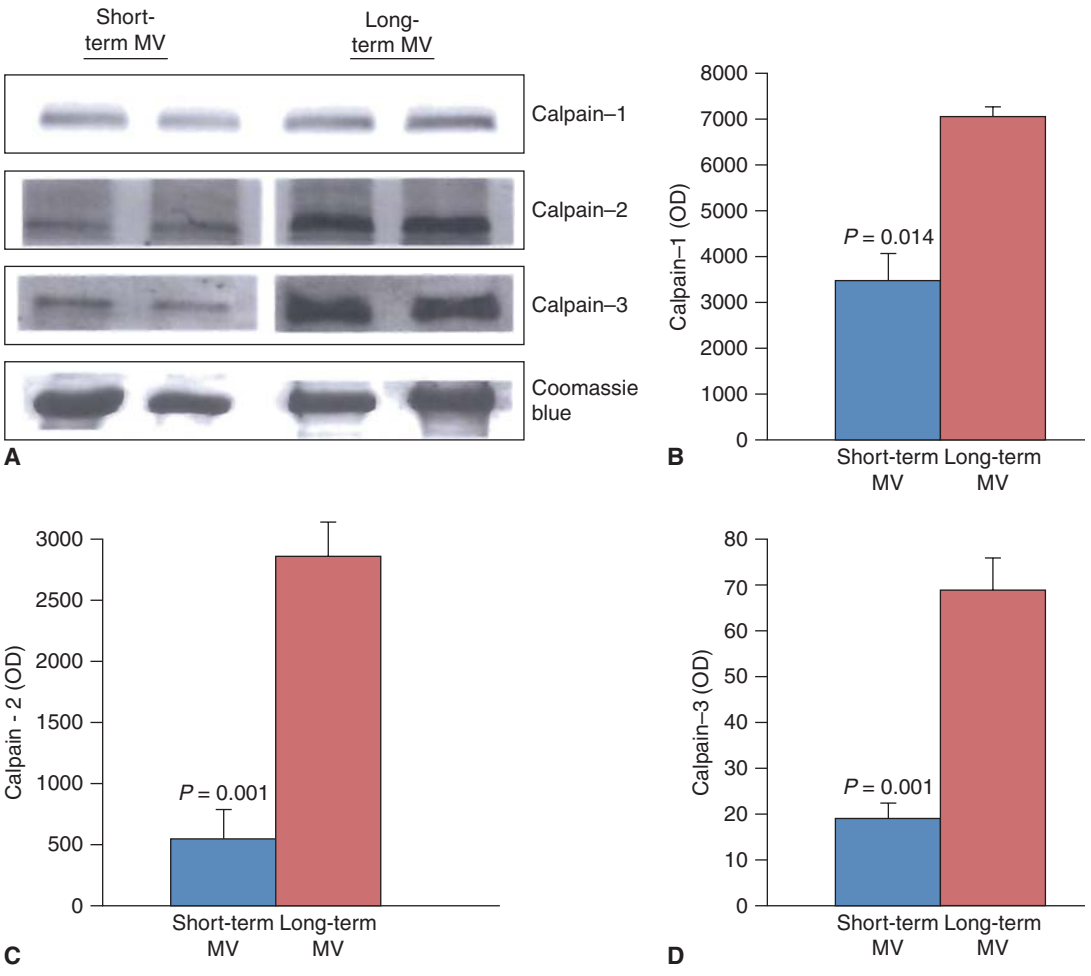

FIGURE 43-3 Expression of calpain isoforms in diaphragms of short-term and long-term mechanical ventilation (MV) groups. Representative immunoblots (**A**) and group mean quantification of protein levels measured in diaphragmatic tissues obtained from the short-term and long-term MV groups for calpain-1 (**B**), calpain-2 (**C**), and calpain-3 (**D**). (Used, with permission, from Jaber et al.[6])

induce atrophy[13] in the same species, which suggests that the rapidity of atrophy development might be augmented with use of PEEP. The increased lung volume at the end of expiration (with use of PEEP) places the passive diaphragm in a relatively shortened position and skeletal muscle atrophies faster when shortened.[14,15]

Atrophy can result from decreased protein synthesis, increased proteolysis, or both. Six hours of CMV in rats decreased the in vivo rate of mixed muscle protein synthesis (averaged for all muscle proteins) by 30% and the rate of myosin heavy-chain protein synthesis by 65%, both of which persisted throughout 18 hours of CMV.[16] In addition, 24 hours of CMV suppressed the messenger RNA levels of insulin-like growth factor-1, which stimulates protein synthesis.[17] Thus, CMV decreases protein synthesis in the diaphragm.

Increased proteolysis has been documented in diaphragmatic strips of animals subjected to 18 hours of CMV.[9] Mammalian cells have four different protein systems and organelles for proteolysis—the calpains,[6] the caspases,[5] the proteasome system,[5,8] and the autophagy-lysosomal system[8]—all of which are activated in the human diaphragm after CMV, a finding previously suggested by animal models.[9,18–20]

CALPAINS

Calpains, which are activated after CMV (Fig. 43-3), do not fully degrade, but only partially cleave proteins in vivo. This renders the proteins amenable to the proteasome.[7] The stimulus for calpain activation in not known, but calcium elevation in the cell is a prerequisite. The reduced (messenger RNA) levels of sarcoplasmatic reticulum calcium adenosine triphosphatase (ATPase; the enzyme that removes calcium from the sarcoplasm), secondary to 24 hours of CMV[21] in animal models may contribute to calpain activation.

CASPASES

Caspases are proteases that can degrade proteins and especially complexes of actin and myosin[18,22] and release

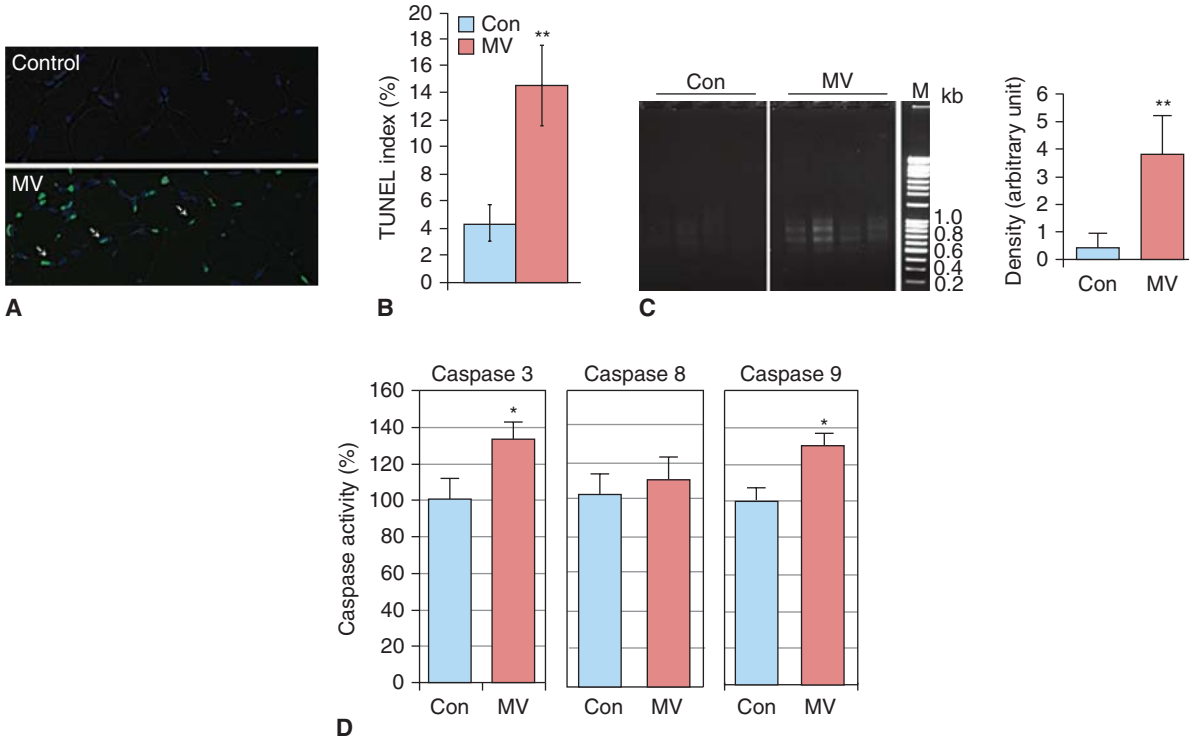

FIGURE 43-4 Apoptosis in the human diaphragm after CMV. CMV results in DNA fragmentation and activates caspases 3 and 9 in human diaphragm. **A.** TUNEL (TdT [terminal deoxynucleotidyl- transferase]-mediated [2′-deoxyuridine 5′-triphosphate]-biotin nick-end labeling) staining was performed on cryosections of control and ventilated human diaphragm. Fragmented genomic DNA was labeled with FITC (fluorescein isothiocyanate) conjugated dUTP (deoxyuridine triphosphate); positive signals appear *green*. Myonuclei are visualized by DAPI (4,6-diamidino-2-phenylindole) staining (*blue*). Note that the positive TUNEL staining signals (*green*) are localized in nuclei stained by DAPI (*blue*). **B.** TUNEL-positive nuclei were counted and normalized to total myonuclei; ratio is shown as the TUNEL index. Control (Con), $n = 9$; MV, $n = 10$. **C.** DNA fragmentation was measured by polymerase chain reaction (PCR)-based detection and visualized by electrophoresis in 2% agarose gel. Density of the PCR products was quantitated with Image J and normalized to the total DNA input. M, DNA markers. Control, $n = 5$; MV, $n = 8$. **D.** Caspase 3, 8 and 9 enzymatic activities from control and MV human diaphragm lysates were measured by fluorometric assay. Results are presented as relative fluorescence units after normalization to total protein amount. Control, $n = 7$; MV, $n = 9$. *, $P < 0.05$; **, $P < 0.01$. (Used, with permission, from Tang et al.[24])

them from the myofibrillar lattice. Upregulation of caspase-3 expression has been documented in the diaphragm secondary to CMV in both humans[5] and in animal models of VIDD.[19] Caspase-3 can be activated by oxidative stress, increased intracellular calcium, and increased calpain activity.[18]

In animal models of VIDD, the decreased volume of the cytoplasm (atrophy) was observed in the presence of decreased number of myonuclei (skeletal muscle cells are multinucleated cells and theoretically a single myonucleus can sustain the necessary gene expression for a limited area of the cytoplasm, a relationship known as the myonuclear domain[23]), so that the myonuclear domain remains constant.[19] This decrease in myonuclear content was mediated by a caspase-3 dependent increase in apoptosis, which was evident as early as 6 hours after the onset of CMV.[19] Both the apoptosis and atrophy were attenuated with caspase-3 inhibition.[19]

CMV-induced apoptosis has also been documented in the human diaphragm (Fig. 43-4).[24] The finding of elevated caspase 9, but not caspase 8, and elevated Bcl2-interacting mediator of cell death (Bim) (and its transcriptional variants), but not Fas or Fas Ligand, suggest that the intrinsic (mitochondrial), rather than the extrinsic apoptotic pathway, is the primary pathway that operates in CMV-induced apoptosis in the human diaphragm, resulting in caspase 3 activation and nuclear DNA fragmentation.[24] Complementary experiments, conducted in vitro, suggest that oxidative stress is a potential proximal activator of *all* of the pathways that have been implicated in VIDD, with mitochondrial dysfunction representing a central component of this cascade.[24] Bcl2-interacting mediator of cell death is probably an important mediator of the oxidative stress-induced activation of the intrinsic apoptotic pathway, and Fos, FoxO1, and Stat3 are the transcription factors that regulate its expression.[24]

AUTOPHAGY–LYSOSOME PATHWAY

The autophagy–lysosome pathway is also upregulated in the ventilated human diaphragm.[8] Autophagy (Greek for self-eating) is a catabolic pathway characterized by the formation

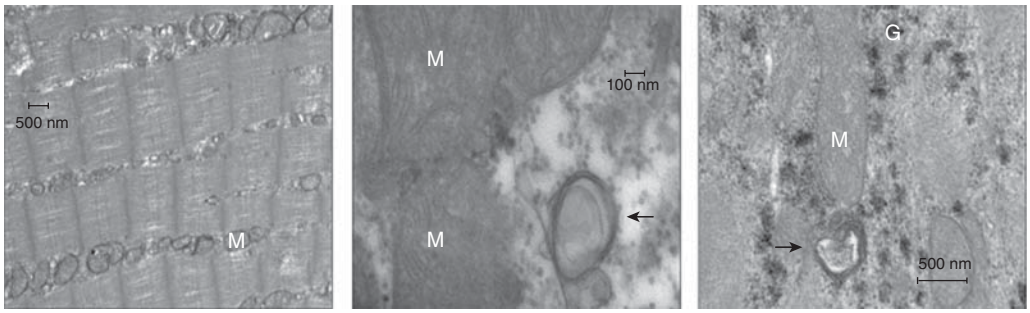

FIGURE 43-5 *Left panel.* Representative electron micrograph of a section of a diaphragm from a control subject showing normal ultrastructure and absence of autophagosomes. *Middle and right panels.* Representative electron micrographs of a section of a diaphragm from a brain-dead organ donor undergoing controlled mechanical ventilation. These sections show autophagosomes (*black arrows*) in close proximity to mitochondria (*M*). *G* indicates glycogen particles. (Used, with permission, from Hussain et al.[8])

of vesicles (autophagosomes) that engulf cytoplasmic organelles and proteins, which then fuse with lysosomes that degrade their contents. This process is a major mechanism for degrading long-lived proteins and organelles. Autophagy occurs at low basal levels to perform homeostatic functions, but can be rapidly upregulated when cells need to generate energy. Hussain et al[8] demonstrated that prolonged CMV triggers the appearance of autophagosomes (Fig. 43-5) and increases the expression of autophagy-related genes in the diaphragm (Fig. 43-6). This is associated with upregulation of the transcription factor FOXO-1. It should be emphasized that these changes are relatively specific to the diaphragm

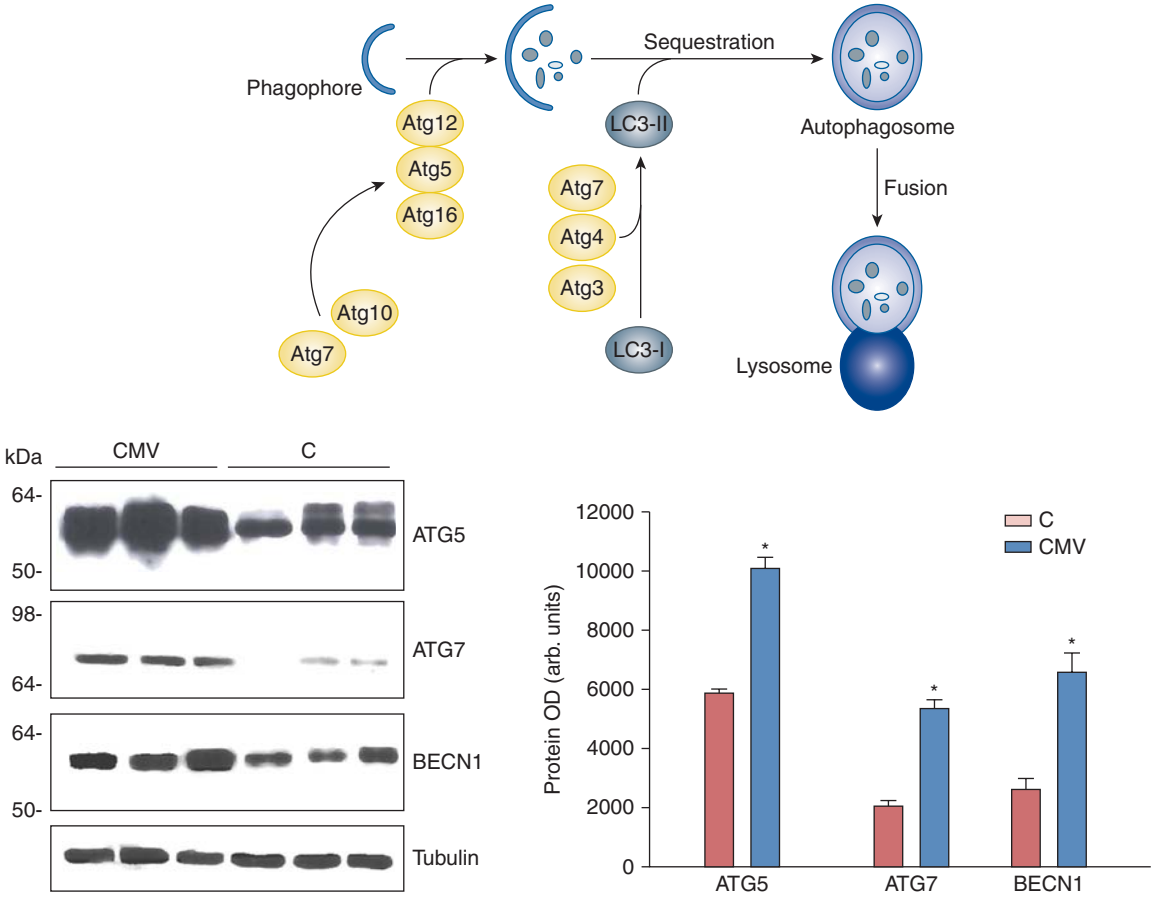

FIGURE 43-6 Autophagy-related genes in the human diaphragm after controlled mechanical ventilation (*CMV*). *Top.* Schematic cartoon of autophagosome assembly. *Left.* Representative immunoblots of BECN1, ATG5, and ATG7 in diaphragms of the control (*C*) and CMV groups. *Right.* Mean values of protein optical densities (*OD*) of BECN1, ATG5, and ATG7 in diaphragms of the C and CMV groups. *, $P < 0.05$ compared with control subjects; *Atg,* Autophagy related genes; *LC3-I, LC3-II,* microtubule-associated protein light chain-3 (LC3)-I or LC3-II; *BECN1,* beclin-1. (Used, with permission, from Hussain et al.[8])

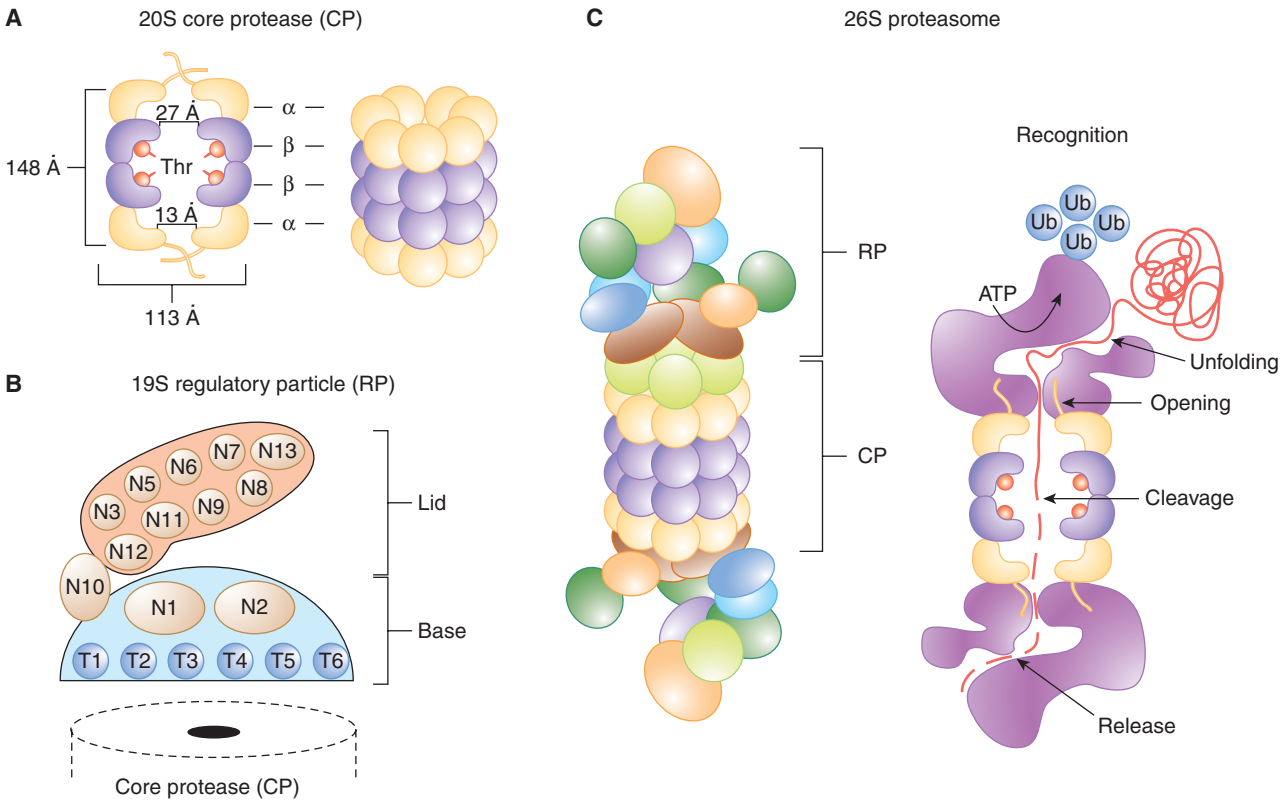

FIGURE 43-7 The 20S and 26S proteasome isoforms. **A.** Organization of the core protease (*CP*) and (**B**) the regulatory particle (*RP*) with its *Lid* and *Base* subparticles. The dimensions of the CP were obtained from the crystal structure of the yeast complex. The *N*-terminal threonine residues that form the protease active sites in the β_1, β_2, and β_5 subunits are indicated. **C.** Proposed structure and sequence of events that lead to the degradation of a ubiquitinated protein by the 26S holoprotease. *ATPase*, adenosine triphosphatase; *N*, RP non-ATPase subunits; *T*, RP AAA-ATPase subunits; *Thr*, threonine; *Ub*, ubiquitin. (Used, with permission, from Vierstra et al.[72])

and are not observed to the same degree in the control limb muscle (quadriceps) of the same patients. Moreover, upregulation of the autophagy-related genes in the diaphragm increases with the time spent on CMV.[8]

PROTEASOME

The proteasome is a multisubunit, multicatalytic complex that exists in two major forms (Fig. 43-7): The core 20S proteasome can be free or bound to a pair of 19S regulators to form the 26S proteasome, which degrades (in an adenosine triphosphate [ATP]-dependent manner) proteins covalently bound to a polyubiquitin protein chain (ubiquitinated proteins). The binding of ubiquitin to protein substrates requires the ubiquitin-activating enzyme (E1), which utilizes ATP-derived energy to form a covalent link with a ubiquitin protein, followed by transfer of the active ubiquitin moiety to a ubiquitin-conjugating enzyme (E2), and finally transfer of this ubiquitin to the protein to be degraded via a ubiquitin ligase (E3) (Fig. 43-8). CMV increases the level of ubiquitin-protein conjugates in the diaphragm,[6,25] which are the substrates of the 26S proteasome (Fig. 43-9). Key enzymes involved in the function of ubiquitin-proteasome pathway are upregulated in the human diaphragm after CMV, such as the skeletal muscle specific ubiquitin ligases (E3 enzymes), muscle atrophy F-box (MAFbx/Atrogin-1), and muscle ring finger-1 (MuRF1),[5,8,25] as well as the E2 conjugases UBC2 and UBC4[8] (Fig. 43-10). The changes in the E3 ligases are relatively specific to the diaphragm and were not observed in the quadriceps (control limb muscle) of the same patients, which were also inactive (Fig. 43-10).[8]

Interestingly, the activity of the 20S proteasome is elevated in the human diaphragm after CMV.[25] The 20S proteasome is specialized in degrading proteins oxidized by reactive oxygen species. Oxidative damage of a protein results in its partial unfolding, exposing hidden hydrophobic residues.[26,27] Therefore, an oxidized protein does not need to be further modified by ubiquitin conjugation to confer a hydrophobic patch, nor does it require energy from ATP hydrolysis to unfold. It should, however, pointed out that the expression of various α subunits of the 20S proteasome was not increased in human diaphragms after CMV.[8]

Oxidative Stress

CMV is associated with augmented oxidative stress in the human diaphragm, as evidenced by the rise in protein

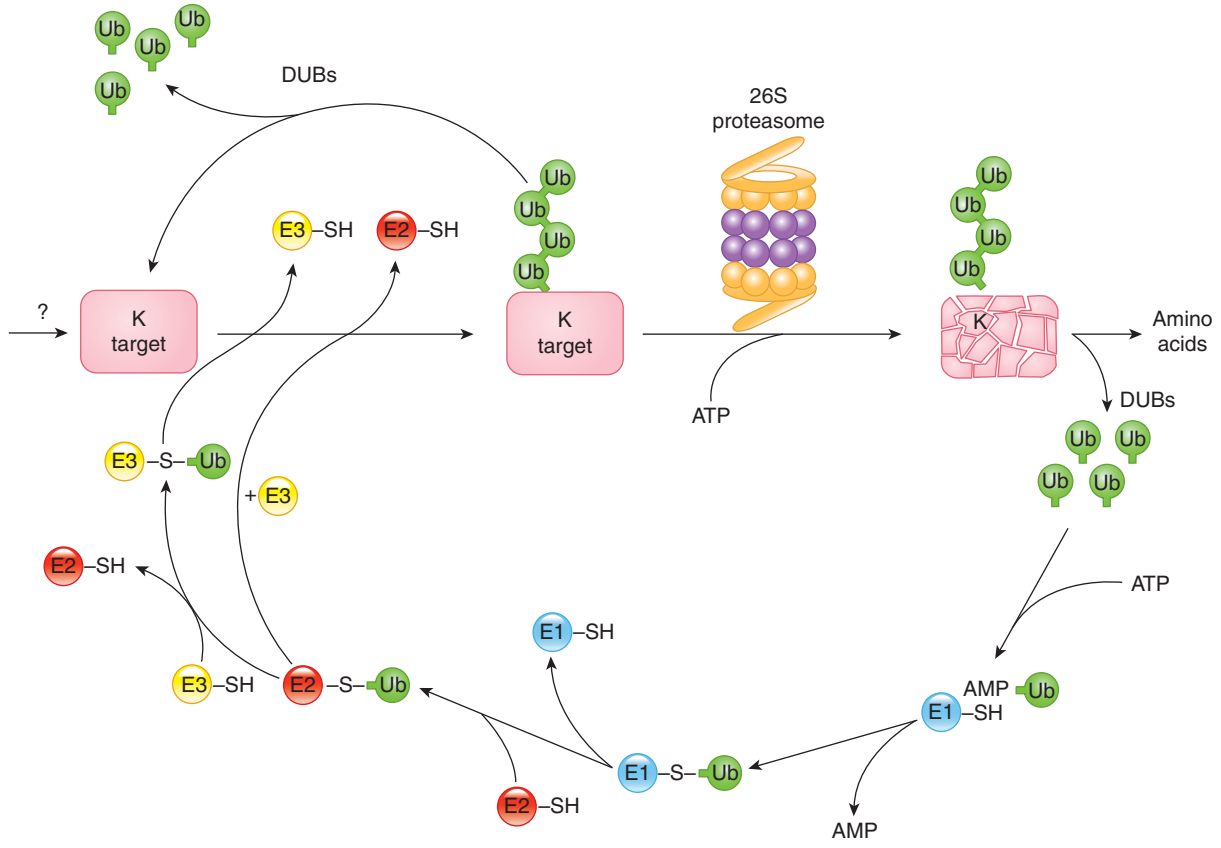

FIGURE 43-8 The ubiquitin–proteasome pathway of proteolysis. Proteins degraded by the ubiquitin–proteasome pathway are first conjugated to ubiquitin (*Ub*). The process of linking ubiquitin to lysine residues in proteins destined for degradation involves the activation of ubiquitin by the E1 enzyme in an adenosine triphosphate (*ATP*)-dependent reaction. Activated ubiquitin is transferred to an E2 carrier protein and then to the substrate protein, a reaction catalyzed by an E3 enzyme (E3 ligase). This process is repeated as multiple ubiquitin molecules are added to form a ubiquitin chain. Once a conjugate is assembled bearing a chain of multiple Ubs, it is either recognized by the 26S proteasome and degraded in an ATP-dependent process or the conjugate is disassembled by deubiquitinating enzymes (*DUBs*), releasing the ubiquitin and target intact. In ATP-dependent reactions, ubiquitin-conjugated proteins are recognized and bound by the 19S complex, which releases the ubiquitin chain and catalyzes the entry of the protein into the 20S core proteasome. Degradation occurs in the core proteasome, which contains multiple proteolytic sites within its two central rings. The ubiquitin is not degraded but is released and reused. *ADP*, adenosine diphosphate; *K*, lysine; *SH*, sulfhydryl. (Used, with permission, from Vierstra et al.[72])

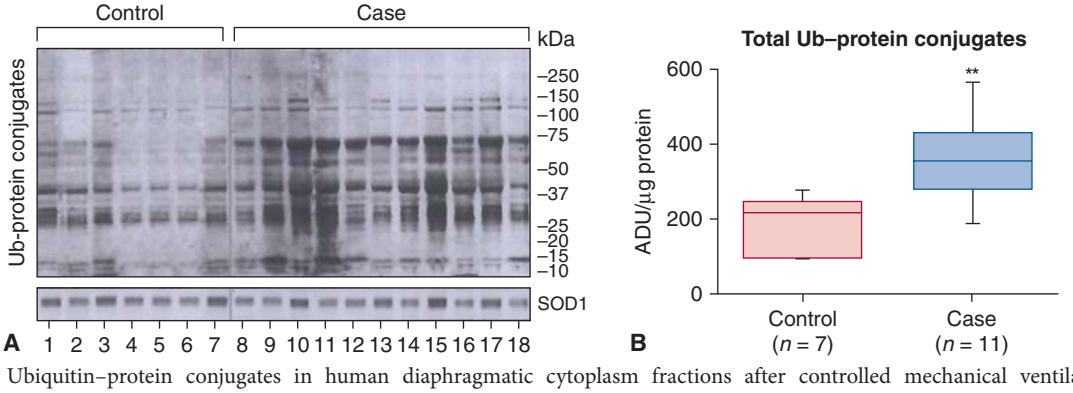

FIGURE 43-9 Ubiquitin–protein conjugates in human diaphragmatic cytoplasm fractions after controlled mechanical ventilation (CMV). **A.** Immunoblotting results for ubiquitin (*Ub*)–protein conjugates in seven control and eleven case specimens. The fact that the control diaphragms show ubiquitination of many bands is consistent with the concept that ubiquitination is a normal process for protein turnover. The superoxide dismutase (*SOD*) 1 protein-loading control did not differ between lanes. **B.** Case diaphragms exhibited approximately twice the amount of ubiquitinated proteins, suggesting that case diaphragms are exhibiting an upregulation of ubiquitination. **, $P < 0.01$; *ADU*, arbitrary density units. (Used, with permission, from Levine et al.[25])

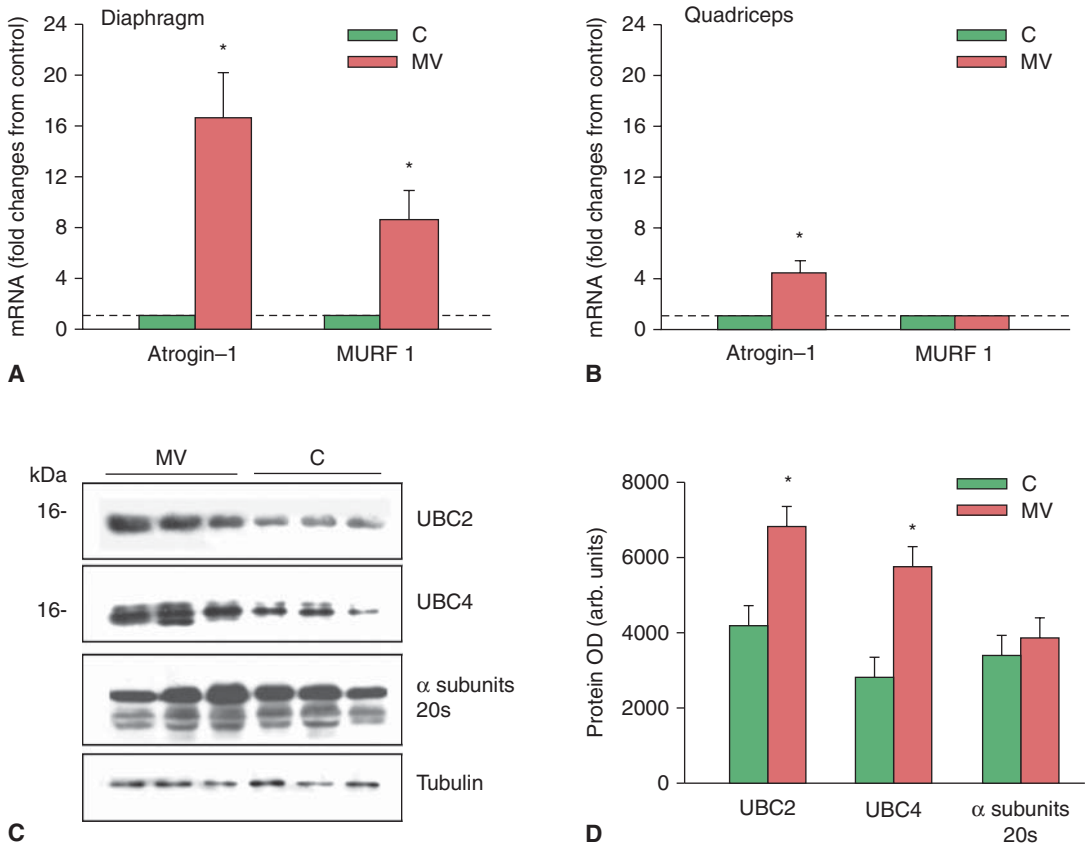

FIGURE 43-10 Proteasome ligase expression after controlled mechanical ventilation (CMV). **A.** Changes in messenger RNA (*mRNA*) expression levels of *Atrogin-1* and *MURF1* in the diaphragms of control (*C*) subjects and subjects undergoing CMV. *, $P < 0.05$ compared with control subjects. **B.** Changes in mRNA expression levels of *Atrogin-1* and *MURF1* in the quadriceps muscles of control subjects and subjects undergoing CMV. *, $P < 0.05$ compared with *C* subjects. **C.** Representative immunoblots of UBC2, UBC4, and a subunits of the 20S proteasome in diaphragms of the *C* and the *CMV* groups. **D.** Mean values of protein optical densities (*OD*) of UBC2, UBC4, and a subunits of the 20S proteasome in diaphragms of the *C* and *CMV* groups. *, $P < 0.05$ compared with control subjects. (Used, with permission, from Hussain et al.[8])

oxidation (elevated 4-hydroxy-2-nonenal [HNE]-protein adduct formation[8] and protein carbonylation,[8,24] as well as the increased levels of superoxides documented by dihydroethidium staining.[24] Animal models of VIDD have also documented other indices of oxidative stress, such as lipid peroxidation (elevated 8-isoprostane,[9] total lipid hydroperoxides,[28,29] and thiobarbituric reactive substance content[30]), and have provided direct evidence of oxidative stress by the increased emissions of dichlorofluorescein (a molecule that fluorescences upon reacting with reactive oxygen species within cells) when diaphragmatic strips from CMV-treated animals are incubated in vitro with the dye.[31] Animal models of VIDD suggest that the onset of oxidative injury is rapid, occurring within 6 hours after the institution of CMV in rats[28] and is long lasting, being present after 3 days of CMV in piglets.[30] The mechanism(s) of oxidative stress generation remain elusive. Interestingly, the messenger RNA levels of both nuclear-encoded cytochrome C oxidase IV and the mitochondria-encoded cytochrome C oxidases I, II, and III are reduced in the diaphragm after CMV. These observations indicate the presence of a functional impairment of the coupling between electron donors and acceptors as well as mitochondrial energy production,[24] and point to the mitochondria as potential sources of oxidative-stress generation in VIDD. The initial oxidative stress may result from the sudden change in the functional status of the diaphragm as it switches from continuous, intermittent contraction to passive rest (as occurs with CMV). Because noncontracting muscle fibers do not require major mitochondrial energy production, this altered functional status may place a "brake" on normal mitochondrial function. This may, in turn, cause mitochondrial reactive oxygen species accumulation and eventual leak.[24]

The response of antioxidant enzymes in the diaphragm to CMV is controversial. Consistent with a mitochondrial role in this oxidative stress, the mitochondria-resident antioxidant gene, superoxide dismutase-2 (SOD 2), is significantly induced in the human diaphragm after CMV, whereas cytosolic superoxide dismutase-1 (SOD 1) is not.[24] Glutathione levels are reduced in the diaphragm, but this may simply be the result of oxidative-stress development.[5]

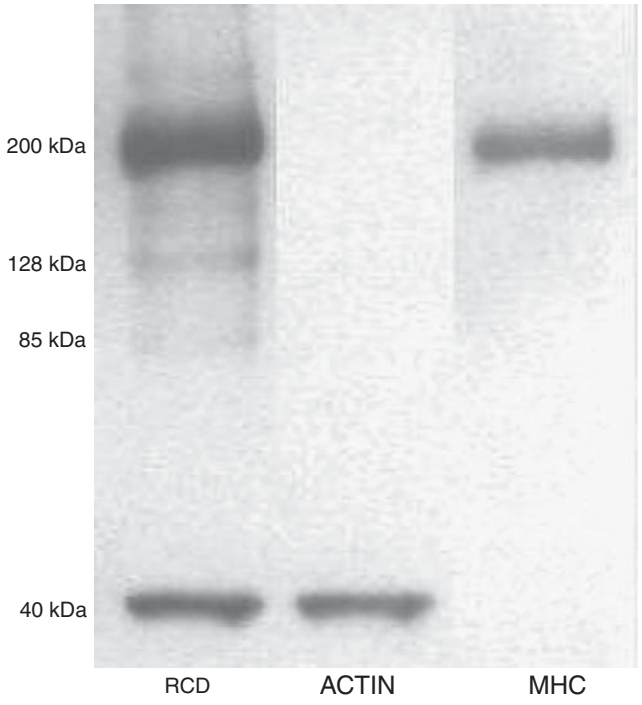

FIGURE 43-11 Illustration of Western blots using monoclonal antibodies to identify oxidized proteins with molecular masses of approximately 200 to 40 kDa. *Left lane*. Reactive carbonyl derivatives (*RCD*), which are the footprints of protein modifications induced by oxidative stress in insoluble proteins isolated from the diaphragm of an animal exposed to controlled mechanical ventilation (CMV) for 18 hours. *Middle* and *Right lanes*. the same membrane stripped of the 2,4-dinitrophyenylhydrazone antibody (the antibody recognizing RCD was removed) and then sequentially re-probed with monoclonal antibodies specific for rat skeletal muscle actin and all myosin heavy chain (*MHC*) isoforms. (Used, with permission, from Zergeroglu et al.[28])

Oxidative stress can modify proteins involved in energetics, excitation–contraction coupling, intracellular calcium regulation, and force generation.[32] In humans[8] and in animal models of VIDD,[28] diaphragmatic protein oxidation was evident in proteins with molecular masses of about 40 and 200 kDa. These findings raise the possibility that actin (40 kDa) and/or myosin (200 kDa) undergo oxidative modification during CMV (Fig. 43-11), which is expected to compromise diaphragmatic contractility. This intriguing possibility awaits confirmation by more specific identification of the modified proteins. Interestingly, decreased levels of both myosin heavy chains and α-actin were documented in human diaphragms after CMV.[25]

Oxidative stress, and especially 4-hydroxy-2-nonenal (produced in the diaphragm under conditions such as sepsis, resistive breathing,[33] and CMV[8]), can reduce the activity of plasma membrane calcium ATPase.[34] This would retard calcium removal from the diaphragmatic myofibers and contribute to calcium accumulation and calpain activation.[18] Oxidative stress could injure various intracellular structures-organelles, activate proteolysis (especially through the 20S proteasome), and induce apoptosis.[24]

Structural Injury

CMV leads to a significant increase in the prevalence of ultrastructural abnormalities in the human diaphragm, consisting of disruption of the normal myofibrillar organization with enlarged spaces containing disorganized sarcomeric material (Fig. 43-12). The longer the duration of CMV, the greater the degree of injury in the human diaphragm.[6] Animal models of VIDD have also documented structural abnormalities of different subcellular components of diaphragmatic myofibers, progressively developing after 2 to 3 days of CMV in rabbits.[13,35,36] The changes consisted of disrupted myofibrils, increased numbers of lipid vacuoles in the sarcoplasm, and abnormally small mitochondria containing focal membrane disruptions. Similar alterations were observed in the external intercostal muscles of ventilated animals,[36] but not in hindlimb muscles.[13] The structural abnormalities have detrimental effects on diaphragmatic contractility. The number of abnormal myofibrils is inversely related to the force output of the diaphragm.[13] The mechanisms of injury have not been elucidated, but may involve activation of calpains, which have the ability to degrade several sarcomeric proteins, and direct cellular injury secondary to augmented oxidative stress.[37]

Diaphragmatic Force and Endurance

MEASUREMENTS IN HUMANS

A major problem in documenting whether VIDD compromises diaphragmatic contractility in humans is the difficulty in accurately evaluating respiratory muscle function in critically ill patients undergoing mechanical ventilation, especially because these patients show variable levels of cooperation. An alternative, although technically demanding, approach is to obtain simultaneous recordings of esophageal (Pes) and gastric (Pga) pressures (their difference being transdiaphragmatic pressure [Pdi]), during bilateral magnetic phrenic nerve stimulation.[38,39]

The magnitude of the negative deflection in tracheal pressure (Ptr) during twitch stimulation of the phrenic nerves against an occluded airway can be used as a surrogate of Pdi in intubated patients,[39,40] and has the major advantage of not requiring the placement of esophageal and gastric balloon catheters. Jaber et al performed serial measurements of twitch Ptr in critically ill patients who were ventilated for approximately 1 week. Twitch Ptr decreased progressively during the period of CMV, with a mean reduction of 32 ± 6% at 6 days (Fig. 43-13).[6] These data provide the best available evidence for the occurrence of contractile dysfunction as a component of VIDD in humans.

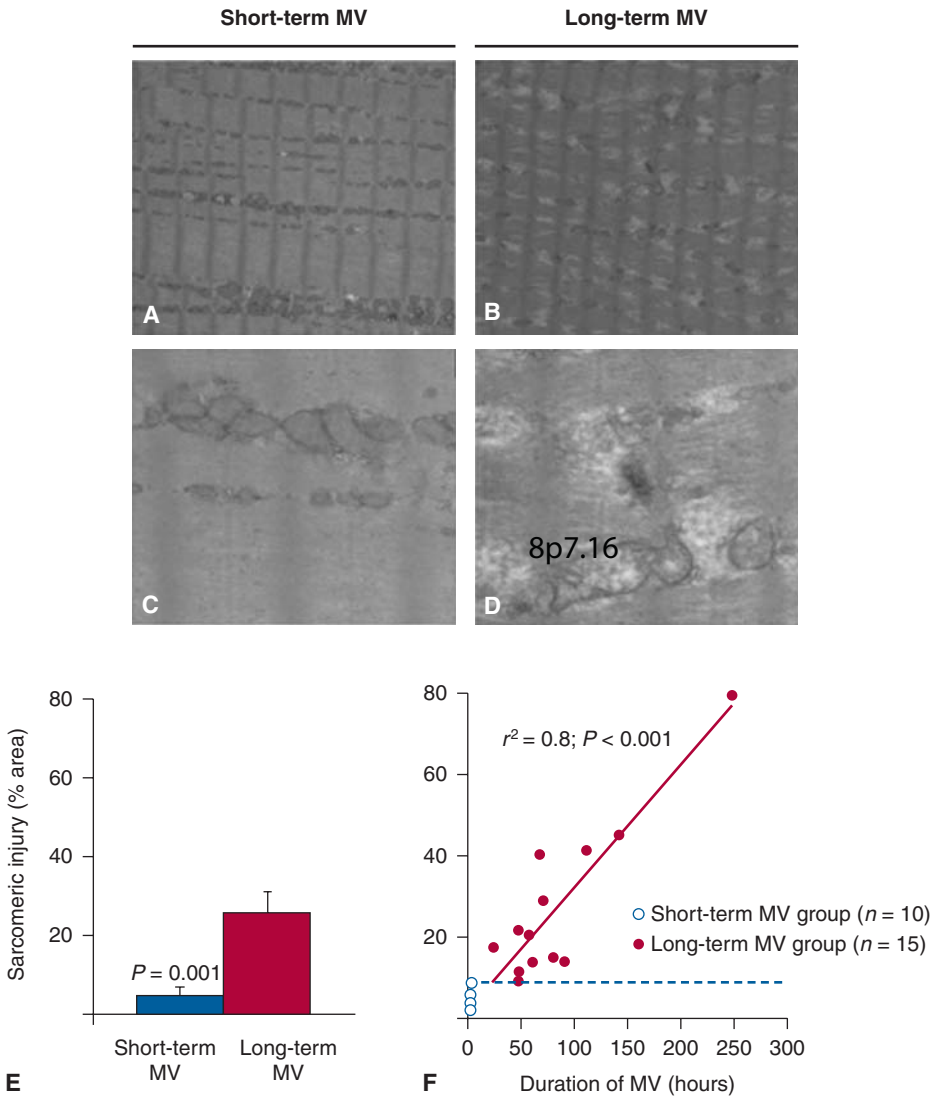

FIGURE 43-12 Relationship between duration of mechanical ventilation (*MV*) and diaphragmatic injury. Representative electron microscopy images of longitudinal ultrathin sections obtained from the diaphragms of the short-term MV (**A** and **C**) and long-term MV (**B** and **D**) groups are shown, at both low (A and B) and high (C and D) magnitude amplification. Note the disorganization of sarcomeric structure, which is only present in the long-term MV group images. **E.** Quantitative analysis of the prevalence of these findings in the two groups. **F.** Significant correlation between the degree of diaphragmatic injury and the duration of MV (*horizontal dashed line* indicates highest value of injury measured in short-term MV group). (Used, with permission, from Jaber et al.[6])

Several intriguing indirect data support this finding. Twitch Pdi elicited by magnetic stimulation of the phrenic nerves was reduced in mechanically ventilated patients[39] and in patients ready to undergo weaning trials,[38] as compared to normal subjects. Recently, Hermans et al[41] assessed diaphragmatic force production in twenty-five mechanically ventilated intensive care unit patients using cervical magnetic stimulation of the phrenic nerves in a prospective single-center study. Seven patients were evaluated more than once during their intensive care unit stay. A longer duration of mechanical ventilation was associated with more severe diaphragmatic force loss, irrespective of the ventilator mode used. Impairment of diaphragmatic force was also correlated with the amount of sedation the patients received. The authors, however, were unable to determine whether sedative use is an independent risk factor for diaphragmatic weakness in ventilated patients or simply a marker of more prolonged periods of mechanical ventilation. It should be emphasized that the above observations are not specific evidence for the presence of VIDD, because other factors can lead to muscle weakness in the intensive care unit and modes other than CMV were used. Nevertheless, VIDD may have contributed to the reduction in diaphragmatic contractility in the patients who received full ventilator support (CMV).

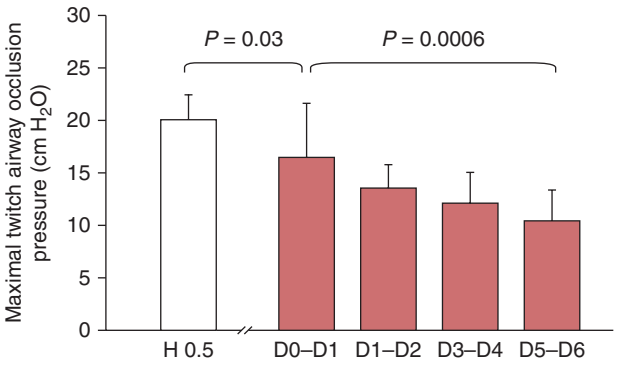

FIGURE 43-13 Relationship between duration of mechanical ventilation (MV) and diaphragmatic function. Maximal twitch airway occlusion pressure generated by magnetic stimulation of the phrenic nerves at different time points in short-term MV (*open bar*; $n = 6$) and long-term MV (*solid bars*; $n = 6$) groups. *D*, number of days of MV; *H*, number of hours of MV. (Used, with permission, from Jaber et al.[6])

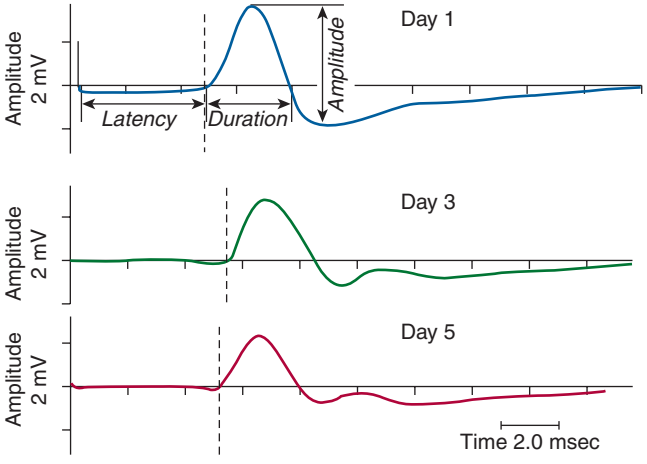

FIGURE 43-14 Neural and neuromuscular transmission to the diaphragm during experimental VIDD. The evoked compound muscle action potential (CMAP) tracings of the diaphragm upon electrical stimulation of the phrenic nerves in vivo from one piglet on days 1, 3, and 5 of CMV, respectively. The time from the stimulus to the onset of CMAP (latency) does not change after 3 to 5 days of CMV, whereas the amplitude of CMAP is progressively reduced. This indicates that the neural and neuromuscular transmission are not affected when VIDD develops and that the contractile dysfunction resides within the diaphragmatic myofibers. (Used, with permission, from Radell et al.[43])

MEASUREMENTS IN INTACT ANIMALS

CMV leads to decreased diaphragmatic force generating capacity in various animal species. In the intact diaphragm studied in vivo, Pdi generation upon phrenic nerve stimulation declines at all stimulation frequencies (20 to 100 Hz).[13,30,42,43] The decline ensues early (1 day in rabbits,[13] 3 days in piglets[30,43]) and is progressive: Pdi decreasing to 63% of the control value after 1 day of CMV and to 49% of the control value after 3 days of CMV in rabbits.[13] Within a few days (3 days in rabbits, 3 to 5 days in piglets, 11 days in baboons), the pressure-generating capacity of the diaphragm declines by 35% to 50%. The endurance of the diaphragm is also compromised.[42]

The decrease in force-generating capacity that ensues with CMV is not caused by changes in lung volume[30] or abdominal compliance.[42,43] Neural and neuromuscular transmission remain intact as evidenced by the lack of change in phrenic nerve conduction (latency) and stable response to repetitive stimulation of the phrenic nerve (Fig. 43-14).[43] In contrast, the compound muscle action potential declines progressively, suggesting that excitation–contraction coupling or membrane depolarization may be involved (Fig. 43-14).[43] Thus, the CMV-induced impairment in diaphragmatic force-generating capacity appears to reside within the myofibers.

IN VITRO MEASUREMENTS

The isometric (both twitch and tetanic) tension development by isolated diaphragmatic strips in vitro[10–12,43,44] confirm the in vivo findings and suggest that the decline in contractility is an early (12 hours) and progressive phenomenon,[44] the isometric force declining by 30% to 50% after 1 to 3 days of CMV in rats. The effects of CMV on diaphragm in vitro fatigability are controversial.

Drugs and Ventilator-Induced Diaphragm Dysfunction

All information regarding the role of drugs in the development of VIDD comes from animal models. Anesthetics can be excluded as causes of VIDD because studies that used appropriate controls (to the extent feasible, viz., a group of anesthetized spontaneously breathing animals) concluded that the decreased contractility was the result of mechanical ventilation per se (and not anesthetic use).[13]

Neuromuscular blockers[11,42] cannot solely account for the decreased contractility secondary to CMV, because decreased contractility was also observed in studies that did not use these drugs.[13,44] Nevertheless, the effects of 24 hours of CMV and aminosteroidal neuromuscular blockers (rocuronium) are synergistic in depressing diaphragmatic contractility, in inducing atrophy of type IIx/b fibers, and in upregulating the ubiquitin ligase (E3) muscle ring finger-1 (MuRF1) (but not the E3 muscle atrophy F-box/Atrogin-1)[29]—a synergism not observed with different doses of benzylisoquinoline neuromuscular blockers (cisatracurium).[45]

CLINICAL RELEVANCE

Clinical Context

VIDD should be suspected in patients who fail to wean after a period of CMV. The weaning failure is related to respiratory muscle weakness. Other causes of respiratory

muscle weakness should be ruled out,[46] although several may coexist with VIDD.

Ventilator-Induced Diaphragm Dysfunction Prevention

VENTILATOR STRATEGY

Because data in humans are lacking, suggestions are based on animal models and speculations. The time spent in CMV must be curtailed to the extent possible, especially in older individuals, because the effects of aging and CMV are additive.[47] Although CMV induced similar losses (24%) in diaphragmatic isometric tension in both young and old animals, the combined effects of aging and CMV resulted in a 34% decrement in diaphragmatic isometric tension as compared to young control animals.

When feasible, partial support modes should be used. Partial support modes can be used in conditions traditionally considered as indications for CMV, such as acute lung injury and/or acute respiratory distress syndrome[48,49] although complete CMV with the use of neuromuscular blockers in the first 48 hours of severe acute respiratory distress syndrome may be beneficial.[3] In a rabbit animal model, assisted (flow-triggered pressure limited) ventilation from the onset of ventilator support resulted in attenuation of the force loss induced by CMV (Fig. 43-15).[50] Similarly, adaptive support ventilation was able to prevent any deleterious effect of mechanical ventilation on the piglet diaphragm.[51] Thus, it stands to reason that preserving diaphragmatic contractions during mechanical ventilation should attenuate the force loss induced by CMV, although other forms of partial ventilator support (pressure support, synchronized intermittent mandatory ventilation) have not been experimentally tested. Pressure support was able to prevent increased proteolysis in the diaphragm when compared to CMV, although its effects on contractility were not reported.[52] It should be stressed that these suggestions originate from studies in healthy animals. The extent to which these same phenomena occur in critically ill patients with various diseases is not known. During sepsis in rats, albeit of short duration (4 hours), CMV protected the diaphragm against injury,[53] which raises the question about the effects of CMV on the diaphragm of septic (not healthy) humans.

Assisted modes or even noninvasive ventilation in hypercapnic patients with chronic obstructive pulmonary disease[54–56] is an alternative to the use of CMV in weaning-failure patients[57]—a strategy based on the premise that respiratory muscle fatigue (requiring rest to recover) is the cause of weaning failure.[58,59] Fatigue is expected to occur because the load that the respiratory muscles of weaning-failure patients is increased to the level that would predictably produce fatigue of the respiratory muscles[60] if patients were allowed to continue spontaneous breathing without ventilator assistance. Evidence, however, does not support the existence of low-frequency fatigue (the type of fatigue that is long-lasting, taking more than 24 hours to recover) in patients who fail to wean despite the excessive respiratory muscle load.[38] This is because physicians typically terminate a weaning trial and place a patient back on the ventilator before low-frequency fatigue has had time to develop. Thus, no reason exists to completely unload the respiratory muscles with CMV for fatigue reversal when weaning is typically terminated.[57]

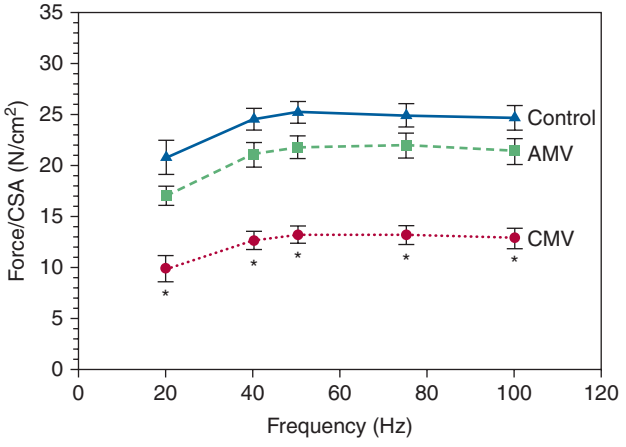

FIGURE 43-15 Diaphragmatic tetanic force at various stimulation frequencies in control, assisted mechanical ventilation (*AMV*), and controlled mechanical ventilation (*CMV*) in rabbits. Values are mean ± SE (standard error). *, $p < 0.01$, CMV versus control and AMV; *CSA*, cross-sectional area. (Used, with permission, from Sassoon et al.[50])

INTERMITTENT DIAPHRAGMATIC CONTRACTIONS

When CMV is inevitable, short periods of diaphragmatic activity have been suggested as preventive countermeasure. This could be achieved with either phrenic nerve stimulation or short periods of intermittent spontaneous breathing. As little as 30 minutes of pacing of one hemidiaphragm each day attenuated atrophy in this hemidiaphragm during prolonged CMV in a tetraplegic patient compared to the nonpaced hemidiaphragm.[61] In rats subjected to 24 hours of CMV, either 5 or 60 minutes of spontaneous breathing every 6 hours did not preserve diaphragmatic force. Rats receiving CMV developed reduced cross-sectional areas of type I and type IIx/b diaphragmatic fibers, which was not observed in intermittently spontaneously breathing rats, yet no difference was observed in the cross-sectional areas between the CMV and intermittently spontaneously breathing rats.[62] Whether more frequent or longer intervals of spontaneous breathing might be more effective in preventing VIDD awaits experimental proof.

PHARMACOLOGIC APPROACHES

Antioxidant supplementation could decrease oxidative stress and thus could attenuate VIDD. Accordingly, when

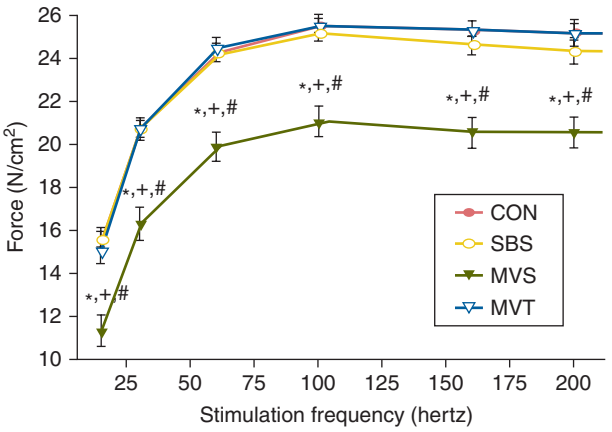

FIGURE 43-16 Force-frequency curves of in vitro diaphragm strips from control (*CON*), spontaneously breathing (*SBS*), mechanical ventilation (*MVS*), and mechanical ventilation animals receiving Trolox (*MVT*). Values represent means ± SEM (standard error of mean). *, Significantly different from CON group, $p < 0.05$; +, significantly different from SBS group, $p < 0.05$; #, significantly different from MVT group, $p < 0.05$. (Used, with permission, from Betters et al.[63])

rats were administered the antioxidant Trolox (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid, a water-soluble analog of vitamin E) (Fig. 43-16) or apocynin (a nicotinamide adenine dinucleotide phosphate oxidase inhibitor with antioxidant properties) from the onset of CMV, its detrimental effects on contractility and proteolysis were prevented.[63,64]

A similar approach is adopted by nature itself! Various dormant animals immobilized for prolonged periods of time prevent muscle atrophy through a decrease in metabolic rate that reduces reactive oxygen species formation, and a concomitant rise in antioxidant enzymes.[65,66] Interestingly, a combination of vitamins E and C administered to critically ill surgical (mostly trauma) patients was effective in reducing the duration of mechanical ventilation as compared to nonsupplemented patients.[67] It is tempting to speculate that part of this beneficial effect was mediated by preventing VIDD. Thus, when CMV is used, concurrent administration of antioxidants seems justified and a meta-analysis suggests that they are beneficial in critical care patients.[68]

Administration of leupeptin (an inhibitor of lysosomal proteases and calpain) at the beginning of CMV prevented the development of diaphragmatic contractile dysfunction and atrophy[20] in experimental animals. This raises the possibility of future clinical trials of protease inhibitors in patients to prevent VIDD.

Recovery from Ventilator-Induced Diaphragm Dysfunction

There is no established or experimentally tested therapy for VIDD. Theoretically, resumption of spontaneous breathing would retrain the respiratory muscles, yet the time course of recovery of normal function is unknown. A major concern is that diaphragmatic disuse associated with CMV would increase its susceptibility to subsequent contraction-induced injury once respiratory efforts are resumed, similar to other skeletal muscles.[69] Rats receiving 24 hours of CMV exhibited a 26% decline in maximal specific diaphragmatic force with no apparent injury to the cell membrane or evidence of inflammation.[70] Resumption of spontaneous breathing for 2 hours did not exacerbate contractile dysfunction in these rats or induce membrane injury or macrophage invasion.[70] Reloading, however, was associated with increased myeloperoxidase activity and neutrophil infiltration in the diaphragm, which is expected to cause injury at a later time point, if reloading were continued.[70] Further studies are needed to elucidate the recovery response of the diaphragm that has developed VIDD as spontaneous respiratory muscle activity is resumed.

IMPORTANT UNKNOWNS

All data on animal models of VIDD have been obtained in previously healthy animals. Human data also have been obtained in brain-dead organ donors who did not have severe infections. Thus, the extent to which the deleterious effects of CMV on diaphragmatic function and biology occur in critically ill patients is unknown.

Modes of partial ventilation support attenuate the deleterious effects of CMV in animal models of VIDD. Whether this is also the case in humans is a clinically important question. Furthermore, the actual amount of assist necessary to prevent VIDD is also unknown.

Pharmacologic approaches used successfully to prevent VIDD in animal models have not been tested in human trials. Thus, no drugs has demonstrated clinical efficacy in the prevention or treatment of human VIDD.

Once VIDD is suspected, the best approach is to reload the diaphragm with abrupt or gradual reduction in the level of ventilator assistance, although the optimal rate of assist reduction is not known.

THE FUTURE

Microarray analysis has identified 354 differentially expressed gene products in the diaphragms of animals subjected to CMV compared to control animals.[71] Intense research is required to unravel the mechanisms of VIDD. Animal models can be used to study the effects of CMV on the diaphragm of a critically ill organism, and to determine the best approach to reload the diaphragm once VIDD has developed. Clinical trials of different ventilator strategies (different levels of assist) and of pharmacotherapy to prevent VIDD should be designed and conducted. Finally, pharmacologic approaches for VIDD recovery are the next logical step of research in the field.

SUMMARY AND CONCLUSION

Over the last two decades researchers have discovered that mechanical ventilation can damage the previously normal respiratory muscles. CMV imposes a unique form of skeletal muscle disuse: The diaphragm is simultaneously unloaded, electrically quiescent, and phasically shortened by cyclical lung inflation or tonically shortened when PEEP is used. The respiratory muscles are not some inert mechanical pump that can be replaced cavalierly by the ventilator. The respiratory muscles should remain as active as possible because they are plastic and vulnerable.

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44

BAROTRAUMA AND BRONCHOPLEURAL FISTULA

Andrew M. Luks
David J. Pierson

This chapter considers the possible origins of extraalveolar air in ventilated patients and then reviews the manifestations and most frequent clinical settings of its various forms. After a discussion of general principles of management and a review of reported therapeutic approaches, it presents logical steps for prevention in susceptible patients and points out important gaps in the existing evidence base pertaining to this important topic. Although all the clinical forms of barotrauma are touched upon, most attention is devoted to those that pose a threat to life.

Only overt extraalveolar air is covered in this chapter. The reader is referred to Chapter 42 for a discussion of lung damage at the tissue or subcellular level related to mechanical lung distension and the application of positive pressure to the airways. Because data from laboratory studies are covered extensively in that discussion, this chapter deals primarily with barotrauma as a complication in patients, referring mainly to the adult clinical literature. As will be apparent, although the latter is replete with anecdotes and observational reports, this focus primarily on human data means that the evidence base in terms of prospective studies and "hard data" available to the clinician is remarkably limited. Spontaneous pneumothorax and other forms of extraalveolar air encountered in patients who are not intubated or receiving mechanical ventilation are not dealt with extensively here, nor is decompression-related barotrauma or bronchopleural fistula complicating lung resection.

DEFINITIONS

Pneumothorax, subcutaneous emphysema, and other clinical forms of extraalveolar air occurring in association with mechanical ventilation are commonly referred to as *barotrauma*. This term is doubly unfortunate, *trauma* connoting iatrogenic injury and *baro* implying that it is pressure, rather than volume, shear force, or some other factor that produces it. In fact, these implications of both roots of the word are probably incorrect, and the expression *ventilator-associated extraalveolar air* would be technically more appropriate. Similarly, the term *bronchopleural air leak* would be more accurate than *bronchopleural fistula*, because of the implications of inflammation and suppuration associated with the word *fistula* in surgical and other settings. Like *barotrauma*,

however, the latter is so ingrained in clinical usage that change is unlikely, and the more familiar terms are used in this chapter, as elsewhere in this book.

Although extraalveolar air appearing during ventilator support may not be caused by the ventilator itself, the expression *ventilator-induced lung injury* would seem as applicable to clinical barotrauma as to parenchymal damage associated with mechanical stretch and overdistension. Again, however, owing more to convention than to logical etymology, the term *ventilator-induced lung injury* is generally reserved for the latter, in this book and in the broader literature.

Usually, barotrauma in mechanically ventilated patients is automatically assumed to be a complication of mechanical ventilation. As with nosocomial pneumonia, however, ventilatory muscle dysfunction, and most of the other adverse developments to which ventilated patients are prone, whether the ventilator per se is responsible is usually unclear, because patients ill enough to require endotracheal intubation, supplemental oxygen, positive-pressure ventilation, and management in an intensive care unit (ICU) tend to have numerous other predispositions to such complications. Each of these things would be better thought of as complications *associated with*, rather than *of*, mechanical ventilation.[1,2]

TABLE 44-1: POSSIBLE ORIGINS OF EXTRAALVEOLAR AIR

Upper respiratory tract
Fractures of facial bones, mandible, etc.
Other traumatic mucosal disruption
Dental extractions and other oral surgical procedures
Intrathoracic airways
Airway rupture or laceration in blunt or penetrating chest trauma
Complications of intubation or airway instrumentation
Foreign body in upper or lower airways
Bronchoscopy-related procedures (e.g., transbronchial biopsy, bronchial brushing, or transbronchial needle aspiration)
Lung parenchyma
Penetrating trauma
Surgical procedures
Diagnostic procedures as above
Thoracentesis
Percutaneous needle aspiration or biopsy
Alveolar rupture
Gastrointestinal tract
Perforation of esophagus or abdominal viscus
Infection with gas-producing organisms
Pleural empyema
Acute mediastinitis
Necrotizing fasciitis or other soft-tissue infection
Exogenous source (air from outside the body)
Penetrating trauma
Thoracentesis or closed pleural biopsy
Surgical procedures (e.g., chest tube insertion, tracheotomy, or mediastinoscopy)

PATHOPHYSIOLOGY

Mechanism of Alveolar Disruption

Barotrauma in a patient receiving positive-pressure ventilation has a number of potential causes (Table 44-1).[3] Most often extraalveolar air during mechanical ventilation results from overdistension of alveoli and rupture of their walls down a pressure gradient from airspace into bronchovascular sheath, as illustrated in Figure 44-1.[4] This mechanism was worked out many years ago in elegant animal experiments by C.C. and M.T. Macklin:[5,6] "…pulmonic interstitial emphysema and its sequelae—air in the mediastinum, peritoneal cavity, subcutaneous tissues, and pleural cavity—are present in many conditions; differing widely in their cause, their clinical manifestations and their seriousness. All of these conditions, however, have a single common factor, a gradient of pressure between the alveoli and vessel sheath, and hence an opportunity for air to gain access to the interstitial tissues of the lung."[6]

According to the work of the Macklins,[5,6] the basic requirement for alveolar rupture is the presence of a pressure gradient between the alveoli and their surrounding structures. Interalveolar walls are probably not susceptible to such pressure gradients, as they are very thin and the pressures between adjacent alveoli are probably equal. Any sudden increase in alveolar pressure (or presumably a fall in perivascular interstitial pressure), however, may establish a gradient sufficiently large to disrupt alveolar walls at their bases (see Fig. 44-1), introducing air into the pulmonary interstitium. Alveolar overdistension would tend to thin and stretch the alveolar membranes, facilitating rupture once the pressure gradient was established. This mechanism can readily be understood in the case of extraalveolar air following sudden deceleration injury, such as falling into water from a height,[7] but it likely is the main means of alveolar rupture in the majority of other clinical settings as well.[3,4,8]

Spread of extraalveolar air via bronchovascular sheaths after alveolar rupture was dramatically demonstrated by Jamadar et al when pneumomediastinum developed in a patient undergoing liquid ventilation.[9] After the liquid medium was removed from the bronchial tree and alveoli, computed tomography of the chest demonstrated persistence of the radiopaque perfluorocarbon fluid in the bronchovascular sheaths, confirming the mechanism elucidated a half-century earlier by the Macklins.

Other Possible Sources of Extraalveolar Air

Beyond clinical barotrauma that occurs as a direct complication of mechanical ventilation, it is important to be cognizant of other possible sources not related to the ventilator itself (Table 44-2).[3,8] Distinguishing these causes from barotrauma secondary to mechanical ventilation itself may be challenging in some circumstances, particularly when adequate clinical history is lacking. Pneumothorax appearing within the first few hours following initiation

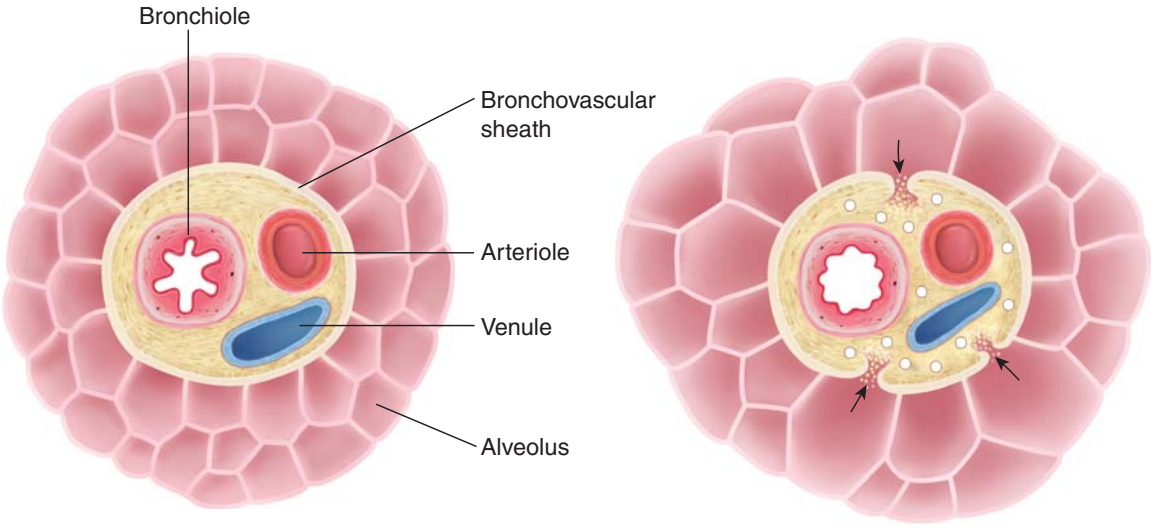

FIGURE 44-1 Mechanism of alveolar rupture during mechanical ventilation. Pressures between adjacent alveoli equalize rapidly, but, especially in the presence of high alveolar volume, increased alveolar pressure, in comparison with that in the adjacent bronchovascular sheath, establishes a pressure gradient that may result in rupture of the alveolar wall, allowing passage of air into the interstitial tissue of the bronchovascular sheath. (Used, with permission, from Maunder et al.[4])

of mechanical ventilation may be the result of previous trauma, overinflation during manual ventilation, or procedures such as central line attempts before intubation. Even in patients already receiving ventilator support, the appearance of extraalveolar air may represent "pseudobarotrauma"—external trauma to the lung from attempts at placing central venous access or various endoscopic procedures—rather than "spontaneous" alveolar rupture.

TABLE 44-2: POSSIBLE MECHANISMS FOR "BAROTRAUMA" IN MECHANICALLY VENTILATED PATIENTS

- Airway disruption or alveolar rupture before initiation of ventilatory support
  - Trauma (penetrating or blunt)
  - Resuscitation (mouth-to-mouth or manual ventilation)
  - Airway laceration or perforation during intubation attempts
  - Attempted central line placement (e.g., via the internal jugular or subclavian route)
  - Biopsy or surgical procedure
- Direct laceration of visceral pleura or airway during mechanical ventilation ("pseudobarotrauma")
  - Central line placement
  - Thoracentesis or chest tube placement
  - Transbronchial biopsy or bronchial brushing
- "Spontaneous" alveolar rupture
  - Manifestation of a primary disease process
  - Complication of ventilator-associated pneumonia or sepsis
  - Inadvertent alveolar overdistension (e.g., right main bronchus intubation or manual ventilation)
  - Related to ventilator management per se (e.g., tidal volume, positive end-expiratory pressure, recruitment maneuvers, or breath-stacking)

Air originating in the upper respiratory tract can dissect downward from the head and neck and produce subcutaneous emphysema, pneumomediastinum, and conceivably even pneumothorax. During mechanical ventilation, this could occur in the presence of negative intrathoracic pressure, as with vigorous efforts against a partially occluded airway or in severe patient–ventilator dyssynchrony. Reported causes of pneumomediastinum from air dissection from above include facial or mandibular fractures,[10] retropharyngeal abscess,[11] and dental extractions, particularly if these involve the lower molar teeth and air-turbine drilling.[12]

Mediastinal air and other barotrauma can also originate in the intrathoracic airways, as after blunt or penetrating chest trauma,[13,14] as a complication of bronchoscopic procedures, during percutaneous dilatational tracheotomy,[15] or from perforation by a foreign body. Injury to the upper airway or laceration of the posterior membranous trachea may occur during attempted endotracheal intubation, particularly when a stylet is used, and this has been associated with clinical barotrauma in numerous reports.[16–20]

Endoscopic procedures[21–23] and other interventions may rupture or perforate the esophagus, providing access for air into the mediastinum. In many instances, but not always, signs of mediastinitis accompany the appearance of pneumomediastinum following esophageal procedures.[8] Air in the mediastinum is also a characteristic feature of Boerhaave syndrome,[24] and the typical history of vigorous retching after a large meal may be absent.

Most often the origin of clinical barotrauma is the lung parenchyma, but even then the mechanism may be other than "spontaneous" alveolar rupture. Other possibilities include penetrating trauma that lacerates pulmonary tissue, surgical procedures involving the intrathoracic structures, bronchoscopic procedures, and transthoracic needle

aspiration. When acute mediastinitis or pleural empyema involves gas-producing organisms, palpable or radiographically detectable extraalveolar air may result; gas arising from soft-tissue infections such as clostridial gangrene may also be confused with barotrauma.

Finally, exogenous air may find its way into the pleural space, subcutaneous tissues, or mediastinum. Most commonly this occurs during or following thoracentesis, chest tube insertion, tracheotomy,[25] or mediastinoscopy. Rarely, air may enter the soft tissues following cutaneous injury to an extremity[26] or elsewhere in the body, producing subcutaneous emphysema that could be confused with barotrauma.

Airway Pressure versus Alveolar Distension

For many years, a primary goal of mechanical ventilation was to limit peak airway pressures, based on the belief that high peak airway pressures were a primary mediator of barotrauma.[27–31] The desire to avoid high peak airway pressures was a main driver in the introduction of pressure-targeted modes of ventilation and the different forms of high-frequency ventilation.[3] As discussed in Chapter 42, however, a large body of evidence now supports the conclusion that it is excessive volume, not airway pressure per se, and especially not peak airway pressure measured outside the patient, that primarily determines the occurrence and severity of ventilator-induced lung injury.

Peak airway pressure during mechanical ventilation can be influenced by a number of factors (Table 44-3), most of which do not affect (or reflect) alveolar volume. This can readily be understood by envisioning the various potential sources for high peak airway pressure as sensed at the ventilator's manometer. Increased resistance to airflow in the ventilator circuit or endotracheal tube, or in the patient's conducting airways, will be reflected in an increased peak inspiratory airway pressure. Likewise, an increase in chest wall pressure, as with coughing, chest strapping, or massive generalized edema, will increase peak airway pressure without increasing transalveolar pressure or alveolar volume. Even increased pressure at the alveolar level should not cause disruption of alveolar walls unless this pressure is unevenly distributed between adjacent alveoli or between alveoli and the adjoining bronchovascular sheath.

This conclusion becomes obvious when one considers the common activities that markedly raise peak airway pressure without causing alveolar rupture.[3] Normal persons routinely generate peak airway pressures up to 200 cm H_2O or more during a cough or sneeze.[32] In a study of fifty-six normal male subjects ranging in age from 6 to 64 years, Cook et al[33] found their mean individual maximum peak expiratory airway pressures to be 237 ± 45 cm H_2O. In that study, the subjects sustained these pressures for at least 1 to 2 seconds, and even longer periods of sustained high peak airway pressures can be maintained during the Valsalva maneuver, during which pressures as high as 200 torr (286 cm H_2O) have been documented.[34] Airway pressures well above 100 cm H_2O are routinely achieved and held by trumpet players[35] without causing barotrauma. Alveolar rupture is extremely rare in wind instrument players, as it is in glass blowers, weight lifters, and other healthy people after coughing, sneezing, or straining.[3,36]

TABLE 44-3: POSSIBLE CAUSES OF HIGH PEAK AIRWAY PRESSURE DURING MECHANICAL VENTILATION

High inspiratory flow (increases proximally measured peak airway pressure at any given total airway resistance)
High resistance in the ventilator circuit or endotracheal tube
Inspissated secretions
Smaller-than-usual endotracheal or tracheostomy tube
Kinking
Obstructed distal orifice
High resistance in the patient's airways
Bronchospasm
Secretions
Airway edema
Neoplasm, stenosis, or foreign body in trachea or main bronchus
Alveolar overdistension
Decreased compliance of the lung parenchyma
High pleural or transthoracic pressure
Coughing
Agitation, shivering, or seizures
Splinting as a consequence of chest wall pain
Pneumothorax or pleural effusion
Ascites or abdominal packs or binding
Head-down position
Bandages, casts, or restraints
Other causes of intraabdominal hypertension or reduced chest wall compliance

In addition, for any given airway resistance, varying inspiratory flow will also vary the pressure developed as a given volume is delivered to a patient's lungs, but will not affect end-inspiratory alveolar pressure. For any given volume-targeted inspiratory waveform, shortening inspiratory time will increase peak airway pressure but will not affect overall lung distension if the set tidal volume is unchanged; in fact, higher proximal airway pressures will decrease delivered alveolar volume because of increased compressed volume in the tubing. Conversely, increasing inspiratory time will lower peak airway pressure but could even increase alveolar distension over a series of breaths if insufficient time were provided for complete exhalation, resulting in air-trapping and endogenous positive end-expiratory pressure (auto-PEEP).

It should be remembered that peak inspiratory pressure can also be increased as a result of problems with respiratory system compliance such as low pulmonary parenchymal compliance caused by acute respiratory distress syndrome (ARDS) or pulmonary edema, chest wall problems such as circumferential burns or chest wall edema, and abdominal distension. Such situations will be reflected in an elevated plateau pressure. If this value is high relative to the pressure outside the lung parenchyma—a question

that can be sorted out using esophageal manometry[37]—the transpulmonary pressure difference will be high and the patient may be at increased risk for barotrauma. High plateau pressures in the setting of increased extrapulmonary pressure, on the other hand, will be associated with a small transpulmonary pressure difference and a lower risk of alveolar rupture.

The Importance of Ventilator Mode and Other Settings

To date, no studies have definitively established that the particular ventilator mode or other ventilator settings such as tidal volume or PEEP affect the incidence of barotrauma. The lack of effect secondary to tidal volume in conventional volume-control ventilation can best be seen by comparing the incidence of barotrauma in the era before and after the widespread adoption of lung-protective ventilation in patients with ARDS. In six large series published between 1974 and 1983, including data from 2980 mechanically ventilated patients, the incidence of detectable extraalveolar air ranged from 4% to 11%, with most in the range of 5% to 7%.[28,30,38–41] Although some patients with acute lung injury and ARDS were included in these series, barotrauma was not specifically examined in those conditions. As Tables 44-4 and 44-5 demonstrate, the incidence of barotrauma has not declined significantly since lung-protective ventilation became a part of clinical practice, despite a general impression that this complication is now encountered less frequently than in the past.[42]

In trials comparing low and high tidal-volume strategies,[43–48] as well as trials in which both arms were managed with lower tidal volumes,[49–53] the incidence of barotrauma does not differ significantly from that documented in earlier periods. Further support for a lack of a role for tidal volume comes from studies that examined risk factors for the incidence of barotrauma, which revealed that tidal volume had no significant effect.[47,54,55]

It is not clear whether other, less commonly used modes of ventilation affect the incidence of barotrauma. Several studies on the use of high-frequency oscillatory ventilation in acute respiratory failure, for example,[56–58] have documented incidence rates of pneumothorax or barotrauma of 8% to 9%, although a retrospective review of high-frequency oscillatory ventilation use at three centers in Toronto documented a much higher incidence rate of 21.8%.[59] A randomized trial comparing airway pressure release ventilation to conventional volume-targeted lung-protective ventilation, in patients with acute respiratory failure following trauma, found no difference in the incidence of barotrauma with the two approaches.[60]

The use of noninvasive ventilation has increased substantially in recent years, particularly for the management of acute exacerbations of chronic obstructive pulmonary disease. One report suggests the incidence of barotrauma is less than 5% with this modality,[61] but, overall, less data are available on this question compared to the other support modalities.

By increasing alveolar distension, increased levels of PEEP might be expected to cause more barotrauma. As with tidal volume, however, no studies have established a strong relationship in this regard. Eisner et al[62] examined 718 patients enrolled in the ARDS Network clinical trials and found that higher levels of PEEP correlated with increased likelihood of developing clinical barotrauma during the first 4 days

TABLE 44-4: INCIDENCE OF BAROTRAUMA IN RANDOMIZED TRIALS COMPARING LOW AND HIGH TIDAL VOLUME STRATEGIES IN PATIENTS WITH ACUTE RESPIRATORY DISTRESS SYNDROME

Study (Reference)	Tidal Volume Used in High Tidal Volume Group (N)	Tidal Volume Used in Low Tidal Volume Group (N)	Incidence of Barotrauma in High Tidal Volume Group: N(%)	Incidence of Barotrauma in Low Tidal Volume Group: N(%)
Amato et al[44]	12 mL/kg (24)	≤6 mL/kg (29)	10 (42)[b]	2 (7)
Brochard et al[45]	10 to 15 mL/kg[b] (58)	6 to 10 mL/kg (58)	7 (12)[c]	8 (14)
Stewart et al[47]	10 to 15 mL/kg[a] (60)	≤8 mL/kg (60)	4 (7)[d]	6 (10)
Brower et al[46]	10 to 12 mL/kg[a] (26)	≤8 mL/kg (26)	1 (3.8)[e]	2 (7.7)
ARMA Study[43]	12 mL/kg[a] (432)	<6 mL/kg (429)	48 (11)[e]	43 (10)
Villar et al[48]	9 to 11 mL/kg[a] (50)	5 to 8 mL/kg (53)	4 (8.4)[f]	2 (4)
Total	**(650)**	**(655)**	**74 (11.4)**	**64 (9.6)**

Tidal volume based on actual weight minus estimated weight gain secondary to water and salt retention.

[a]Tidal volume based on predicted body weight.

Definitions of barotrauma used in included studies:

[b]Pneumothorax, pneumomediastinum, and subcutaneous emphysema.

[c]Pneumothorax requiring a chest tube.

[d]Pneumothorax, pneumomediastinum, pneumoperitoneum, or pneumopericardium on chest radiograph.

[e]Pneumothorax, pneumomediastinum, pulmonary interstitial emphysema, or pneumatocele ≥2 cm within 28 days of randomization.

[f]Not defined.

(relative hazard: 1.5), although the 95% confidence interval included 1 (0.98 to 2.3). More recently, two large randomized studies[49,51] comparing the use of high and low PEEP strategies in patients with ARDS ventilated at low tidal volumes (≤6 mL/kg predicted body weight) showed no significant differences in the incidence of barotrauma. Even if data did suggest an association between PEEP and increased risk of barotrauma, this finding could be interpreted in two ways: either higher levels of PEEP predispose to barotrauma, or sicker patients (who require higher levels of PEEP) are more likely to develop barotrauma.

End-inspiratory plateau pressure is another variable that could affect alveolar distension and, therefore, the risk of barotrauma, but consistent evidence of such a link is also lacking. Boussarsar et al[54] reviewed the findings of eleven studies (2270 patients) that reported the incidence of barotrauma in patients with ARDS and noted that end-inspiratory plateau pressure was the only ventilator management-related variable that correlated statistically with the occurrence of barotrauma. In an international study of 5183 mechanically ventilated adult patients with a wide variety of diagnoses, however, Anzueto et al[63] found no correlation between any ventilator setting or pressure measurement and the development of barotrauma; several recent large randomized trials of ventilator management in ARDS in which plateau pressures were different between the two arms of the study showed no differences in barotrauma incidence (see Table 44-5).[43,51,52] One reason why plateau pressure may not be convincingly related to the risk of barotrauma may be because plateau pressure represents the difference between pressure in the airways and the atmosphere and, hence, total respiratory system compliance, whereas the risk of barotrauma is more a function of the pressure difference between the alveoli and bronchovascular sheath. Plateau pressure may be high but if this is caused by factors outside the lungs, such as increased abdominal distension or chest wall edema, the elevated pressures may not lead to alveolar rupture.

THE IMPORTANCE OF PROPER MANUAL (BAG) VENTILATION

A circumstance in which tidal volumes and airway pressures are delivered substantially above desirable levels is manual (bag) ventilation, an adjunctive ventilation method used immediately following intubation, during cardiopulmonary resuscitation, in association with airway suctioning, and chest physiotherapy, and during patient transport.[64] The volumes delivered and the pressures generated are typically not monitored and can vary substantially, depending on the size of the operator's hands, whether one hand or two is used, and other factors. Tidal volumes during manual ventilation ranged between 838 mL and 1674 mL in one study, with a mean value of 170% of the ventilator's set tidal volume.[65] In a bench study, in which experienced respiratory therapists performed manual ventilation on a lung model to simulate ventilating a 70-kg patient, delivered tidal volumes varied from 400 mL to more than 1000 mL, with airway pressures

TABLE 44-5: INCIDENCE OF BAROTRAUMA IN MULTICENTER RANDOMIZED TRIALS IN WHICH BOTH GROUPS OF PATIENTS RECEIVED LUNG-PROTECTIVE VENTILATION

Study (Reference)	Control Group (N)	Intervention Group (N)	Incidence of Barotrauma in Control Group: N(%)	Incidence of Barotrauma in Intervention Group: N(%)
Brower et al[49]	Low PEEP (273)	High PEEP (276)	27 (10)[b]	30 (11)
Mancebo et al[50,a]	Supine ventilation (60)	Prone ventilation (76)	4 (6.7)[c]	7 (9.2)
Meade et al[51]	Conventional PEEP; plateau pressure <30 cm H_2O (508)	High PEEP; plateau pressure <40 cm H_2O (475)	47 (9.1)[c]	53 (11.2)
Mercat et al[52]	PEEP 5 to 9 cm H_2O (382)	PEEP set to reach plateau pressure 28 to 30 cm H_2O (385)	22 (5.8)[d]	26 (6.8)
Papazian et al[53]	No paralysis (162)	48 hours of paralysis with *cis*-atracurium (177)	19 (11.7)[e]	9 (5.1)
Total	**(1385)**	**(1389)**	**119 (8.6)**	**125 (9.0)**

Abbreviation: PEEP, positive end-expiratory pressure.

All trials used predicted body weight to determine the tidal volume.

[a]Patients in this trial were allowed to receive up to 10 mL/kg in the control (supine) and intervention (prone) arms. Average tidal volumes delivered were 8.6 ± 1.6 mL/kg in the supine group and 8.3 ± 1.7 mL/kg in the prone group.

Definitions of barotrauma used in included studies:

[b]Pneumothorax, pneumomediastinum, pulmonary interstitial emphysema, or pneumatocele ≥2 cm within 28 days of randomization.

[c]New pneumothorax, pneumomediastinum, pneumoperitoneum, or subcutaneous emphysema on chest radiograph or chest tube insertion for known or suspected spontaneous pneumothorax.

[d]Pneumothorax, defined as needing a chest tube between days 1 and 28 of the study.

[e]Pneumothorax, pneumomediastinum, subcutaneous emphysema, or pneumatocele ≥2 cm within 28 days of randomization.

sometimes exceeding 100 cm H_2O.[66] Indeed, the development of clinical barotrauma during manual ventilation has been reported several times.[67–69]

The Importance of the Underlying Disease Process

The occurrence of alveolar rupture during mechanical ventilation is influenced markedly by the presence and nature of underlying lung pathology. Barotrauma is rare in patients with normal lungs—for example, in routine postoperative ventilation[39] or in paralytic states such as high cervical spinal cord injury or Guillain-Barré syndrome. In contrast, barotrauma is more common in patients with underlying obstructive or restrictive lung disease.[42,63] In an observational cohort study of 5183 patients who underwent mechanical ventilation for more than 12 hours in 361 ICUs in twenty countries,[70] barotrauma was observed in 154 patients (2.9%).[63] The incidence of barotrauma, defined as pulmonary interstitial emphysema, pneumothorax, pneumomediastinum, pneumoperitoneum, or subcutaneous emphysema, was 2.9% in patients with chronic obstructive pulmonary disease, 4.2% in pneumonia, 6.3% in asthma, 6.5% in ARDS, and 10.0% in chronic interstitial lung disease.[63] Logistic regression analysis identified the last three of these conditions as independent risk factors for development of barotrauma. An earlier analysis by Gammon et al[71] of 168 consecutive patients who underwent mechanical ventilation at one center found with multivariate analysis that of all variables examined, only the presence of ARDS correlated with development of pneumothorax.

The Spread of Extraalveolar Air Once Alveolar Rupture Occurs

Because pressures in the interstitium and bronchovascular sheath tend to be slightly less than those in the alveoli at peak lung inflation, there is a tendency for air to move into these areas once the alveolar walls are disrupted.[4–6] Although this is also accepted as the mechanism of the spread of extraalveolar air in spontaneously breathing patients, it is particularly facilitated by positive-pressure ventilation, especially when large tidal volumes are used. Figure 44-2 depicts the possible routes of spread once air leaves the alveolus. Except for systemic air embolism, which is uncommon, and pulmonary interstitial emphysema, the common pathway for all the clinical forms of barotrauma is pneumomediastinum.[8] Once in the mediastinum, air follows the path of least resistance and may rupture through the delicate mediastinal fascia and overlying pleura into the pleural space. Why this occurs in some patients and not in others may be determined by local pleural scarring in some cases, but is usually not readily apparent.

The spread of extraalveolar air to a wide variety of locations in the body can be understood through reference to the fascial planes of the neck, mediastinum, and retroperitoneum, as shown in Figure 44-3.[4] Three distinct cervical

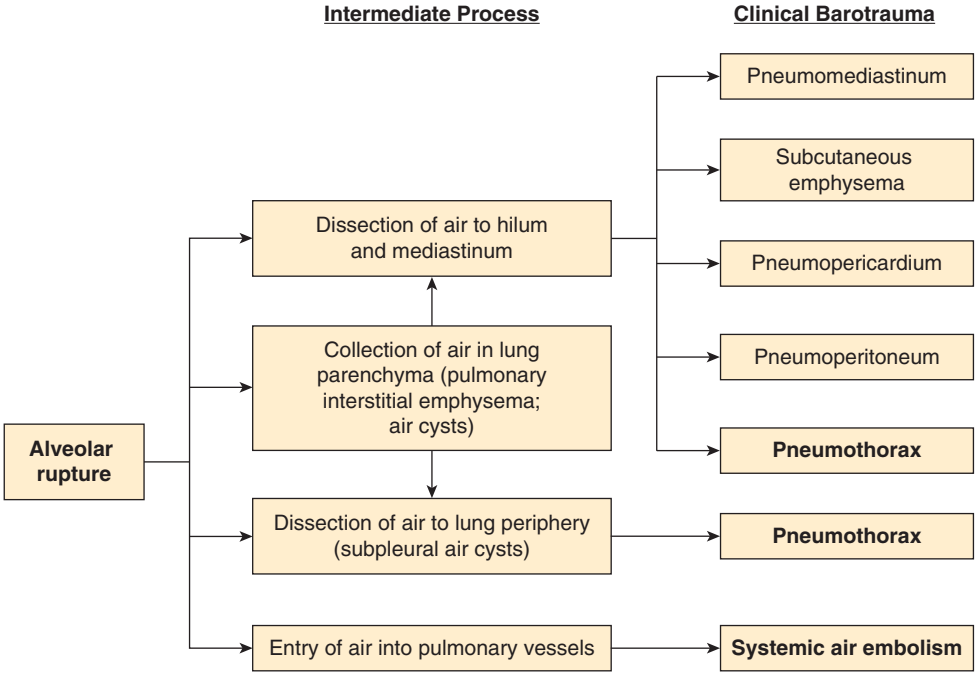

FIGURE 44-2 Pathogenesis of the various forms of barotrauma, with those of greatest clinical importance in bold type. In addition to being associated with use of mechanical ventilation, pneumothorax can also occur as a result of puncture or laceration of the visceral pleura during central line placement or other procedures or traumatic injuries such as rib fractures.

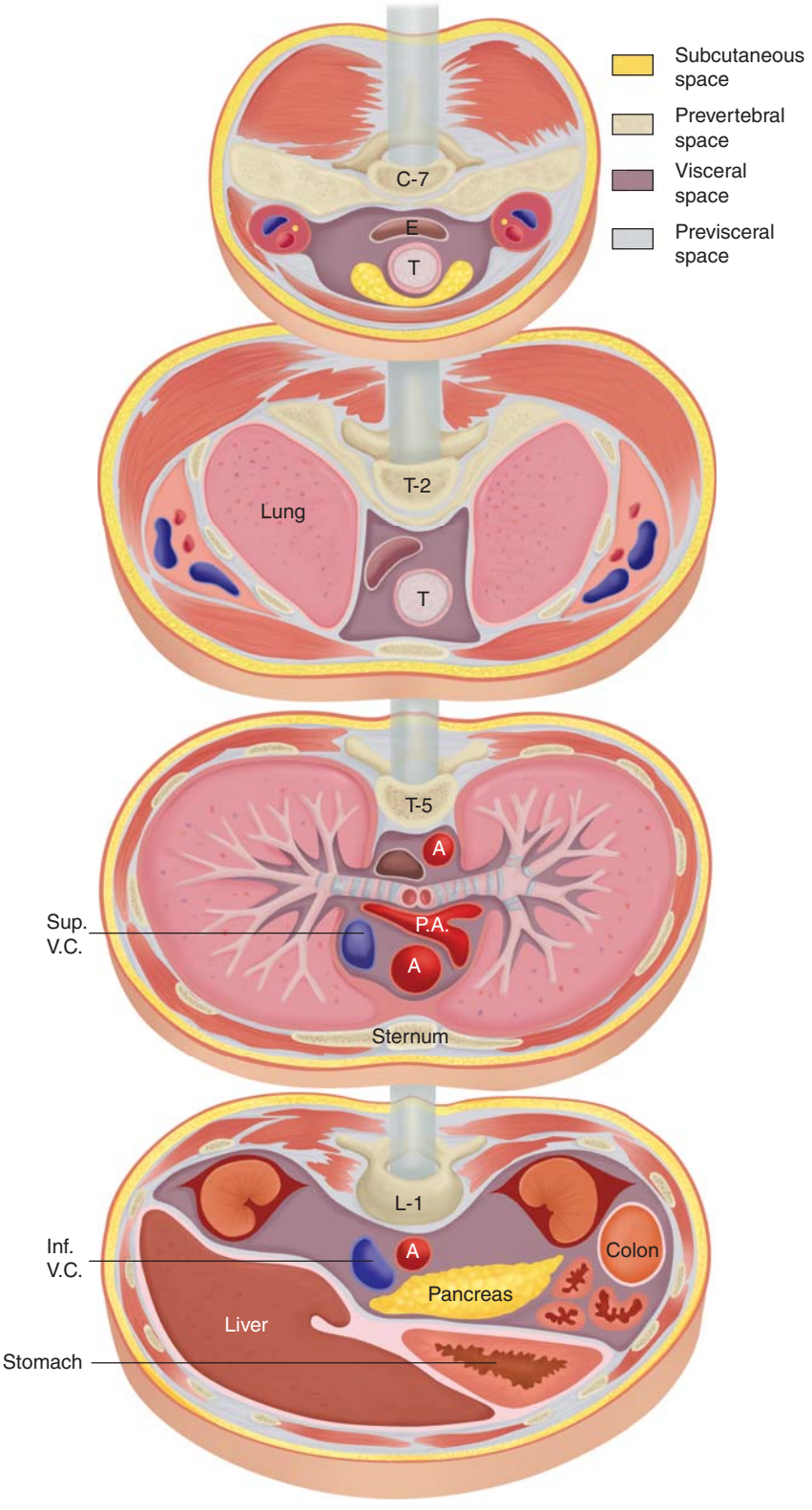

FIGURE 44-3 Fascial planes of the neck, mediastinum, and retroperitoneum, as depicted at the levels of C-7, T-2, T-5, and L-1, respectively. Because the soft-tissue compartments are continuous, air can dissect into a wide variety of anatomic locations. (Adapted, with permission, from Maunder et al.[4])
Abbreviations: A, aorta; E, esophagus; inf.V.C., inferior vena cava; P.A., pulmonary artery; Sup.V.C., superior vena cava; T, trachea.

compartments exist—a previsceral space lying between the deep cervical fascia and the pretracheal fascia, a visceral space lying between the pretracheal fascia and the prevertebral fascia, and a prevertebral space situated behind the prevertebral fascia. These cervical compartments continue via the mediastinum through the thorax and trunk, providing the potential for the spread of air into the retroperitoneal space.

Air may continue to leave the airways, as shown in Figure 44-1, so long as the alveolar rent is large enough and a sufficient pressure gradient exists. If this path of least resistance leads up the mediastinum and into the soft tissues of the neck and upper chest, subcutaneous emphysema may become massive, spreading extensively over the body. Occasionally the pressure gradient and local anatomy favor passage of air into the retroperitoneal space, from which it decompresses into the peritoneum,[72–76] causing massive abdominal distension. When the extraalveolar air has reached the pleural cavity, the resultant pneumothorax may rapidly increase with successive positive-pressure breaths. Air readily leaves the torn alveolus and passes into the pleural space, but cannot return between inspirations because of the collapsibility of the lung and mediastinum. A ball-valve mechanism is created and fatal tension pneumothorax can rapidly result. Figure 44-4 depicts examples of the various forms of barotrauma that can result from these mechanisms.

Bronchopleural Fistula

After evacuation of a pneumothorax via tube thoracostomy, air may continue to leak into the pleural space and via external suction into the pleural collection device. Such a bronchopleural air leak tends to be perpetuated by the very measures often required to reinflate the collapsed lung and to maintain gas exchange in patients with severe acute respiratory failure. Once a rent exists at either the alveolar or visceral pleural level, the higher the pressure gradient between airways and pleural space, the greater will be the tendency of the bronchopleural fistula to leak. It therefore stands to reason that management should focus on decreasing airway pressure and minimizing pleural suction. As discussed later (see the section Management: Bronchopleural Fistula), however, little experimental evidence is at hand to support this hypothesis, and the management needs of critically ill patients often prevent the realization of these goals.

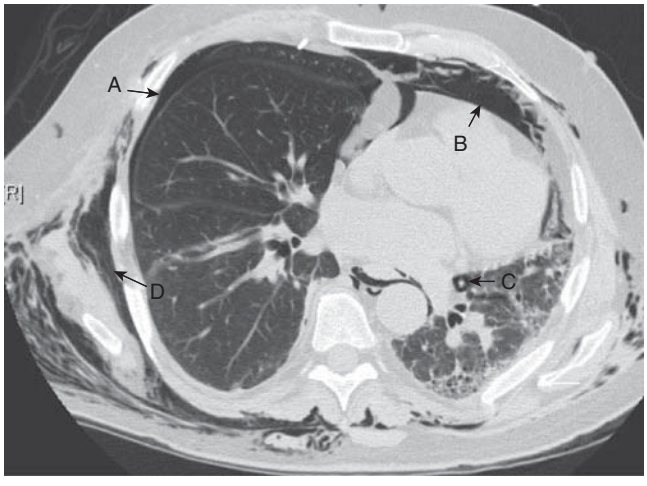

FIGURE 44-4 Computed tomography image through midchest showing multiple manifestations of pulmonary barotrauma in the same patient including: (**A**) pneumothorax; (**B**) pneumomediastinum; (**C**) pulmonary interstitial emphysema represented by a halo of air surrounding a vascular structure; and (**D**) subcutaneous emphysema.

CLINICAL MANIFESTATIONS

The different clinical forms of barotrauma shown in the right-hand column in Figure 44-2 vary considerably in their clinical manifestations, relative frequency, and potential for doing harm to the patient. Table 44-6 lists the nine categories of extraalveolar air that are discussed in the remainder of this chapter, and shows their relative frequency in ventilated patients, along with their relative seriousness and potential threat to life. With few data from prospective studies of the incidence of the different forms of barotrauma across the broad range of patients managed on mechanical ventilation, the frequencies listed in Table 44-6 are based on the our clinical experience and what little information can be gleaned from the literature. Tension pneumothorax and systemic air embolism are always potentially fatal events. Beyond these, however, the effects of barotrauma on survival, organ dysfunction, ICU stay, and other outcomes, separate from those of the underlying disease, are largely unknown.

Pulmonary Interstitial Emphysema and Cystic Dilation

Air in the interstitium of the lung can be identified at autopsy in patients who die with clinical barotrauma associated

TABLE 44-6: CLINICAL FORMS OF BAROTRAUMA DURING MECHANICAL VENTILATION

Form	Relative Frequency	Potential Threat to Life
Pulmonary interstitial emphysema	++++	+
Intraparenchymal air cysts	++	++
Pneumomediastinum	++++	++
Pneumopericardium	+	+++
Subcutaneous emphysema	+++	+
Pneumoperitoneum	+	++
Systemic air embolism	+	++++
Pneumothorax	+++	++++
Bronchopleural fistula	++	++

with positive-pressure ventilation, and is easily demonstrated using computed tomography (CT) scanning (see C in Fig. 44-4).[77–79] With appropriate technique pulmonary interstitial emphysema may also sometimes be detected on plain radiographs of the chest, and be present without other signs of extraalveolar air.[80,81] A variety of patterns have been described.[81] Parenchymal stippling, thought to represent multiple small pulmonary vessels and their air-distended vascular sheaths in cross section, has been referred to as a "salt-and-pepper" pattern.[80] Air dissection within the pulmonary interstitium is believed responsible for lucent mottling,[81] with small cyst-like lucencies that may increase progressively in size on successive films. Other signs of pulmonary interstitial emphysema include lucent streaks, believed to be produced by air dissecting toward the hilum along the course of larger pulmonary vessels, and perivascular halos in the perihilar regions of the lung, representing such air collections seen end-on. All these signs are most readily seen in the presence of diffuse pulmonary consolidation or atelectasis, which increases the radiographic contrast between parenchyma and extraalveolar air.

Although it is well-defined pathophysiologically (see Figs. 44-1 and 44-2), pulmonary interstitial emphysema in mechanically ventilated adult patients has doubtful practical clinical importance, primarily because of the realities of bedside imaging in the ICU. Several older studies described pulmonary interstitial emphysema in critically ill patients,[30,31,82–84] and in some instances it has been shown to precede the development of pneumothorax. The subtle changes identifying this entity, however, are beyond the resolution of most bedside radiologic tools. In one study attempting to elucidate the patterns and risk factors for barotrauma in ventilated patients, the investigators abandoned their initial plan to determine whether pulmonary interstitial emphysema precedes pneumothorax because they could not reliably or reproducibly detect the former.[85] In our experience, the degree of resolution and interexposure consistency required to detect and follow this radiographic finding are beyond the capabilities of most portable X-ray units, that must frequently shoot through bandages and bedding, with suboptimal positioning and patients who cannot hold still or take a deep breath.

Intrapulmonary cystlike air collections in patients with ARDS have been recognized with increased frequency since the use of CT in such patients became commonplace. The early studies of Maunder et al[86] and Gattinoni et al[87] demonstrated the heterogeneous nature of lung involvement in ARDS, and especially late in the course of this disorder large collections of free air within the pulmonary parenchyma are common (Fig. 44-5). Pneumothorax also seems to be common in this setting, although no study published to date has documented this observation objectively.

Small subpleural air collections, also identified on CT scans occur frequently during the course of ARDS.[88] These collections probably represent centrifugal dissection of air through the interstitium to the visceral pleura, and are the likely source for pleural air in some patients.

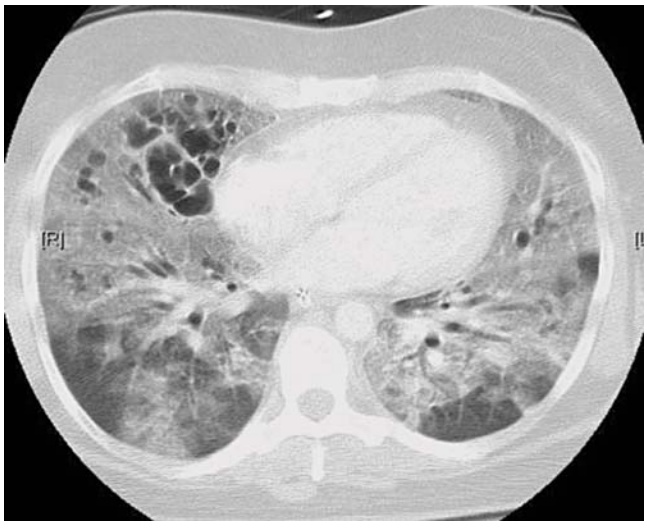

FIGURE 44-5 CT image through the midchest in a patient with ARDS receiving mechanical ventilation with PEEP. Parenchymal involvement is markedly inhomogeneous, with relatively normal areas in the dependent lung zones, widespread ground glass opacities in both lungs and intraparenchymal cystic air collections, primarily in the anterior portions of the right lung.

Pneumomediastinum

The mechanisms for alveolar rupture and the spread of air to the mediastinum illustrated in Figures 44-1 and 44-2 apply to spontaneously breathing, nonintubated patients as well as to those receiving mechanical ventilation.[8] In the former, symptoms referable to pneumomediastinum are frequent and characteristic. Stabbing precordial chest pain is the most common complaint,[89–91] occurring in 80% to 90% of patients.[4,92] "Hamman's crunch," a crunching or clicking sound best heard over the retrosternal area synchronous with cardiac systole,[93] can be detected in many patients who present with spontaneous pneumomediastinum. It is not specific, however, and may occur in patients with spontaneous pneumothorax without evidence of pneumomediastinum.[94]

Symptoms may be unobtainable from an intubated, critically ill patient, however, and the physical findings characteristic of pneumomediastinum may be hard to detect amid the hubbub of the ICU. Most often, pneumomediastinum is first detected radiologically, usually as an incidental finding. The most common appearance is a radiolucent area paralleling the left-heart border. This is readily detected in the presence of fluid density in the adjacent lung tissue, as with pneumonia or pulmonary edema. A thin, vertically oriented white line representing the mediastinal pleura may be seen when the pneumomediastinum is bordered by normal lung parenchyma. Once detected, a pneumomediastinum can often be traced cephalad beyond the hilum and into the neck. Other radiographic findings include highlighting of the aortic knob, which is surrounded by more lucent gas density than usual, and the "continuous diaphragm sign" described by Levin (Fig. 44-6).[95] Many patients with

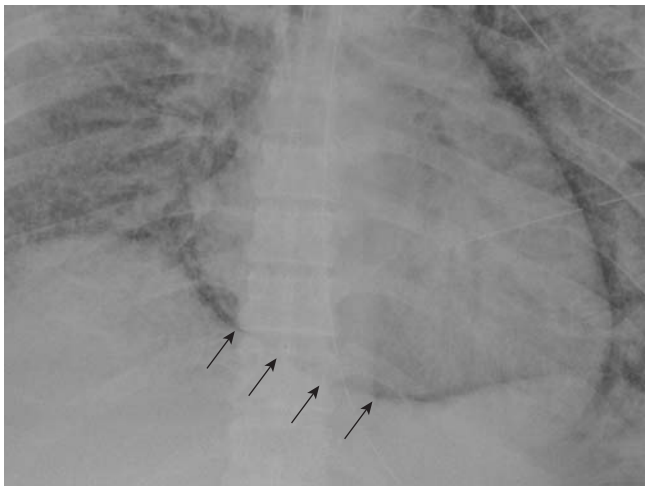

FIGURE 44-6 The "continuous diaphragm sign" of pneumomediastinum in a patient with barotrauma complicating ARDS. An unbroken radiolucent line denoted by the *arrows* extends from one hemidiaphragm to the other, rendering the inferior heart border clearly visible.

ventilator-associated pneumomediastinum also develop subcutaneous emphysema, which is typically more obvious radiographically.

Pneumomediastinum is frequently the first sign of barotrauma, and a substantial number of cases go on to development of pneumothorax. In one retrospective study,[85] thirty-four of 139 intubated patients had radiographic signs of barotrauma at some point in their ICU course. Pneumomediastinum was the initial manifestation in twenty-four of the thirty-four patients, and a pneumothorax was subsequently diagnosed in ten (42%).

Pneumopericardium

Dissection of air into the pericardium can follow alveolar rupture, and pneumopericardium may occasionally be the only sign of barotrauma. Long known as a complication of respiratory distress syndrome in neonates, it has been reported in adults as well,[96,97] particularly following blunt chest trauma,[98,99] and complicating severe bacterial pneumonia.[100,101] Although hemodynamically significant pneumopericardium in ventilated adults is not generally considered likely, presumably because the adult pericardium communicates less readily with the rest of the mediastinum than is the case in neonates, one group[96] reviewed eighty-one previously published cases and found 37% of them to have been hemodynamically significant. Several patients in this series were said to have required emergency pericardiocentesis. Adding to the uncertainty about the frequency and clinical importance of pneumopericardium in ventilated adult patients is the difficulty often encountered by portable radiographic devices to distinguish air in the pericardium from the much more common finding of pneumomediastinum.

Subcutaneous Emphysema

Although subcutaneous emphysema is commonly observed both radiographically and on physical examination around chest tube insertion sites, most often this form of barotrauma is encountered in the neck and upper anterior chest as it is vented from the superior mediastinum. When present in only small amounts, subcutaneous air produces the typical findings of crepitance on palpation. If the leak continues, as may be seen in severe ARDS when excessive tidal volumes and high inflation pressures are used, obvious distortion of the neck and anterior chest wall can be seen, and palpation shows a characteristic "pneumatic sponginess" as the skin and subcutaneous tissues are depressed to touch the underlying ribs. Air is commonly noted outlining the pectoralis musculature on routine chest radiology; chest CT reveals the spread of air throughout the soft tissues and in all fascial planes (Fig. 44-7).

From the neck and chest wall the air can spread literally everywhere in the body, collecting especially in areas with loose subcutaneous tissue, such as the upper arms and axillae and the abdominal wall. Periorbital accumulation may become extensive enough to force the eyelids shut. Radiographic studies obtained for other reasons in patients with widespread subcutaneous emphysema may reveal air in a variety of unexpected locations (Fig. 44-8).

Although it may be uncomfortable for the patient and distressing to the caregivers at the bedside, subcutaneous emphysema is nearly always clinically benign. Air in the subcutaneous tissues or dissecting along deeper fascial planes poses little if any direct threat to the adjacent tissues. The air tends to collect in areas with loose connecting tissue, whose blood supply is not compromised by the stretching and other distortion. Like pneumomediastinum, this form of barotrauma serves mainly as an indicator rather than constituting a management problem per se. It signifies the presence of a substantial air leak, and should alert the

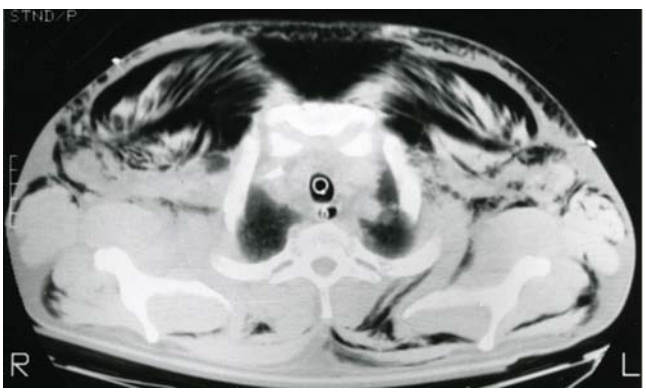

FIGURE 44-7 Example of widespread subcutaneous emphysema in a patient with barotrauma complicating ventilator management in severe ARDS. CT image through the shoulders, at the most cephalad extension of the lung apices, showing air widely dispersed under the skin and outlining the musculature.

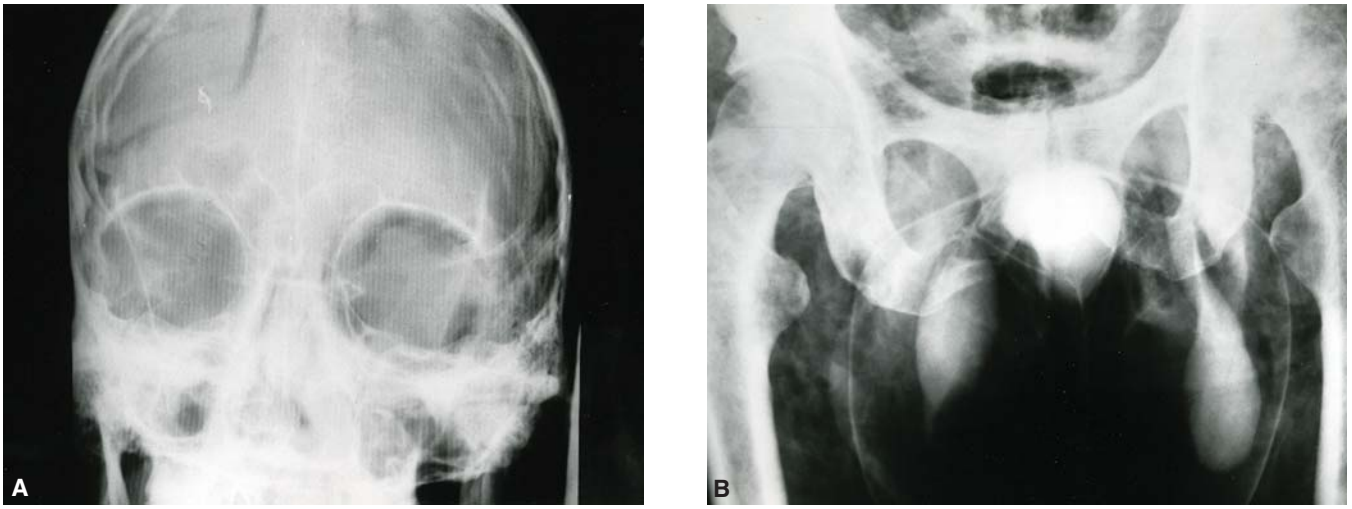

FIGURE 44-8 Examples of widespread subcutaneous emphysema in patients with barotrauma complicating ventilator management in severe ARDS. **A.** A bedside skull film showing air beneath the scalp on the left and in the orbit surrounding the ocular globe. A craniotomy defect can be seen on the right. **B.** Demonstration of tension pneumoscrotum in a different patient with widespread extraalveolar air including pneumoperitoneum and extensive subcutaneous emphysema.

clinician to the possibility of pneumothorax, but therapy for the subcutaneous air itself is seldom indicated. Airway compromise[102] hemodynamic collapse,[103] and manifestations of abdominal compartment syndrome,[17] have been reported in the context of large-airway disruptions and the use of high inflation pressures, although these instances are rare.

Pneumoperitoneum

Figure 44-3 shows how air from the lung that reaches the mediastinum can spread to the retroperitoneal space and thence into the peritoneum itself. The appearance of free air in the peritoneal cavity in a patient receiving mechanical ventilation[74] poses a diagnostic dilemma, even when subcutaneous emphysema and other signs of the wide spread of extraalveolar air are present. Avoidance of an exploratory laparotomy or other invasive procedure may be exceedingly difficult in such circumstances. Determining the partial pressure of oxygen (P_{O_2}) of aspirated peritoneal gas has been reported as a means of differentiating pneumoperitoneum from a ruptured abdominal viscus from air dissecting into the peritoneum under positive-pressure ventilation after alveolar rupture,[104] although the accuracy of this procedure has not been validated by others.

Although rare, accumulation of air in the peritoneum as a result of barotrauma during positive-pressure ventilation can cause or contribute to increased intraabdominal pressure[72] and, conceivably, abdominal compartment syndrome. Generally, however, air in the retroperitoneal and peritoneal spaces poses no intrinsic threat to health, and produces no physical signs other than subcutaneous emphysema and abdominal distension. In exceptional instances, air from ventilator-associated barotrauma can even dissect into the scrotum (see Fig. 44-8B) presumably via the peritoneum.

Systemic Air Embolism

Systemic air embolism may occur more commonly as a manifestation of barotrauma during mechanical ventilation than has previously been believed. Marini and Culver[105] describe the cases of two young adult patients with ARDS, necrotizing pneumonia, and prior pneumothoraces, in whom enlarging intraparenchymal air cysts and pulmonary interstitial emphysema were noted. While in a semi-upright position, each of these patients developed sudden neurologic events (facial twitching, hemiparesis, and seizures), evidence of acute myocardial injury, and focal livedo reticularis over the shoulder and anterior chest. Focal angioedema of the face subsequently developed. No other explanation for these events could be found, and in each patient there was evidence for recurrent episodes of air embolism. One patient survived without long-term sequelae; the other died of refractory hypoxemia and hypotension. Other cases of fatal air embolism as a manifestation of barotrauma have been reported.[106,107] In one instance, a patient being ventilated with PEEP for ARDS was found at postmortem examination to have air in the coronary and cerebral circulations, as well as in the pulmonary veins.[107]

Morris et al[108] reported the occurrence of venous air embolism via the inferior vena cava, as detected with transesophageal echocardiography, in three surgical patients, two with ARDS and one with multiple trauma. One 26-year-old patient developed an acute myocardial infarction on the thirteenth day of ARDS, while on 30 cm H_2O of PEEP, and transesophageal echocardiography revealed continuous bubbling of air in the inferior vena cava. In the other two patients transesophageal echocardiography revealed inferior vena cava bubbles without prior clinical signs of systemic air embolism. Each of these patients had had previous evidence for extraalveolar air, and the authors postulated that the

bubbling originated from subcutaneous or intraperitoneal air that gained entry into the splanchnic venous system.

Several cases of cerebral air embolism have been seen in association with mechanical ventilation in patients with traumatic lung contusion.[109,110] In several reports, gas bubbling has been observed in the left atrium and left ventricle (but not on the right side) during ventilation with large tidal volumes and PEEP, with cessation during apnea and disappearance or diminution when lower tidal volumes and PEEP were used.[110,111] Cerebral air embolism has also been reported as a feature of barotrauma in patients receiving noninvasive ventilation via face mask.[112,113]

In some patients, once alveolar rupture occurs during mechanical ventilation, decompression into the bronchovascular sheath by the mechanism described by Macklin[5,6] may fail to occur, allowing pulmonary interstitial air to accumulate under pressure as tension air cysts.[88] Development of such cysts has been observed to precede the appearance of tension pneumothorax in several instances.[88,114] In ARDS, Marini and Culver[105] postulate that, in the presence of such intraparenchymal air collections, the strong retractive tendency of the infiltrated parenchyma may tether open vascular channels that have been disrupted by inflammation or shear stress, allowing entry of air.

Systemic air embolism should be considered when patients receiving positive-pressure ventilation (especially for ARDS or with high levels of PEEP) develop unexplained agitation, changed mental status, focal neurologic findings, seizures, or disturbances in cardiac rhythm. The finding of focal livedo reticularis, particularly over the neck, shoulder, or anterior chest wall, should raise the strong suspicion of this complication, as should the occurrence of focal angioedema of the face or neck.

Pneumothorax

Pneumothorax in patients receiving positive-pressure ventilation manifests in three ways. Commonly it is first detected on a routine chest radiograph without clinical signs. The findings may be subtle. Typical radiographic signs of pneumothorax, such as a rim of lucency without lung markings completely surrounding the lung, demarcated by the visceral pleura and denser lung tissue, may be absent. Often the only indication of free pleural air is an increase in overall lucency in one hemithorax or one area of the lung, particularly the lower zone (Fig. 44-9). In some cases the deep sulcus sign, (Fig. 44-10) seen when radiographs are taken with the patient in the supine position, is the only clue to the presence of the pneumothorax. Physical signs of pneumothorax (diminished chest wall excursion, increased percussion resonance, and diminished breath sounds) can rarely, if ever, be detected in a patient who does not have a tension pneumothorax.

The second presentation for pneumothorax in the ventilated patient is with a change in laboratory or bedside monitoring findings, but without an obvious change in the patient's clinical state. Worsening oxygenation,[115] an increase in peak inspiratory airway pressure with accompanying rise in the plateau pressure, or a fall in lung–chest wall compliance may signal the development of a pneumothorax that has affected pulmonary function but has not yet become hemodynamically significant.

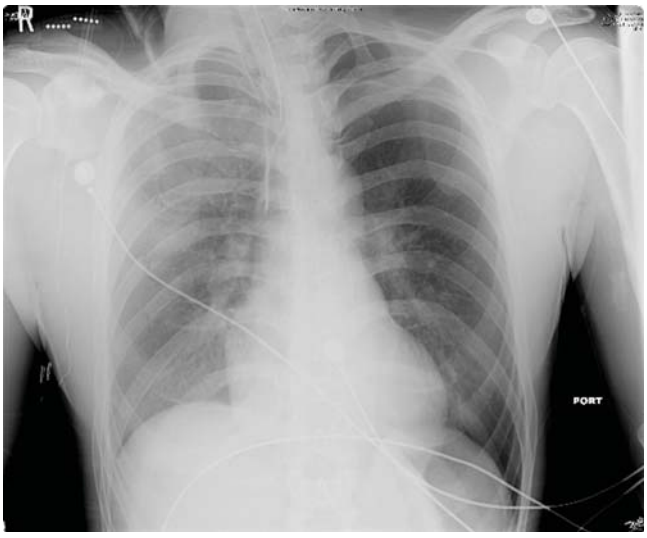

FIGURE 44-9 Loculated left-sided anterior pneumothorax in a patient receiving mechanical ventilation. Lung markings are present throughout the left hemithorax and there is no visible air laterally between the parietal and visceral pleurae. With anterior pneumothorax the only signs may be an increase in overall lucency in one hemithorax, typically confined to the lower lung field, and an increase in the clarity of the left-heart border.

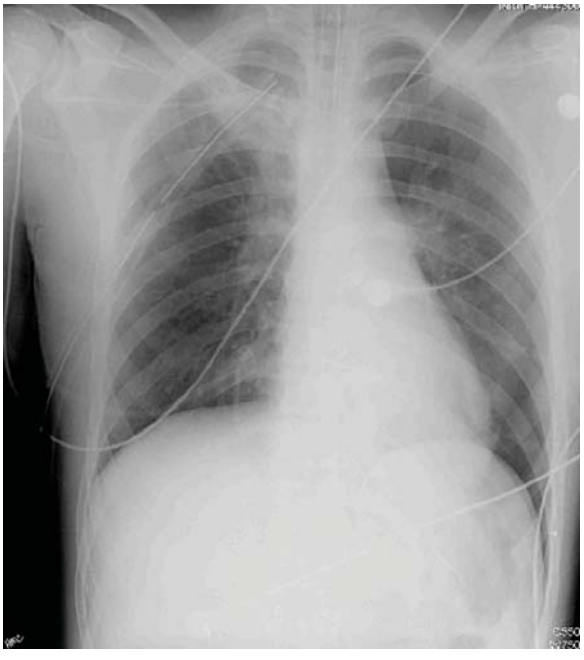

FIGURE 44-10 The deep-sulcus sign in a patient receiving mechanical ventilation in the supine position following trauma. The costophrenic sulcus on the left is substantially deeper than the sulcus on the right. There is no visible air laterally between the parietal and visceral pleurae on the left. The patient already has a chest tube on the right side from a pneumothorax detected on that side at the time of admission.

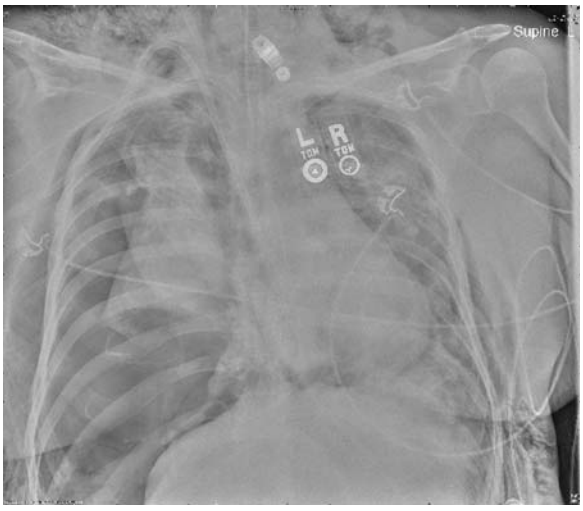

FIGURE 44-11 Tension pneumothorax in a patient receiving mechanical ventilation for ARDS. There is a large pneumothorax on the right with associated collapse of the right lung and shift of the heart and mediastinal structures toward the left side of the chest. A smaller left pneumothorax is also present. Although features of chest radiographs, including shift of the mediastinal structures, are strongly suggestive of the diagnosis of tension pneumothorax, the diagnosis is typically made clinically at the bedside before chest radiography is performed.

Tension pneumothorax is the third presentation (Fig. 44-11). This is primarily a bedside diagnosis, in that the complication is defined better by its adverse effects on cardiovascular function than by its radiographic characteristics. The latter include mediastinal displacement away from the pneumothorax, reversal of the diaphragmatic curve, and overall enlargement of the affected hemithorax, but these signs can occur in the absence of adverse physiologic effects, and the physiologic effects of pleural tension may be present without them. Most commonly the patient with tension pneumothorax presents with agitation and respiratory distress, hypotension, and other signs of cardiovascular collapse. Although tension pneumothorax is uncommon in spontaneously breathing patients, even in the presence of total lung collapse, the clinician should assume that every radiographically detected pneumothorax in a patient on mechanical ventilation can rapidly accumulate under tension.

Tables 44-7 and 44-8 list a number of clinical settings in which acute pneumothorax should be suspected or anticipated in the ventilated patient.

Bronchopleural Fistula

The presence of a bronchopleural air leak following insertion of a chest tube could potentially create several important clinical problems (Table 44-9). Unfortunately, relatively little is known about the natural history of this entity, and few data exist to substantiate the individual points in the table.

Bronchopleural fistula is a relatively uncommon complication, even in institutions managing large numbers of patients with ARDS and other forms of acute respiratory failure. Of 1700 patients ventilated during a 4-year period at a major trauma center in the early 1980s, thirty-nine (2%) developed a bronchopleural air leak that persisted at least 24 hours after chest tube insertion.[116] Postsurgical leaks, such as bronchial stump breakdown, were not included in this series. The leak varied in size in these patients from only intermittent bubbling into the chest drainage device to 900 mL/breath. Despite this, refractory hypercapnia causing arterial pH <7.30 occurred in only two patients, suggesting that inability to excrete CO_2 is very uncommon when bronchopleural fistula occurs as a complication during ventilator management.

Bronchopleural fistula occurred in two distinct settings in this study.[116] It was either the result of direct lung injury (e.g., blunt chest trauma or instrumentation) occurring

TABLE 44-7: WHEN TO SUSPECT A PNEUMOTHORAX IN THE VENTILATED PATIENT

Clinical change in patient's status
Sudden or progressive increase in inspiratory peak or plateau airway pressure
Hypotension or cardiovascular collapse
Sudden onset of agitation and respiratory distress ("fighting the ventilator")
Suggestive findings on chest radiograph
General increase in volume of one hemithorax
Deep sulcus sign: downward displacement of costophrenic angle and/or hemidiaphragm
Increase in relative radiolucency of one lung or part of one lung

TABLE 44-8: CLINICAL SITUATIONS SUGGESTIVE OF A HIGH RISK OF PNEUMOTHORAX

Use of large tidal volumes (e.g., >8 to 10 mL/kg) in patients with acute lung injury or underlying chronic pulmonary disease
Use of high levels of PEEP (e.g., >15 cm H_2O)
High peak airway pressure (e.g., >50 to 60 cm H_2O), especially if increasing on the same inspiratory flow settings
Acute respiratory distress syndrome (ARDS), especially late in its course (e.g., 2 to 3 weeks)
Severe underlying obstructive lung disease (COPD, asthma)
Severe bullous lung disease (e.g., idiopathic congenital giant bullous emphysema)
Pulmonary infection complicating ARDS
Pulmonary parenchymal disease accompanied by cystic changes (e.g., *Pneumocystis jiroveci* pneumonia, lymphangioleiomyomatosis, cystic fibrosis)
Presence of pulmonary interstitial emphysema or pneumomediastinum, and especially their new development on serial chest radiographs, suggesting alveolar rupture and increased likelihood of spread to pleural space

Abbreviations: ARDS, acute respiratory distress syndrome; *COPD*, chronic obstructive pulmonary disease; *PEEP*, positive end-expiratory pressure.

TABLE 44-9: POTENTIAL ADVERSE EFFECTS OF BRONCHOPLEURAL FISTULA IN THE VENTILATED PATIENT

Effect	Problems	Comment
Incomplete lung expansion	Atelectasis Worsened ventilation–perfusion mismatching ?Failure of leak to close	Occurs mainly with very large leaks (e.g., tracheobronchial injury) or with underlying restrictive lung disease
Loss of effective tidal volume	Incomplete expansion of other lung areas Worsened ventilation–perfusion mismatching	Attempts to compensate with increased delivered tidal volume may increase leak and exacerbate problem
Inability to remove CO_2	Acute respiratory acidosis	Unusual; life-threatening academia rare
Loss of positive end-expiratory pressure	Incomplete lung expansion Hypoxemia	May not be correctable in presence of large or multiple leaks
Pleural space infection	Infected secretions from airways pass through pleural space	Increases morbidity and ?mortality rates; ?additional source for sepsis
Factitious ventilator triggering	Ineffective ventilation	Caused by transmission of negative pressure from chest tube to central airways

within 24 hours of the onset of mechanical ventilation, or a manifestation of spontaneous alveolar rupture considerably later in the clinical course. In the latter circumstance, most often seen in patients with ARDS, bronchopleural fistula first developed a mean of 13 days after the onset of positive-pressure ventilation. This case series, reported in the context of ventilator management three decades ago, remains the only published study of the incidence of persistent bronchopleural air leak as a feature of barotrauma.

As discussed earlier for barotrauma in general, it is not known whether bronchopleural fistula as a complication of ventilator support has become less common with the use of lung-protective ventilation. Likewise, the effect of this complication on patient outcomes remains unknown. Development of a bronchopleural fistula appears to identify patients as having a poor prognosis, but whether the fistula plays an independent role remains to be established.[116,117]

MANAGEMENT

General Principles

Of the clinical forms of barotrauma (see Table 44-6), pneumothorax and systemic air embolism present a threat to the life of the patient and thus require immediate treatment. All of the others should be considered primarily as signs, either of the severity of the pulmonary disease or of the possibility of inappropriate ventilator management. Extraalveolar air is not easily recognized at the bedside except in the case of subcutaneous emphysema and tension pneumothorax. Nevertheless, there is often a temptation to initiate therapy directed at the barotrauma itself. More important, however, is therapy of the underlying primary disease. Certain ventilator adjustments, though, are appropriate in order to reduce the likelihood of further damage. These should include reducing PEEP, tidal volume, and minute ventilation to the lowest values compatible with acceptable patient support, and consideration of lung-protective ventilation and permissive hypercapnia as discussed elsewhere in this volume for reducing the likelihood of lung damage.

Pulmonary Interstitial Emphysema and Cystic Dilation

As mentioned earlier (see the section Clinical Manifestations), although pulmonary interstitial emphysema is an important intermediate step between alveolar disruption and clinical barotrauma, it is difficult to detect reliably on either physical exam or portable radiography obtained in the ICU. With the increasing use of CT in patients with ARDS and other settings of acute respiratory failure, however, these forms of barotrauma are increasingly recognized. Along with intraparenchymal air cyst formation, pulmonary interstitial emphysema is an important sign that alveolar overdistension is occurring, and that tension pneumothorax and other forms of barotrauma are more likely to occur. Their recognition is an indication to monitor the patient closely, and to modify the ventilator settings to reduce alveolar overdistension if this is clinically feasible. Aside from these measures, however, there is no specific treatment for these phenomena. Although CT-guided percutaneous catheter drainage of intraparenchymal air cysts has been reported,[118] documentation of the clinical necessity of this is scant.

Subcutaneous Emphysema

In the great majority of cases, subcutaneous emphysema requires no treatment other than to treat the underlying lung pathology so that the leak will cease. Rarely, accumulation of massive amounts of air in the chest and abdominal walls can be physiologically important and require surgical decompression.[119,120] Most accounts of such intervention provide

little to convince the reader that the air was compromising vital organ function. If the air leak is massive and continuous, however, as can be seen in tracheal perforation as a complication of attempted intubation, urgent intervention may be warranted. In such instances, circulatory compromise, oliguria, and other manifestations of the abdominal compartment syndrome (such as increased bladder pressure) should be evident, and should improve dramatically upon release of the subcutaneous air.[17]

Pneumoperitoneum

Continued air leak resulting in massive spread of extraalveolar air during positive-pressure ventilation can lead to accumulation of air in many soft-tissue spaces. This air poses no threat to the tissues themselves, although in the case of pneumoperitoneum it can cause diagnostic confusion. Critically ill patients with barotrauma are also susceptible to perforating stress ulcers, mesenteric ischemia, and other potential causes of free air in the peritoneal cavity, particularly if they have experienced a period of hypotension. Even in the presence of widespread subcutaneous emphysema and other forms of extraalveolar air, it may not be possible to exclude a surgical abdomen without laparotomy. One report documented the use of measured oxygen tension in the gas aspirated from the peritoneal cavity,[104] but this has yet to be confirmed by other investigators. Aside from the need to exclude an abdominal emergency unrelated to barotrauma, the presence of free air in the retroperitoneal tissue planes or peritoneal cavity generally poses no danger to the patient, and will be resorbed once the need for positive-pressure ventilation diminishes.

Systemic Air Embolism

The diagnosis of systemic air embolism is based on the clinical setting rather than on any specific test. Demonstration of air bubbles in the left atrium or left ventricle by echocardiography is highly suggestive of ongoing extraalveolar air entry, but CT and magnetic resonance imaging have not proven to be helpful in this condition.

No therapy is convincingly effective. Although hyperbaric oxygen therapy is often recommended, its efficacy has not been shown in controlled trials. Traditionally, it has been recommended that patients with air embolism be placed in the left lateral decubitus position to move the air collection out of the right ventricular outflow tract; evidence supporting this recommendation, however, is lacking and data from several animal studies suggest it may not be effective at improving patient hemodynamics.[121–123] Administration of high concentrations of oxygen in order to raise partial pressure of arterial oxygen (Pa_{O2}) and hasten bubble absorption has also been recommended,[122,124] while reductions in PEEP, tidal volume, and minute ventilation should be carried out, if feasible, so as to reduce the likelihood of further air entry into the vasculature.

Pneumothorax

Because of the threat of tension pneumothorax, chest tube drainage is advisable anytime free pleural air is detected during positive-pressure ventilation. There is little reported experience in this setting with the small catheter drainage sets often used for treating uncomplicated primary spontaneous pneumothorax, and the use of a larger, standard chest tube and drainage system is advisable. The routine application of suction (e.g., 20 cm H_2O) is customary in the United States, although this is not the case in all areas of the world; chest tube suction should be applied or increased if the lung does not fully reinflate, although, as noted earlier, application of suction may perpetuate a bronchopleural fistula by maintaining a large gradient between the airways and pleural space. Once the lung is fully inflated and there is no residual air leak, the tube is placed to water seal and removed, usually after an additional day. No evidence supports the use of "prophylactic" thoracostomy tubes in patients at high risk for pneumothorax.

Bronchopleural Fistula

DIAGNOSIS AND QUANTITATION OF AIR LEAK

In pneumothorax, once a chest tube is inserted and external suction applied, air is evacuated from the pleural space, as shown by bubbling through the water seal of the chest drainage device. If there is no persistent communication between the airways and the pleural space, this bubbling will cease once the lung is fully reinflated. Air may continue to leak into the pleural space for minutes to a few hours, but in most instances this soon stops. When it does not, and the bubbling continues for 24 hours or more, a bronchopleural air leak (bronchopleural fistula) is present. Most such leaks are small—a few bubbles through the water seal in synchrony with the inspiratory phase of the ventilator—although they may reach several hundred milliliters per breath.

Although precise quantitation of the air leak is rarely needed for clinical management, several methods for doing this have been described. The leaked volume can be estimated by subtracting the expired from the inspired tidal volume as long as the leak exceeds 100 to 200 mL/breath and the measurements are made at the same point in the ventilator circuit to avoid error secondary to compression in the inspiratory limb. Other techniques have been described in the literature but they are more difficult to set up, have lower overall clinical utility, and are, as a result, better suited for research purposes.[125,126]

Although it is seldom necessary to quantitate the leak precisely for patient management, it is sometimes useful to determine whether the gas leaking into the pleural drainage unit originates in the patient's airways or from the room, as may occur around the chest tube insertion site or with breaks in the circuit between the patient and the drainage unit. Removal of the chest tube is unwise in the presence of a bronchopleural air leak, but may be indicated if there is an external leak, because the same circuit break that introduces

air may also permit ingress of contaminating organisms. Most leaks from the patient's airways vary with the respiratory cycle, and stop or diminish during exhalation when intrathoracic pressure is lower. A more definitive test is to withdraw a sample of leaked gas from the connecting tubing under sterile conditions and to pass it through a capnometer; except in cases of proximal bronchial disruption, gas from the patient's airways will contain CO_2, whereas air from the room will not.

Bishop et al[127] collected leaked gas in nine patients with bronchopleural fistulas complicating ARDS. Total delivered minute ventilation in these patients ranged from 16.6 to 42.6 L/min (mean: 23.9 L/min), with 4% to 53% of each tidal volume lost through the fistula (mean: 25%). As the proportion of total minute ventilation lost through the leak increased, so did the fraction of the patients' total CO_2 production that exited through the chest tube.[127] In several patients, more CO_2 was excreted through the chest tube than through the endotracheal tube. Thus, at least in ARDS, gas leaked through a bronchopleural fistula has participated in gas exchange and is similar to gas exiting via the trachea.[127] This observation is consistent with the finding that unmanageable CO_2 retention is unusual in bronchopleural fistula,[116] and suggests that respiratory acidosis in most patients with such a fistula is a manifestation of the severity of their underlying lung disease rather than of the air leak per se.

Measurements of oxygen consumption, CO_2 production, respiratory quotient, and resting energy expenditure can be erroneous in patients with significant bronchopleural air leaks because of the CO_2 lost through the chest tube.[128] Accurate measurement of CO_2 production in patients with ARDS requires collection of the leaked gas, although dead-space-to-tidal-volume ratio can be determined using the usual technique of endotracheally expired gas collection, because the proportion of CO_2 excreted via trachea and fistula are approximately equal.[128]

GENERAL MEASURES

In general, management of the patient with a bronchopleural fistula is the same as if the fistula were not there, provided that a functioning chest tube and a pleural drainage system are in place. Table 44-10 lists a number of commonsense measures that should be taken to diminish the magnitude of the leak and the probability of further pulmonary parenchymal damage.

Weaning the patient from positive-pressure ventilation altogether would be optimal from the standpoint of decreasing the leak. When this is not feasible, a ventilator strategy should be selected that minimizes both minute ventilation and mean intrathoracic pressure. Respiratory alkalosis should be avoided, and consideration should be given to permissive hypercapnia in patients with very low lung–chest wall compliance and high minute ventilation requirements. Because the "lost" volume participates in gas exchange, delivered tidal volume should not be increased beyond a certain point to "chase" the air leak.

TABLE 44-10: PRINCIPLES OF VENTILATOR MANAGEMENT IN THE PATIENT WITH A BRONCHOPLEURAL FISTULA

- Use the lowest number of mechanical breaths that permits acceptable alveolar ventilation (reduce both mean airway pressure and number of high-pressure breaths)
  - Wean the patient completely if possible
  - Partial ventilatory support may be preferable to total ventilatory support (e.g., pressure-support ventilation)
  - Avoid or correct respiratory alkalosis (to minimize minute ventilation)
- Limit effective (returned) tidal volume to 6 to 8 mL/kg or less
- Minimize inspiratory time
  - Keep inspiration-to-expiration ratio low (e.g., 1:2)
  - Use high inspiratory flow (e.g., 70 to 100 L/min)
  - Avoid end-inspiratory pause and inverse-ratio ventilation
  - Use low-compressible-volume ventilator circuit to minimize delivered tidal volume
- Minimize both dialed-in and endogenous positive end-expiratory pressure
- Use the least amount of chest tube suction that maintains lung inflation
- Explore positional differences; avoid placing the patient in positions that exacerbate leak
- Treat bronchospasm and other causes of expiratory airflow obstruction
- Consider specific or unconventional measures (e.g., independent lung ventilation, endobronchial measures) if the patient remains unstable or develops clinically harmful, uncorrectable respiratory acidosis despite the above measures
- Treat the underlying cause of respiratory failure, maintaining nutritional and other support, with the goal of discontinuing mechanical ventilation as soon as possible

Positive end-expiratory pressure (both dialed-in and endogenous) and pulmonary hyperinflation should be minimized. In a study using older-generation ICU ventilators and circuits, the use of high inspiratory flows and low-compressible-volume, low-compliance ventilator tubing independently and additively decreased auto-PEEP,[129] although whether these measures are necessary with current-generation ventilators and circuits is uncertain. High inspiration-to-expiration ratios and end-inspiratory hold should be avoided. Vigorous therapy for bronchospasm and obstructing airway secretions should be pursued.

SPECIFIC MEASURES

As stated previously, the role of a bronchopleural fistula in the overall prognosis of acute respiratory failure has not been established, and available data suggest that the great majority of such fistulae have little impact on gas exchange. Of all the clinical forms of barotrauma, however, this is the one that has been the subject of the most published reports of novel approaches to therapy. Most of the literature consists of descriptions of techniques for decreasing the size of the leak, and available clinical reports consist almost exclusively of anecdotal descriptions of immediate and short-term

physiologic changes that lack both longer-term outcome data and convincing evidence that "conventional" ventilator management had been inadequate. The subjects of most of these reports have been critically ill patients, many of whom have died in spite of the short-term physiologic improvements documented under the reported intervention.

Several reports have described the use of independent lung ventilation via double-lumen endotracheal tube and two ventilators in patients with bronchopleural fistula.[130–136] The reported experience with this strategy is limited to about ten patients, although the technique has no doubt been used in other unpublished cases. As with the use of this ventilator technique in other settings, improved gas exchange has generally been achieved, but in nearly all the reported cases, the necessity of switching to this complicated and expensive technique is unconvincingly described, a problem shared with many of the other strategies described further below. Placement and maintenance of a double-lumen endotracheal tube in a critically ill patient require considerable expertise, and the small lumens of these tubes make bronchial hygiene difficult in patients with significant secretions.

Many older reports documented the use of high-frequency jet ventilation (HFJV) in bronchopleural fistula,[137–143] but enthusiasm has waned and there are few new reports of the use of this technique in the last two decades or more.[144,145] Clinical experience with HFJV in patients without underlying lung disease, as in traumatic bronchial disruption or during tracheobronchial surgery, has generally been positive.[143,146] When bronchopleural fistula, however, occurs as a manifestation of barotrauma complicating severe diffuse pulmonary disease, both short-term and outcome results have been discouraging. In one study of seven patients with severe ARDS and large air leaks, when HFJV was adjusted to provide the same mean airway pressures as resulted from conventional ventilation, oxygenation and/or effective alveolar ventilation deteriorated in every patient, and the size of the leak increased in five of seven patients.[147] Because of this experience, the use of HFJV as treatment for bronchopleural fistula complicating severe acute respiratory failure has been abandoned in the authors' institution. High-frequency oscillatory ventilation has been reported in two cases of bronchopleural fistula,[148] but whether this technique offers any advantage over adjustments in conventional ventilation remains to be seen.

Several approaches have been reported for decreasing the size of the air leak through manipulation of the pleural drainage system.[149–152] The total patient population in which these approaches have been reported is very small, and no new reports of their successful use have appeared in more than 20 years. Their application becomes progressively more difficult as the number of chest tubes increases in a given patient, and incomplete lung expansion on the side of the leak is a common problem.

Commercial chest drainage units vary considerably in their ability to handle air leaks. In one bench study, the maximum leak flow that four widely used commercial chest drainage units could accommodate varied from 5.8 to 35.5 L/min.[153] In a subsequent study using an animal model of bronchopleural fistula, two older but commonly used devices became ineffective at leak flows as low as 4 to 5 L/min because of increased resistance.[154] A freestanding suction pump independent of wall suction (Emerson suction pump) consistently demonstrated the highest capacity to evacuate leaked air in these studies, and when flow through a bronchopleural fistula exceeds 4 to 5 L/min the use of such a device is recommended. We are unaware of studies evaluating the performance of the current generation of pleural drainage systems with respect to evacuating large air leaks.

Several approaches have been reported for plugging or otherwise sealing bronchopleural air leaks using the flexible or rigid bronchoscope,[144,155–165] including the use of endobronchial one-way valves[166,167] and expandable stents.[168] Very few of the patients comprising these case reports and small series, however, have had bronchopleural fistulas in the setting of ventilator-associated barotrauma.[156,162,163] Most of the reported experience is with bronchopleural fistulas following lung resection.[169]

Although it is tempting to think that the ultimate therapy for bronchopleural fistula would be direct surgical closure, this is seldom possible for technical reasons in settings other than acute traumatic tracheobronchial disruption. If the fistula is localized and associated with a necrotizing pneumonia, resection of the affected lobe may be feasible. A bronchopleural air leak following lung biopsy or other procedure, in a patient without pneumonia or acute respiratory failure, may be amenable to surgical repair by thoracoscopy or thoracotomy. In most instances of barotrauma, however, the air leak is a manifestation of the severity of the underlying pulmonary disease, and direct suture or cautery of the leak or leaks is simply not technically possible.

The clinician seeking the best way to manage a patient with bronchopleural fistula complicating positive-pressure ventilation is poorly served by the existing experimental literature, which consists largely of technical descriptions and anecdotal reports of immediate changes in leak size and arterial blood-gas values, and is virtually devoid of evidence that the therapies described affect patient outcome. There is an understandable desire to intervene when something so obvious as a bronchopleural fistula develops during the course of ARDS or other form of severe acute respiratory failure. Yet, except for the unusual circumstance of inability to reinflate the affected lung, evidence for harm by the air leak per se is strikingly lacking, and all the reported techniques for diminishing it have the potential for serious harm to the patient.

The clinician should approach any unconventional therapeutic measure with caution, realizing that it constitutes experimental, unproven, and potentially harmful therapy for a condition that may be more a sign of an adverse prognosis than its mechanism. Table 44-11 summarizes a number of principles for the approach to managing patients with bronchopleural fistula complicating severe acute respiratory failure, taken mainly from clinical experience in an area whose scientific basis remains woefully inadequate.

TABLE 44-11: EIGHT GENERAL OBSERVATIONS ABOUT MANAGING BRONCHOPLEURAL FISTULA IN THE PATIENTS WITH ACUTE RESPIRATORY DISTRESS SYNDROME

1. Bronchopleural fistula in the patient with ARDS is a manifestation of the severity of the underlying disease, perhaps initiated or exacerbated by its management, that will not resolve until the ARDS resolves or improves.
2. Bronchopleural fistula in ARDS is physiologically significant in only a minority of cases (perhaps 10%), even in the presence of hypercapnia.
3. Reducing the leak size per se typically has little effect on gas exchange as measured by arterial blood gases.
4. Measures directed at decreasing the size of the leak will generally prove unsuccessful until the underlying lung injury improves.
5. When the ARDS improves, the bronchopleural fistula will nearly always improve without specific therapy.
6. None of the specific measures (e.g., high-frequency ventilation, bronchoscopic interventions, etc.) discussed in the text has been shown to affect patient outcome.
7. Patients almost never die *of* bronchopleural fistula. They die *with* bronchopleural fistula, usually *of* multiple organ failure and occasionally of gas exchange failure because of ARDS.
8. Careful attention to general management principles (Table 44-10) is more important than any specific measure to decrease the leak.

Abbreviation: ARDS, acute respiratory distress syndrome.

PREVENTION

The degree to which all forms of clinical barotrauma are iatrogenic, as a result of how ventilator support is used in severe respiratory failure rather than primarily of the underlying pathology, remains unclear. Nonetheless, from the material discussed in this chapter several general principles emerge that are reasonable if not scientifically proven to reduce the likelihood of barotrauma during mechanical ventilation. Table 44-12 summarizes these principles.

The large (e.g., 12 mL/kg) tidal volumes traditionally used in ventilating adult patients originated many years ago in studies of individuals with normal lungs who were undergoing anesthesia. These tidal volumes are inappropriate for patients with diffuse lung disease, either restrictive (e.g., ARDS) or obstructive (e.g., chronic obstructive pulmonary disease or severe asthma). For such patients considerably smaller tidal volumes (e.g., 6 mL/kg, proportioned to predicted body weight) should be used, especially when PEEP is present with its attendant risk for local or overall pulmonary hyperinflation. Other patients should be ventilated with tidal volumes not exceeding 8 to 10 mL/kg predicted body weight.

PEEP, whether externally applied or endogenous, increases the likelihood of pulmonary hyperinflation, particularly when the lungs are heterogeneously involved, as is now recognized to be the case in ARDS. Insofar as hyperinflation predisposes to alveolar disruption, PEEP should be used cautiously in ARDS, and auto-PEEP should be sought in all ventilated patients and minimized when present. Because of the increased propensity of patients with ARDS to develop barotrauma late in the course of this disorder, and the apparent association of alveolar rupture with ongoing pulmonary infection and inflammation, scrupulous attention to infection control measures in all aspects of the care of such patients seems especially important.

TABLE 44-12: PRACTICAL MEASURES TO REDUCE THE LIKELIHOOD OF BAROTRAUMA DURING MECHANICAL VENTILATION

- Use small tidal volumes (6 mL or less per kilogram predicted body weight) and other aspects of lung-protective ventilation in patients with ARDS or obstructive lung disease, particularly in the presence of PEEP (dialed-in or endogenous)
- Avoid hyperventilation except where deliberately employed for specific indications
- Use PEEP cautiously in patients at increased risk for alveolar rupture, including those with:
  - ARDS
  - Any unilateral, patchy, or cavitary lung disease
  - Nosocomial pneumonia or sepsis
  - Obstructive lung disease (e.g., COPD or asthma)
  - Cystic lung disease (cystic fibrosis, *Pneumocystis jiroveci* pneumonia, lymphangioleiomyomatosis)
- Monitor respiratory system compliance as PEEP is applied or increased; decrease PEEP if compliance falls with increasing levels
- Monitor all ventilated patients for auto-PEEP; take specific measures to reduce auto-PEEP if its presence could be harmful to the patient:
  - Reduced minute ventilation, with normocapnia or hypercapnia
  - High inspiratory flow (e.g., 70 to 100 L/min)
  - Low-compressible-volume, low-compliance ventilator circuit
- Use extreme care in high-risk patients when placing subclavian or internal jugular lines or performing thoracentesis. Where available, use ultrasound guidance
- Take special care to avoid nosocomial pneumonia:
  - Practice good hand cleansing and other infection control techniques
  - Avoid circuit interruption

Abbreviations: ARDS, acute respiratory distress syndrome; *COPD*, chronic obstructive pulmonary disease; *PEEP*, positive end-expiratory pressure.

IMPORTANT UNKNOWNS

Surprisingly little is known about barotrauma complicating mechanical ventilation in terms of pathogenesis, clinical implications, optimum management, and prevention. The literature on this topic consists mainly of anecdotal observations and reports of interventions, the latter generally incompletely documented and at best with short-term physiologic endpoints. Although tension pneumothorax, air embolism, and, rarely, pneumomediastinum and subcutaneous emphysema, produce potential threats to life, whether the other forms of barotrauma discussed in this chapter

exert independent effects on morbidity, mortality, or the natural history of acute respiratory failure is not known. Even bronchopleural fistula, one of the more dramatic forms of clinical barotrauma, has not been shown to affect any patient-relevant outcome. The trend toward use of smaller tidal volumes, particularly in patients with acute lung injury or obstructive lung disease, would be expected to reduce the incidence of barotrauma, although to date the available data has not shown this to be the case.

THE FUTURE

If the use of lower inflating pressures and distending volumes during mechanical ventilation, which is becoming widespread largely as a result of the demonstration that such measures reduce mortality in patients with acute lung injury, also reduces the risk of alveolar disruption, then clinical barotrauma should become less frequent. The lack of evidence that special devices or unconventional approaches to ventilator support reduce the incidence of barotrauma or hasten its resolution once present may lead to their being used less often in patient management, which may lessen costs and the risk for attendant complications. In view of the lack of evidence that specific measures impact the severity or natural course of barotrauma, focusing on prevention through less injurious ventilatory support and better general care during critical illness is likely to be more beneficial than the continued search for specific interventions for its management.

SUMMARY AND CONCLUSION

Part of a spectrum of complications occurring during mechanical ventilation that includes ventilator-induced lung injury, extraalveolar air can be the result of alveolar disruption from overdistension or be caused by several other mechanisms. As a possible result of the ventilator settings used, barotrauma is always of clinical concern. Among its several clinical forms, however, those of greatest importance are systemic gas embolism and pneumothorax, as these can be fatal. Rarely, pneumopericardium and subcutaneous emphysema can also create a threat to life, and pneumoperitoneum poses a dilemma with respect to the possibility of a ruptured abdominal viscus. Bronchopleural fistula is an indicator of pathology that needs attention, but is usually not physiologically important and seldom requires specific measures targeted at the leak site. Barotrauma from alveolar rupture tends to occur in severely ill patients, and whether this complication independently contributes to mortality or morbidity remains unknown. Prevention of barotrauma, and management once it occurs, consist primarily of practicing sound general ventilator management, including limiting distending volumes and static airway pressures, to stop or reduce the passage of air into the bronchovascular sheaths and elsewhere.

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45

OXYGEN TOXICITY

Robert F. Lodato

The importance of the physiology and toxicology of oxygen (O_2) breathing have increased in recent years. The past 25 years have witnessed a remarkable upsurge of knowledge and interest in "oxidative stress" throughout all of biology. The use of O_2 continues to grow, from critically ill to ambulatory patients and even to recreational use at "oxygen bars."[1] Recent advances in patient care have refocused attention on the optimum use of O_2. For example, currently, strategies to protect the lung from mechanical injury during mechanical ventilation emphasize the use of lower tidal volumes. But such strategies may impair gas exchange, resulting in higher requirements for inspired O_2 fraction (FI_{O_2}).[2]

Lavoisier initially characterized O_2 as "highly respirable air"[3] and "vital air" before eventually giving it the name "principle oxygine" (acidifying principle) in 1777. He took the name from the Greek roots "oxy" (acid) and "gen" (to form), because initially O_2 was incorrectly believed to be the essential principle in the formation of acids.[4] Normobaric hyperoxia may be defined as an inspired O_2 tension, PI_{O_2}, between 160 and 760 torr (i.e., between 0.21 and 1.0 atmosphere [atm] of pressure), whereas hyperbaric hyperoxia denotes that PI_{O_2} is greater than 760 torr.

J.B.S. Haldane[5] and others[6] speculated, and it is now generally accepted, that life on earth began anaerobically when the earth's atmosphere was virtually devoid of O_2. Gilbert[6] postulated that in this primordial reducing atmosphere, the first living cells used hydrogen, diffusing into the cell from the environment, as an energy source (e.g., metabolizing carbohydrates to methane and water). Gilbert[6] speculated further that because hydrogen would also reduce essential cellular constituents and thereby poison the cell, these early cells also had to develop antihydrogen defenses and actively transport hydrogen ions out of the cell. As the atmosphere was transformed from a reducing to an oxidizing one, O_2 replaced hydrogen as an energy source. Therefore, to avoid O_2 poisoning, cells then had to develop antioxygen and antioxidant defenses. These observations emphasize that as an energy source for cells, O_2 has a dual effect: It is both life promoting and life destroying. This dual nature of O_2 (Fig. 45-1) was noted by Priestley in 1775 shortly after his discovery of O_2: "though pure [oxygen] might be very useful as a medicine, … as a candle burns out much faster in [oxygen] … so we might … *live out too fast*."[7] Indeed, even at ambient concentrations, O_2 is now considered to play a role in the natural process of aging.[8–10] In 1777, Scheele, who independently

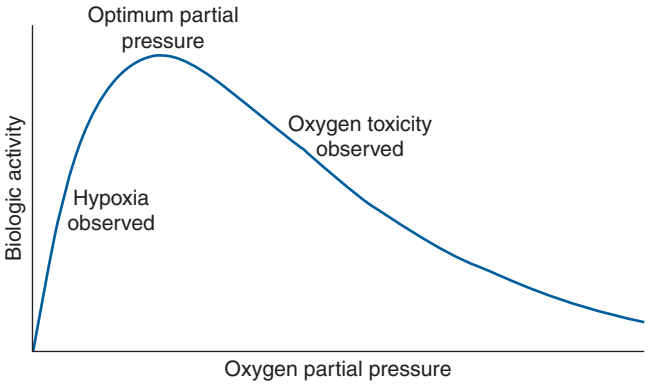

FIGURE 45-1 Dual effect of oxygen on biologic activity. (Used, with permission, from Gilbert.[8])

discovered O_2, noted along with Priestley that O_2 is toxic to plants. In 1785, Lavoisier, who first recognized the vital role of O_2 in the equivalent processes of respiration and combustion, commented explicitly on the dual nature of O_2: "when there is an excess of vital air [oxygen], the animal only undergoes a severe illness; when it is lacking, death is almost instantaneous."[6] In experiments carried out with Laplace, he described right-heart and pulmonary congestion in guinea pigs that died in O_2 under a bell jar before the O_2 was used up.[11,12]

In 1873, Paul Bert became the first to systematically study O_2 toxicity.[11] He documented the toxicity of O_2, particularly the lethality of hyperbaric hyperoxia, in all forms of life from mammals to viruses. He concluded that "no living thing is exempt from damage that can be produced by oxygen."[13] Grand mal seizures are the most notorious toxic effect of hyperbaric hyperoxia and have been referred to as the "Paul Bert effect."[11] J.B.S. Haldane experienced such seizures himself.[11] The pathophysiologic effects of hyperbaric hyperoxia have been reviewed elsewhere.[11,13–18] This chapter focuses on the effects of normobaric hyperoxia.

RESPIRATORY EFFECTS OF OXYGEN BREATHING

The best known and most studied effects of normobaric hyperoxia concern the respiratory system. Lavoisier was the first to note changes in the lungs of animals that died from hyperoxia, "…the lung was very flaccid, but bright red, even on the outside, and highly congested with blood…."[19] In 1899, J. Lorrain Smith became the first to systematically study the pulmonary pathology of normobaric hyperoxia, specifically, a 4-day exposure to a FI_{O_2} of 0.74 to 0.80 in mammals. The diffuse intense lung damage from O_2 toxicity described by Smith, and many others since, has been named the "Lorrain Smith effect."[11]

The symptoms and physiologic changes in healthy human volunteers associated with normobaric hyperoxia are the subject of several reviews.[11,13,16,17,20–30] Table 45-1 lists the respiratory effects of O_2 breathing.

TABLE 45-1: RESPIRATORY EFFECTS OF OXYGEN BREATHING (NORMOBARIC HYPEROXIA)

Depression of respiration
Stimulation of respiration
Pulmonary vasodilation; ventilation–perfusion mismatching
Hypercapnia
Absorption atelectasis
Acute tracheobronchitis; decreased mucociliary clearance
Diffuse alveolar damage; adult respiratory distress syndrome
Bronchopulmonary dysplasia

Respiratory Depression and Stimulation, Pulmonary Vasodilation, and Hypercapnia

The depression in respiratory drive is primarily related to decreased stimulation of the hypoxia-sensitive chemoreceptors in the carotid and aortic bodies. These chemoreceptors are the only known O_2 sensors that initiate chemoreflexes.[31,32] Dejours et al showed that the O_2 chemoreceptor drive of respiration, which may account for 10% to 15% of resting ventilation, disappears above an alveolar partial pressure of oxygen (P_{O_2}) of 170 torr, corresponding to a PI_{O_2} of 230 torr, or an FI_{O_2} of 0.30.[16] When O_2 breathing is suddenly initiated, the normal response is twofold.[21,33,34] First, there is a nearly immediate, precipitous decrease in ventilation, whose nadir occurs within 20 to 30 seconds (Fig. 45-2), followed by a gradual return to and slightly above baseline (Fig. 45-3). The acute transient depression is mediated by the arterial chemoreceptor reflexes and may be taken as an index of the level of chemoreceptor activity present during normoxia.[33,35] The subacute mild sustained ventilatory stimulation appears to be secondary to an indirect effect of hyperoxia on the respiratory centers in the brainstem. That is, hyperoxia causes an increase in tissue carbon dioxide tension (P_{CO_2}) secondary to the Haldane effect, or Christian-Douglas-Haldane effect[36] (the increase in blood P_{CO_2}, at a fixed CO_2 content, caused by the release of hemoglobin-bound hydrogen ions and CO_2, bound as carbamino compounds, that occurs on the oxygenation of hemoglobin). Ironically, in one of the earliest reports (1921) of this hyperoxia-induced mild hyperventilation, Dautrebande and Haldane[37] proposed that hyperoxic vasoconstriction of the central nervous system vasculature produces tissue hypercapnia, which, in turn, directly stimulates the respiratory center.

In normal subjects the mild respiratory stimulation induced in the steady state by hyperoxia results in a mild hyperventilation and a mild decrease in partial pressure of arterial carbon dioxide (Pa_{CO_2}) by a few millimeters of mercury, which, in turn, limits the degree of hyperventilation. But in the presence of inspired CO_2, the paradoxical respiratory stimulant effect of O_2 is much more obvious, as noted as early as 1918 by Yamada.[38] When the normally modest fall in Pa_{CO_2} is prevented, (isocapnic) hyperoxia produces a dramatic increase in ventilation (see Fig. 45-3),[39–41] by 21%

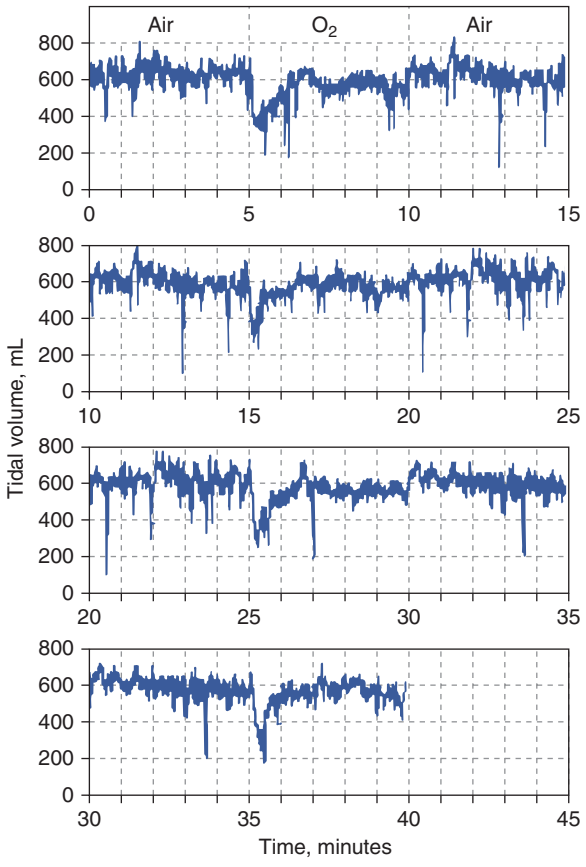

FIGURE 45-2 Acute depression of respiration by normobaric hyperoxia illustrated in a healthy conscious dog breathing from a mask as the inspired gas was alternated between air and O_2 every 5 minutes for 40 minutes. At the onset of each period of O_2 breathing, the continuous record of tidal volume shows a precipitous fall to a mean value of 54% of the normoxia baseline. This decrease in tidal volume is evident by 10 seconds and reaches a nadir at approximately 18 seconds. It is transient, and despite continued hyperoxia, it has returned nearly to baseline by 1.5 minutes. The record is plotted such that the normoxia data at the end of each 15-minute period are repeated on the next line as the beginning of the next 15-minute period to emphasize the repeating, cyclic nature of the alterations in inspired gas and to demonstrate more clearly the response pattern of tidal volume to hyperoxia. (Used, with permission, from Lodato and Jubran.[33])

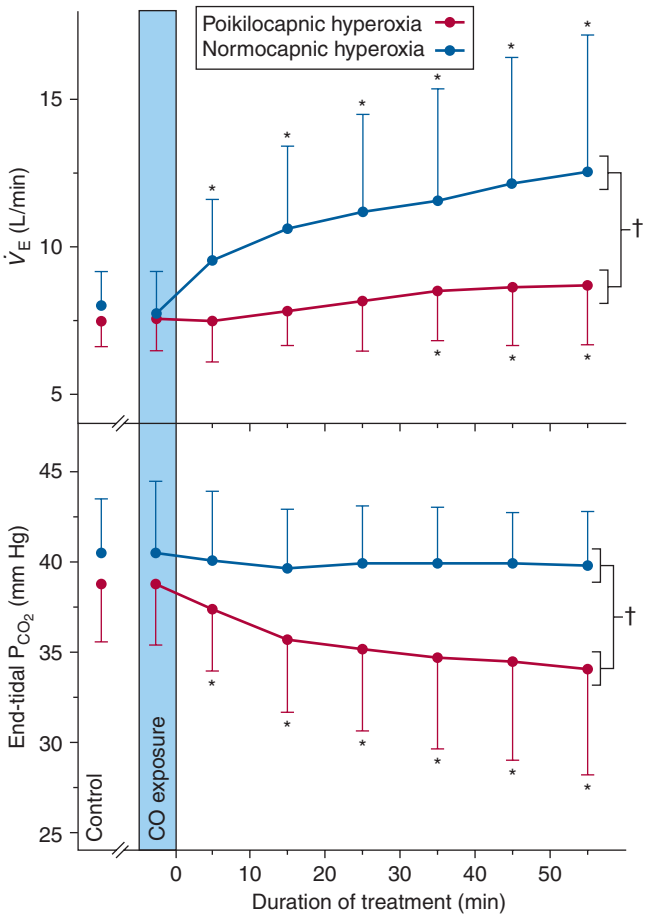

FIGURE 45-3 Steady-state responses of minute ventilation ($\dot{V}_E$) and end-tidal partial pressure of carbon dioxide (P_{CO_2}) to breathing 100% O_2 (hyperoxia) in healthy human subjects (mean ± standard deviation [SD]; n = 14). Poikilocapnic hyperoxia (end-tidal P_{CO_2} was not controlled) produced a mild increase in minute ventilation and a small (4 mm Hg) decrease in end-tidal P_{CO_2}. Normocapnic hyperoxia (CO_2 was added to the inspirate to maintain constant end-tidal P_{CO_2}) produced a marked and progressive increase in minute ventilation. These respiratory stimulant effects of hyperoxia are due largely to the Haldane effect, which results in increased P_{CO_2} in the brain. *Note:* Before time = 0, subjects were exposed to carbon monoxide in this study of CO elimination. (Used, with permission, from Rucker et al.[41])

at FI_{O_2} = 0.30 and by a remarkable 115% at FI_{O_2} = 0.75.[39,40] Becker et al[40] showed that in both poikilocapnic (nonisocapnic) and isocapnic hyperoxia, the Haldane effect is the most important mechanism of the respiratory stimulant effect of hyperoxia in normals. Rucker et al[41] used these observations and showed in normal subjects that, compared with poikilocapnic hyperoxia, isocapnic hyperoxia more rapidly eliminates carbon monoxide and improves cerebral blood flow and O_2 delivery (secondary to the vasodilator effect of the higher level of Pa_{CO_2}) (see Fig. 45-3).

In contrast to the steady-state respiratory stimulant effect of hyperoxia in normals, hyperoxia may instead cause severe respiratory depression in patients with severe chronic obstructive pulmonary disease (COPD). The relative importance of the various mechanisms remains controversial. The conventional view is that hyperoxic hypercapnia is caused by alveolar hypoventilation resulting from reduced hypoxic ventilatory drive secondary to the rise in arterial P_{O_2} (Pa_{O_2}),[42] analogous to "O_2 apnea" in patients recovering from general anesthesia.[17] Other mechanisms include the Haldane effect, deterioration of ventilation–perfusion ($\dot{V}/\dot{Q}$) matching in the lung secondary to hyperoxic release of hypoxic pulmonary vasoconstriction, and development of atelectasis (true shunt). O_2 may also impair $\dot{V}/\dot{Q}$ matching by release of hypoxia-induced bronchoconstriction.[43,44]

The data in both acutely decompensated[45] and stable[46–48] patients with COPD, however, indicate that deterioration of $\dot{V}/\dot{Q}$ matching is the predominant mechanism. Using the multiple inert gas elimination technique in COPD patients, Wagner et al[49] found no systematic changes in the

distribution of $\dot{V}/\dot{Q}$ ratios with 100% O_2. But they did not report attempts to correlate individual changes in Pa_{CO_2} and changes in $\dot{V}/\dot{Q}$ distribution. In mechanically ventilated patients, Dunn et al[50] reported that hyperoxia both worsened $\dot{V}/\dot{Q}$ matching and depressed respiratory drive. For an informative interchange, see Stradling[51] and Aubier et al.[52]

In a more recent study of patients with exacerbations of COPD, Robinson et al[44] used the multiple inert gas elimination technique to compare those patients who retained CO_2 with O_2 with those who did not. In both groups, hyperoxia worsened $\dot{V}/\dot{Q}$ matching by increasing perfusion to relatively poorly ventilated lung units (release of hypoxic vasoconstriction). In only the group who retained CO_2, however, hyperoxia decreased minute ventilation (by 20%) and increased ventilation to overventilated units (increased alveolar dead space). Later, they[53] concluded that in the group that retained CO_2, the largest contribution (46%) was from a decrease in minute ventilation, followed closely (43%) by an increase in alveolar dead space, with a much smaller contribution (11%) from the Haldane effect. The modest Haldane effect was likely secondary to only the modest degree of baseline hypoxemia (mean Pa_{O_2} = 55 mm Hg). They also showed that the risk of hyperoxic hypercapnia is better predicted by a low baseline Pa_{O_2} than by the baseline Pa_{CO_2}.[44]

Neff and Petty[54] showed that severe *chronic* respiratory acidosis (mean P_{CO_2} of 90 torr, mean pH of 7.32) in patients with COPD is well tolerated. Acute hyperoxic respiratory depression can be avoided by using controlled low-flow O_2 administration.[55,56] Hyperoxic hypercapnia may also occur in neuromuscular disease[57] and near-fatal asthma.[58,59]

In a prospective randomized controlled trial[60] of resuscitation of asphyxiated newborn human infants, those resuscitated with room air had better outcomes (Apgar scores, time to first breath, and first cry) than those resuscitated with 100% O_2. These results were attributed, in part, to the respiratory depressant effect of O_2.[60] The current recommendation is that room air is preferred over 100% O_2 for newborn resuscitation.[61]

Absorption Atelectasis

Absorption atelectasis during O_2 breathing occurs in lung units with sufficiently low $\dot{V}/\dot{Q}$ ratios.[62] In such units the rate of capillary absorption of O_2 exceeds the rate of replenishment of alveolar gas during inspiration. This effect depends on the $\dot{V}/\dot{Q}$ ratio, the pattern of ventilation (e.g., the presence of sighs), the FI_{O_2}, the duration of the O_2 exposure, the intrinsic stability of the lung units (e.g., tissue and surfactant factors), and the sensitivity of the local hypoxic pulmonary vasoconstriction to hyperoxic release (which acts synergistically by further lowering the $\dot{V}/\dot{Q}$ ratio). Using the inert-gas elimination technique in healthy nonsmoking subjects, Wagner et al[62] showed that within 30 minutes of breathing 100% O_2, eight of the nine subjects had developed small shunts, averaging 0.5% to 3.2%, with the largest at 10.7% (Fig. 45-4). Theoretically, only approximately 6 minutes is required for the development of such shunts.[63] Clearly, when 100% O_2 breathing is used to quantify a shunt, its magnitude might be overestimated compared to that present during air breathing.

Hyperoxia also enhances absorption from other gas spaces: middle ear and sinuses (causing headache), and

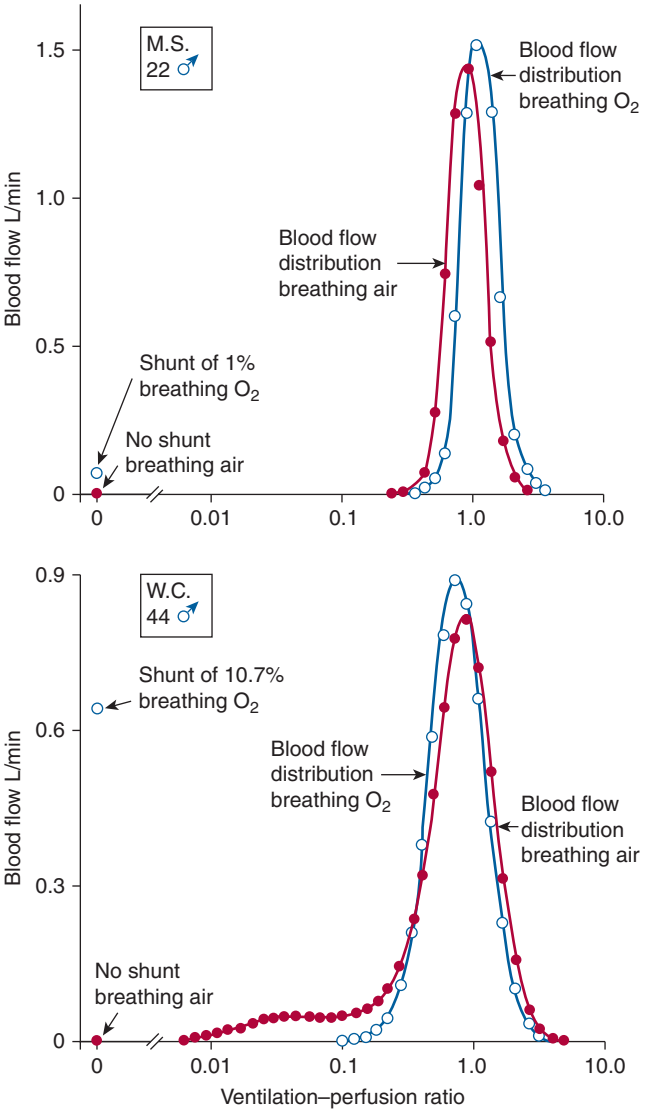

FIGURE 45-4 Distributions of blood flow with respect to ventilation–perfusion ($\dot{V}_A/\dot{Q}$) ratios in two normal subjects while breathing air (normoxia) and after 30 minutes of breathing 100% O_2 (normobaric hyperoxia). *Upper panel.* In the younger subject hyperoxia produced (a) a 1% shunt, indicating a minor degree of hyperoxia-induced atelectasis, and (b) an overall shift of the main body of the distribution to the right to higher $\dot{V}_A/\dot{Q}$ ratios, indicating mild hyperoxia-induced hyperventilation in the steady state. *Lower panel.* In the older subject hyperoxia produced more dramatic changes: The left "shoulder" of the normoxic blood flow distribution (i.e., the blood flow distributed to lung units with low $\dot{V}_A/\dot{Q}$ ratios) was converted by hyperoxia to a 10.7% shunt, indicating substantial amounts of hyperoxia-induced atelectasis, but the main body of the distribution was little altered. (Used, with permission, from Wagner et al.[62])

therapeutically in pneumothorax, bowel obstruction or ileus, and subcutaneous emphysema.[17]

Hyperoxia may also cause atelectasis by interfering with the pulmonary surfactant system,[64] both by injury to the alveolar type II pneumocyte, which synthesizes, secretes, and recycles surfactant, and by injury to the alveolar–capillary interface, resulting in the influx of plasma proteins, which inhibit surfactant function. Hyperoxia-induced atelectasis has also been demonstrated in patients with acute lung injury[65] using the multiple inert-gas elimination technique.

Acute Tracheobronchitis

Comroe et al[66] described acute tracheobronchitis in 1945. Normal subjects breathing 100% O_2 for 24 hours noted substernal distress, cough, sore throat, nasal congestion, eye irritation, ear discomfort, fatigue, and paresthesia, and had a reduction in vital capacity. Symptoms began within 4 and 22 hours after initiating oxygen breathing. Substernal distress was also noted while breathing 75% O_2, but not 50% O_2, for 24 hours. Substernal distress is generally the first symptom noted in normal subjects. It is thought to represent acute tracheobronchitis,[26] but it may also be the result of atelectasis alone.[67] Using fiber-optic bronchoscopy, Sackner et al[68] directly observed evidence of such tracheobronchial inflammation (focal areas of redness, edema, and injection of small vessels of the trachea, depression of mucus velocity) in healthy human subjects after 6 hours of breathing 90% to 95% O_2.

A decrease in vital capacity[66] is considered the best index of O_2 toxicity. In humans, this decrease in vital capacity probably results from the inspiratory pain of the acute tracheobronchitis and from absorption atelectasis. In animals, it is more clearly related to parenchymal lung injury. By impairing an important host defense mechanism, acute tracheobronchitis could predispose to nosocomial pneumonia,[68,69] but this has not been well studied. In rats, hyperoxia also impairs alveolar macrophage function,[70] perhaps adding to the risk of ventilator-associated pneumonia. In healthy subjects with moderate responsiveness to methacholine at baseline, breathing 95% O_2 for 12 hours produced no change in methacholine responsiveness, despite signs and symptoms of acute tracheobronchitis.[71]

Threshold Oxygen Tension for the Development of Oxygen Toxicity

Like other toxic drugs, the effects of O_2 can be viewed in terms of a classical pharmacologic dose–response curve.[13] The dose of O_2 can be expressed as the product of PI_{O_2} and the duration of the exposure (i.e., dose = $PI_{O_2} \times$ time). When plotted, this relationship is a rectangular hyperbola (Fig. 45-5), which expresses the dose–response in terms of vital capacity decrements. The horizontal asymptote of 50% O_2, or 0.5 atm, assumes that at that level of hyperoxia, individuals can be exposed safely for prolonged periods of time.

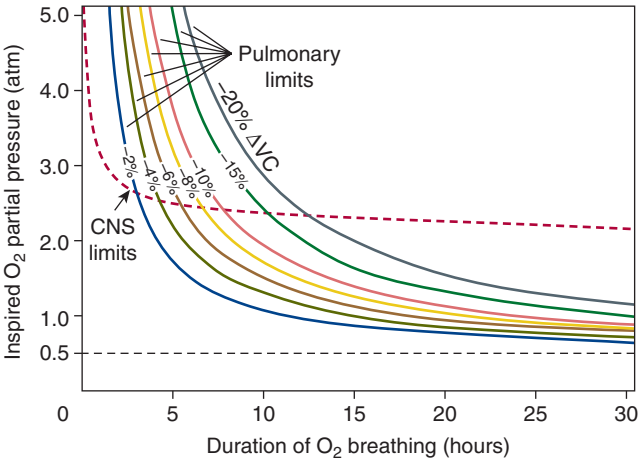

FIGURE 45-5 Oxygen tolerance or dose–response curves for pulmonary and central nervous system (CNS) toxicity in healthy human subjects. Each curve in the family of curves for pulmonary O_2 toxicity is a rectangular hyperbola and represents equivalent O_2 partial pressure-duration "doses" of O_2 exposures. These curves are based on the development of the indicated changes in vital capacity in 50% of the individuals subjected to the indicated O_2 partial pressure-duration exposures. The horizontal asymptote for the lowest pulmonary toxicity curve is at an O_2 partial pressure of about 0.6 atmospheres (atm), indicating that O_2 partial pressures below 0.6 atm appear to be "safe" for exposures of indefinite duration. (Used, with permission, from Lambertsen.[305])

Carpagnano et al[72] reported that breathing 28% O_2 for only 1 hour increased inflammatory markers (8-isoprostane and interleukin-6) in exhaled breath condensate in both healthy subjects and patients with COPD. Vital capacity, however, did not change in either group. These results were likely a manifestation of subclinical tracheobronchitis (see above).

The validity of setting at 0.5 atm the threshold PI_{O_2} for the development of O_2 toxicity, as reflected by a decrease in vital capacity, for exposures of indefinite duration was carefully discussed by Clark and Lambertsen[21] and Clark.[22] Earlier these authors had suggested a less-conservative threshold of 0.6 atm.[73] The rationale for the 0.5-atm PI_{O_2} threshold is based largely on the responses of vital capacity to prolonged hyperoxia in healthy men in the three studies of Comroe et al,[66] Helvey et al,[74] and Michel et al.[75] Figure 45-6 summarizes these exposures and those of two subsequent studies in healthy men.[76,77] Comroe et al[66] exposed nine normal men to a PI_{O_2} of 0.75 atm for 24 hours, with return to air breathing for 15 minutes every 3 hours. They found that five of the nine had chest symptoms and that the group had a modest decrease in vital capacity (mean decrease <300 mL). None of six subjects exposed to PI_{O_2} = 0.5 atm for 24 hours had chest symptoms, and the mean decrease in vital capacity was even less (only approximately 210 mL). They concluded that the safe limit of PI_{O_2} lies between 0.5 and 0.75 atm, probably close to 0.6 atm.[66]

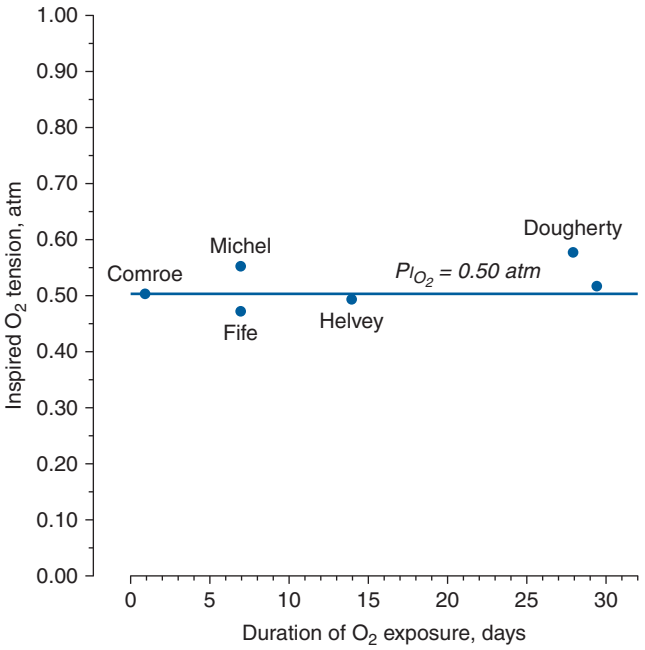

FIGURE 45-6 A summary of studies of prolonged exposure of normal human subjects to an inspired O_2 tension (PI_{O_2}) near 0.5 atm. The points indicate the PI_{O_2} and duration of exposure for the respective studies. The name associated with each point indicates the original reference. Each of these studies reported that the hyperoxic exposure was generally well tolerated, with little or no symptoms of chest tightness, little or no decrease in vital capacity or other pulmonary function tests, and no long-term sequelae. See text for details. (Data from Comroe et al,[66] Helvey et al,[74] Michel et al,[75] Fife et al,[76] and Dougherty et al.[77])

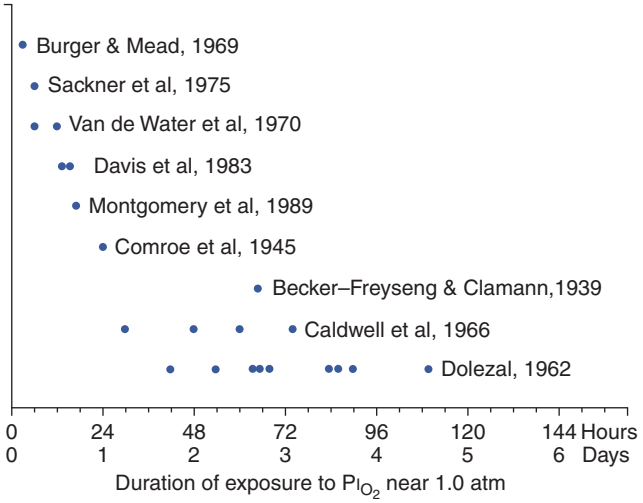

FIGURE 45-7 A summary of studies of prolonged exposure of normal human subjects to an inspired O_2 tension (PI_{O_2}) near 1 atm. The horizontal arrays of points indicate the various durations of exposure within a given study. The names associated with each horizontal array of points indicate the original references. See text for details. (Data from Burger and Mead,[67] Sackner et al,[68] Van de Water et al,[82] Davis et al,[83] Montgomery et al,[80] Comroe et al,[66] Becker-Freyseng and Clamann,[84] Caldwell et al,[85] and Dolezal.[88])

Similar findings were reported by Ohlsson[78] (not plotted in Fig. 45-6) in six men exposed to a PI_{O_2} of 0.78 to 0.88 atm for 53 to 57 hours. Helvey et al[74] found no change in vital capacity, Pa_{O_2}, or chest radiographs after 14 days of exposure to 0.49 atm. Michel et al[75] reported no net change in vital capacity during a 7-day exposure of six normal U.S. Navy men to PI_{O_2} = 0.55 atm. Fife et al[76] studied three subjects at PI_{O_2} of 0.47 atm for 7 days; none developed chest symptoms or a change in vital capacity.

At PI_{O_2} = 0.5 atm for 45 hours, Griffith et al[79] found increased pulmonary clearance of an inhaled tracer and increased albumin in bronchoalveolar-lavage fluid, suggesting the possibility of injury to the alveolar-capillary barrier, or alternatively, only inflamed airways.[80]

Data from the U.S. Navy's Shallow Habitat Air Diving (SHAD) program support 0.6 atm PI_{O_2} as safe for prolonged O_2 exposure.[16] Men tolerated well exposures of 0.51 and 0.57 atm PI_{O_2} for 29.5 and 28 days, without changes in pulmonary function.[16,77,81] With 9-day exposures to mean PI_{O_2} of 0.61 atm (each day, 16 hours at PI_{O_2} = 0.51 atm and 8 hours at PI_{O_2} = 0.81 atm), only one of the three men showed decreased vital capacity (9.7%) and chest discomfort, both coinciding with the daily 8-hour excursions to PI_{O_2} = 0.81 atm.[16,77,81]

Toxicity of Oxygen Near 1 Atmosphere in Normal Subjects

Several studies examining physiologic parameters and other indices of lung injury have also been carried out in humans with exposures at or near a PI_{O_2} = 1 atm (Fig. 45-7). Burger and Mead[67] reported chest pain and tightness and decreases in pulmonary compliance after only 3 hours of breathing pure O_2 at various ambient pressures including 1 atm. The subjects were instructed to refrain from taking deep breaths, yawning, or sighing during the exposure. Postexposure the decrease in compliance and the chest symptoms readily resolved on deep breathing or sighing, suggesting to them that atelectasis rather than direct O_2 toxicity was the etiology. Remarkably, in this study,[67] breathing pure O_2 at only 0.39 atm ambient pressure (PI_{O_2} of only 0.39 atm) produced symptoms that were qualitatively and quantitatively no different from breathing pure O_2 at 1 atm ambient pressure (PI_{O_2} = 1). Yet, breathing with a PI_{O_2} of 1 atm, but in the presence of an equal amount of nitrogen (PI_{N_2} = 1 atm, and total ambient pressure = PI_{O_2} + PI_{N_2} = 2 atm) was virtually no different from control (air breathing at 1 atm ambient pressure). These findings further convinced these investigators that atelectasis, promoted by the lack of nitrogen, was the mechanism of both the chest symptoms and the compliance changes.

As already noted, Sackner et al[68] found bronchoscopic evidence of tracheitis in each of ten normal subjects inspiring a PI_{O_2} of 0.90 to 0.95 atm for 6 hours. None had substernal distress or changes in pulmonary function tests. Tracheal mucus velocity was depressed at 3 hours but was

restored by a β_2-adrenergic agonist. They speculated that the effect on mucus velocity could predispose to bacterial superinfection.[68] In men exposed to 6–12 hours of PI_{O_2} = 1 atm and taking a deep breath every 20 minutes, Van de Water et al[82] found no chest symptoms or changes in pulmonary function or oxygenation.

In fourteen subjects exposed to a PI_{O_2} of 0.95 atm for a mean of 17 hours, Davis et al[83] found that nine had substernal discomfort and six had "mild erythema" on bronchoscopy. Bronchoalveolar lavage fluid showed increased albumin, transferrin, and total protein, consistent with alveolar–capillary leak, but no change in inflammatory cells. In contrast, despite chest pain in subjects breathing PI_{O_2} = 1 atm for 17 hours, Montgomery et al[80] found no changes in pulmonary function tests, solute permeability, or systemic or pulmonary endothelial injury (as reflected by plasma fibronectin and factor VIII). They suggested that the increased albumin and transferrin in bronchoalveolar lavage fluid reported by Davis et al[83] and Griffith et al[79] may not indicate lung parenchymal injury, but may instead have come from the inflamed airways.

Comroe et al[66] studied men exposed to PI_{O_2} = 0.99 atm for 24 hours and found no changes in chest radiographs or oxygenation. Burger and Mead[67] found that breathing pure O_2 at ambient pressure of 0.5 atm, such that PI_{O_2} = 0.5 atm and PI_{N_2} = 0, produced no symptoms but decreased vital capacity.

In 1939 Becker-Freyseng and Clamann[84] reported exposures of two men to a PI_{O_2} of 0.9 atm for 65 hours, or 2.7 days. Both had decreased vital capacity. One developed nausea, vomiting, tachycardia, a febrile tracheobronchitis, dyspnea, and pain in the elbows and knees. The etiology of nausea and vomiting is not clear but could be related to the absorption of bowel gas owing to the absence of nitrogen.[17]

Caldwell et al[85] studied four subjects exposed to PI_{O_2} = 0.98 atm for, respectively, 30, 48, 60, and 74 hours (i.e., 1.25, 2.0, 2.5, and 3.1 days). They were instructed to take five deep breaths and a cough every 2 hours throughout the day but not at night. In addition to chest pain and cough, three of the four had paresthesia, and three had anorexia. They noted decreases in lung volumes, diffusing capacity, but not in the ratio of forced expiratory volume in 1 second to forced vital capacity, and a modest increase in alveolar-arterial (A-a) PO_2 gradient (89 Torr). Chest radiographs were clear. The authors could not exclude atelectasis as the etiology of the decreased vital capacity. The subject with the longest (74 hours) exposure, however, was hospitalized for 2 days postexposure "until his sense of well-being and appetite returned." This subject had dyspnea on exertion for 3 to 4 days postexposure, and his vital capacity did not return to baseline until 24 weeks postexposure.[85] In humans, normobaric hyperoxia does not produce airway obstruction,[71] but may do so in dogs[11,86] and primates.[87] Hyperbaric hyperoxia may produce airway obstruction in humans.[25]

The longest voluntary human exposures to 100% O_2 are by Dolezal.[88] Twelve subjects were exposed to the limit of tolerance. The mean exposure was 74 hours (3.1 days), with a range from 42 hours (1.75 days) to a remarkable 110 hours (4.6 days). P_{CO_2} of the exposure chamber remained high, approximately 7 to 8 torr (1%). In addition to retrosternal pain and cough, the subjects eventually experienced dyspnea, loss of gustatory sensation, anorexia, nausea (after 48 to 60 hours) and vomiting, general weakness, and vertigo (beyond 60 to 72 hours). Three developed fevers of 38.5°C to 39.3°C (101.3°F to 102.7°F). As evidence of additional systemic (nonrespiratory) toxicity, nine of the twelve noted paresthesias and hypesthesias of the finger tips in both hands and feet, which did not resolve until 14 to 21 days postexposure. Vital capacity decreased by 17%, minute ventilation progressively increased by 39% throughout the exposure, and a mild respiratory alkalosis developed. Remarkably, arterial O_2 saturation remained at or near 100% throughout the exposure and was normal postexposure. Dolezal interpreted this intact oxygenation as evidence that pulmonary edema and "hepatization foci," as seen in animal studies, had not developed.[88]

Taken together, these reports seem to imply that evidence for major sustained parenchymal lung injury, or the equivalent of acute respiratory distress syndrome (ARDS), has been much more readily observed in animals than in normal humans.

Toxicity of Oxygen Near 1 Atmosphere in Patients

Most patients who receive prolonged high FI_{O_2} have severe parenchymal lung injury (e.g., ARDS). Intriguing data are available, however, from human patients without major lung disease. In eighteen patients postoperative from cardiac surgery, Singer et al[89] confirmed that short exposures to 100% O_2 for a mean of 24 hours (range 15 to 48 hours) have no demonstrable adverse effects. They found no change in shunt, compliance, dead space, radiologic atelectasis, or clinical course compared to a group who received only the FI_{O_2} (mean: 0.32) required for adequate oxygenation. Singer et al[89] also reported two additional patients who were ventilated with 100% O_2 for 5 and 7 days, respectively. Throughout the 5-day and 7-day periods, these patients showed progressive improvement in Pa_{O_2}, from 368 to 430 torr and from 155 to 404 torr, respectively. The first patient was extubated on the fifth day and subsequently discharged from the hospital. The second patient died on the seventh day of massive pulmonary hemorrhage related to a greatly prolonged bleeding time on anticoagulants.

In a companion paper by the same group, Barber et al[90] reported the effects of ventilating patients with massive cerebral trauma and resultant irreversible, ultimately fatal brain damage, with either 100% O_2 (n = 5) or air (n = 5). Ventilation with the respective gases continued until death, which occurred within 31 to 72 hours, or 1.3 to 3 days (mean: 2.2 days), in the O_2 group and within 50 to 216 hours, or 2.1 to 9 days (mean: 4.3 days), in the air group. None had preexisting lung disease. None had spontaneous respirations. All received tidal volumes greater than 800 mL, periodic tracheal suctioning, frequent changes in body position, and

treatment with corticosteroids. After 2 days, the O_2 group had a lower mean Pa_{O_2} (120 vs. >400 torr, tested on 100% O_2 in both groups), greater shunt and dead space, but no difference in compliance. The O_2 group also had greater worsening of chest radiographs, progressing to multilobar infiltrates, consolidation, or collapse. At autopsy the O_2 group also had greater lung weights. Perhaps the most striking finding was that at autopsy no histologic differences between the groups were apparent. Both had varying degrees of bronchopneumonia, intraalveolar and interstitial edema, atelectasis, congestion, hemorrhage, and intravascular coagulation. Hyaline membranes, however, were "conspicuously absent" in both groups. It seems likely that hyperoxia-induced atelectasis (and perhaps ventilator-induced lung injury, with an 800-mL tidal volume), could explain many if not all of their findings, especially in such patients with no spontaneous respiratory effort.

Hyde and Rawson[91] reported the effects of inadvertent exposure to 83% to 91% O_2 for 12 to 32 days in five intubated patients with neuromuscular disease. The authors made a presumptive diagnosis of hyperoxic pneumonitis based on scattered patchy infiltrates on chest radiographs, fever, and leukocytosis. The postmortem examination of the one patient who died (a depressed patient who was found dead with the respirator disconnected) showed "thickening of the alveolar septa by edema and fibroblastic proliferation … fibrin deposition and increased numbers of lining cells in the alveolar lumina." No hyaline membranes were described. However, interpretation of their findings is confounded by the fact that these patients also had copious secretions, "a major degree of atelectasis" (four of the five patients), and pneumonia (four of five), which are common complications of such patients even in the absence of hyperoxia. Furthermore, unlike ARDS, these patients responded rapidly to minimizing the FI_{O_2}, "vigorous tracheal aspiration (and) meticulous tracheal toilet," and antibiotics. In fact, after these changes in management, all four were weaned from mechanical ventilation within 2 to 5 days.

Perhaps the longest reported exposure of a patient to hyperoxia was that of a 32-year-old man with myasthenia gravis, who was ventilated with 80% O_2 (which could not be lowered for technical reasons) for 150 days, at which time he developed blindness bilaterally with retinal artery constriction and retinal atrophy.[92] Hyperoxia constricts retinal arteries in adults as well as neonates.[93] During the exposure his Pa_{O_2} remained 250 to 300 torr. He remained another 130 days on 60% O_2 (Pa_{O_2} 120 to 160 torr) before weaning from mechanical ventilation on day 280, after which his Pa_{O_2} remained normal (80 to 100 torr). Except for the elevated $P(a\text{-}a)O_2$ gradient, consistent with atelectasis, inadequate control of secretions, or pneumonia, no signs or symptoms of pulmonary O_2 toxicity were reported.

In a brief communication Smith et al[94] reported the absence of any evidence of O_2 toxicity, as determined by radiographs, pulmonary function, bronchoscopy, or histopathology, in forty-one patients treated with high-frequency jet ventilation using a mean FI_{O_2} of 0.92 (range: 0.80 to 0.95) for a mean of 4.1 days (range: 8 hours to 12 days). They suggested that their lack of O_2 toxicity may be secondary to the lack of "stretching and shearing forces" encountered in conventional mechanical ventilation.

More recently, Capellier et al[95] retrospectively studied seventy-four patients with FI_{O_2} ≥0.90 continuously for at least 48 hours. They found that the duration of this exposure in the seventeen survivors was surprisingly long (mean: 5.6 days) and not different form the fifty-seven nonsurvivors (5.9 days). One survivor had exposure to FI_{O_2} ≥0.90 for 15 days and was eventually discharged, breathing spontaneously with a normal Pa_{O_2} on room air. The majority of deaths were related to sepsis and multiorgan failure rather than to progressive hypoxemic respiratory failure. Of the thirty-seven patients exposed to FI_{O_2} ≥0.90 for at least 4 days, only 5 (14%) died with hypoxemia. These authors concluded that the lungs of patients with acute respiratory failure appear relatively resistant to prolonged hyperoxia, that high plateau pressures may be more injurious than high FI_{O_2}, and that a prospective trial may be helpful in clarifying the optimum management of FI_{O_2} for such patients.[95]

Pathology of Pulmonary Oxygen Toxicity: Diffuse Alveolar Damage

In 1958 Pratt[96] was the first to note in patients pathologic changes attributed to hyperoxia. The pathology of pulmonary O_2 toxicity has been reviewed by a number of authors[13,16,20,23–26,28,97,98] and is the subject of a monograph.[11] Because of preexisting lung disease in most human studies, the most persuasive data come from animals. A few studies, however, of hyperoxic pulmonary pathology in humans without preexisting lung disease are available,[99–101] and the findings are consistent those in animals. The histologic pathology of hyperoxia-induced acute lung injury is that of diffuse alveolar damage.[98] *Diffuse alveolar damage* is a descriptive term for the predictable but nonspecific features of acute lung injury from a variety of toxins, including infectious agents, other inhalants, pharmaceutical agents and other ingestants, radiation, and the multiple causes of ARDS, including trauma and sepsis.[98] Hyperoxia has in common with all other causes of diffuse alveolar damage an initial injury to both the alveolar endothelial and epithelial cells.

Diffuse alveolar damage can be divided into two stages, as first defined by Nash et al,[102] and detailed in Table 45-2.[97] The first is an early acute or exudative stage within the first week, characterized by interstitial and intraalveolar edema, intraalveolar hemorrhage and fibrin deposition, sloughing of the alveolar lining cells (type I pneumocytes) with denudation of the alveolar basement membrane, and hyaline membranes, which represent cytoplasmic and nuclear debris from sloughed cells mixed with fibrin.[98] Late in the first week an inflammatory cell infiltrate into the interstitium is evident. The small pulmonary arterioles and alveolar capillaries may show fibrin thrombi. Also by the end of the first week, proliferation of type II pneumocytes appears along the alveolar

TABLE 45-2: DIFFUSE ALVEOLAR DAMAGE IN HUMANS AT 0.8 TO 1 ATMOSPHERES OF OXYGEN

Changes	Time of Occurrence
A. Exudative	
1. Capillary congestion, focal intraalveolar edema, few cases with fibrin thrombi in capillaries and small arteries	Less than 3 days
2. Interstitial edema	After 3 days
3. Hyaline membranes lining alveolar septa	22 hours to 7 days, decreasing or focal thereafter
4. Interstitial mononuclear cell infiltrate (lymphocytes, plasma cells, unclassified cells)	Less than 1 week
B. Proliferative	
1. Alveolar lining cell hyperplasia	Focal at 3 days, diffuse at 1 week
2. Interstitial fibrosis	Focal at 3 days, diffuse at 8 days, severe by 2 weeks

Derived from light microscopic data of Katzenstein et al.[100]

Data from Balentine JD. *Pathology of Oxygen Toxicity*. New York: Academic Press; 1982.

lining, representing a reparative phase; the type II pneumocytes can later differentiate into type I pneumocytes.[98]

The second stage of diffuse alveolar damage[98] is a proliferative or organizing stage and is noted beyond the first week. Fibroblastic proliferation in the interstitium and focal intraalveolar fibrosis appear. Whereas the edema and hyaline membranes have largely resolved, the interstitial inflammatory infiltrate and the alveolar lining cell hyperplasia are still present. A striking interstitial fibrosis develops in association with extensive interstitial deposition of collagen.

The issue of just how sensitive the human lung is to hyperoxic lung injury is still somewhat open to question. Remarkably, as noted above, in patients without prior lung injury who received 100% O_2 for up to 7 days, typical histologic lesions were not found.[89,90] These observations prompted Katzenstein[98] to suggest that humans may be susceptible to significant hyperoxic lung injury only after their lungs are first damaged by other insults. Other authors have concluded simply that no consistent evidence shows that hyperoxia (FI_{O_2} >0.60) is dangerous in acute lung injury or ARDS.[103]

Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia was initially described in 1967[104] and has been reviewed in detail by Balentine[11] and Truog.[105] It is a form of chronic lung disease that follows therapy for idiopathic respiratory distress syndrome of the newborn, or hyaline membrane disease. Bronchopulmonary dysplasia develops in very low-birth-weight infants (≤1500 g at birth). Its incidence and prevalence have risen substantially in recent years because of the markedly increased survival of these infants.[105] It has become the most common cause of chronic lung disease in infants.[106] Its pathologic features include fibrosis and destruction of acinar structures with a resultant combination of scarring and emphysematous changes. It appears to have three contributing mechanisms: (a) ventilator-induced lung injury,[107] (b) hyperoxia, with increased O_2 radicals in the presence of an immature antioxidant defense system,[108] and (c) peribronchial pulmonary edema secondary to the birth-related increased pulmonary blood flow through an immature and injured pulmonary microcirculation.[105] Because high levels of both mechanical ventilation and hyperoxia virtually always occur together in patients with idiopathic respiratory distress syndrome, the relative roles of these two etiologic factors is unclear. Churg et al[109] have described the equivalent of bronchopulmonary dysplasia, including "honeycombing," in three adult patients who also had received the combination of high ventilator pressures and high FI_{O_2} for 3 to 7 weeks. Baboon and other animal models for bronchopulmonary dysplasia exist.[110,111]

In recent years, the risk and severity of bronchopulmonary dysplasia have decreased with the use of antenatal glucocorticoids, less aggressive mechanical ventilation, including limiting the FI_{O_2} and the use of continuous positive airway pressure,[112,113] and postnatal surfactant.[112–114]

NONRESPIRATORY EFFECTS OF OXYGEN BREATHING

The nonrespiratory effects of hyperoxia have been extensively reviewed elsewhere.[11,13,28,115] The best-recognized effects include hemodynamic changes, suppression of erythropoiesis and serum erythropoietin,[116] the Haldane effect (see the section Respiratory Depression and Stimulation, Pulmonary Vasodilation, and Hypercapnia), retinopathy of prematurity (previously called retrolental fibroplasia), and, only at O_2 pressures exceeding 2 atm, seizures.

Retinopathy of Prematurity

Retinopathy of prematurity results from hyperoxic vasoconstriction and injury to the exquisitely susceptible, growing retinal capillaries of premature neonates (<26 weeks gestation).[11,117,118] The resulting paradoxical "hyperoxic hypoxia" and tissue ischemia induces neovascularization within the retina and adjacent vitreous. This retinovitreal neovascularization eventually results in retinal detachment and blindness,[118] a process similar to that in diabetic and sickle-cell retinopathies.[117] Both the incidence and severity of retinopathy of prematurity correlate with the duration of exposure to Pa_{O_2} greater than 80 torr.[119] The pathogenesis of retinopathy of the newborn has two phases.[120] The first phase (20 to 30 weeks postmenstrual age) involves hyperoxia and decreased vascular endothelial growth factor (VEGF) levels, whereas the second phase (31 to 44 weeks) involves hypoxia and increased VEGF levels. Activation of the VEGF receptor

TABLE 45-3: ACUTE HEMODYNAMIC EFFECTS OF OXYGEN BREATHING (NORMOBARIC HYPEROXIA)

Parameter	Effect
Heart rate	Decreased
Cardiac output	Decreased
Right-ventricular stroke work	Decreased
Left-ventricular stroke work	Unchanged
Right- and left-ventricular work rates	Decreased
Systemic arterial pressure	Variably increased, decreased, or unchanged
Pulmonary arterial pressure	Decreased
Pulmonary arterial wedge pressure	Unchanged
Right-atrial pressure	Increased
Systemic vascular resistance	Increased
Pulmonary vascular resistance	Decreased

Data from Lodato.[115]

VEGFR-1 can prevent the hyperoxia-induced retinal vascular degeneration of retinopathy of prematurity.[121] More recently, it has been reported that intravitreal bevacizumab (anti-VEGF) benefitted infants with retinopathy of prematurity.[120] The optimum oxygenation is unclear. The recent SUPPORT trial in premature infants reported that a lower target range of arterial oxyhemoglobin saturation (Sp_{O_2}) (85% to 89% vs. 91% to 95%) increased mortality but decreased severe retinopathy in the survivors.[112,113]

Acute Hemodynamic Effects

The acute hemodynamic effects of normobaric hyperoxia in healthy humans have been studied by a number of investigators[115,122–134] and summarized by Lodato,[28,115,130] who also found virtually identical responses in conscious dogs.[115,130] Table 45-3 summarizes these results. The decrease in heart rate is vagally mediated.[33,123] The decrease in cardiac output is primarily the result of the relative bradycardia, but some studies also have shown an independent contribution from a decrease in stroke volume or diastolic dysfunction.[135] The decrease in cardiac work[115] is primarily the result of the bradycardia, but right-ventricular afterload is reduced by pulmonary vasodilation.[136]

Systemic vasoconstriction is one of the most consistent findings and occurs independently of any changes in P_{CO_2}.[137,138] Virtually all systemic beds constrict during hyperoxia, but in rats the splanchnic circulation vasodilates.[139] The central nervous system vasoconstrictive effect has been used to treat vascular headaches.[17] The mechanisms are not fully understood and appear quite diverse among various vascular beds. Hyperoxic vasoconstriction may be a continuum of the mechanism of hypoxic vasodilation.[140] That is, red blood cells can regulate vasomotor tone depending on their degree of oxyhemoglobin saturation: As saturation rises with hyperoxia (or falls with hypoxia), the red blood cell releases less (or more, respectively) of the vasodilators adenosine 5′ triphosphate [141] and nitric oxide from *S*-nitroso-hemoglobin.[142] In the central nervous system[143,144] and in the human forearm,[145] hyperoxia vasoconstricts by inactivation of endothelium-derived relaxing factor/nitric oxide by superoxide anion.[140,146] In the coronary bed, hyperoxia constricts by closure of adenosine 5′ triphosphate-sensitive potassium channels.[147] In the human retinal artery the reported mechanisms include release of endothelin-1[148] and prostanoids,[149] in addition to the mechanisms above.[138] The human umbilical vein vasoconstricts to hyperoxia via local release of norepinephrine.[150]

Despite the systemic vasoconstriction, systemic arterial pressure is variably affected, owing to the concurrent decrease in cardiac output. Jubran and Lodato[151] showed that the bradycardia is independent of the arterial baroreceptor reflex.

The hemodynamic changes induced by hyperoxia have also been documented in patients with a wide variety of conditions, including general anesthesia,[152] during cardiopulmonary bypass,[153] immediately following coronary bypass surgery,[154] with cardiac risk,[155] congestive heart failure,[135,156,157] sepsis,[158,159] cirrhosis,[160] and children with acyanotic congenital heart disease.[161]

In patients with pulmonary hypertension from a variety of causes (primary, portal, human immunodeficiency virus, atrial septal defect, ventricular septal defect, scleroderma) with mean baseline $Pa_{O_2} = 64$ mm Hg, breathing 100% O_2 has been reported to decrease pulmonary vascular resistance by 24%.[162] A limitation of this study is that cardiac output was calculated from the Fick principle, assuming that hyperoxia did not change O_2 consumption, an invalid assumption.[115]

Oxygen Consumption

Contrary to Priestley's speculation, which he based on his observations of a candle burning more vigorously in O_2 (see above), that hyperoxia may enhance metabolic rate, recent evidence indicates that hyperoxia can actually decrease metabolic rate as measured by O_2 consumption. It has long been established that hyperoxia decreases O_2 consumption in both cells and tissue preparations, but the biochemical mechanisms are unclear.[163] Chapler et al[164] showed that under certain experimental conditions (e.g., acute anemia, autonomic inhibition) in anesthetized dogs, hyperoxia paradoxically decreased O_2 consumption. Lodato[115] showed under more general physiologic conditions in unsedated, intact, healthy, conscious dogs, that hyperoxia (mean Pa_{O_2} = 475 torr) decreased whole-body O_2 consumption by nearly 20% (Fig. 45-8). Unexpectedly, in this study the arteriovenous difference in O_2 content decreased along with the decrease in cardiac output (both by approximately 10%). Paradoxically, O_2 delivery (cardiac output × arterial O_2 content) did not change, and O_2 extraction (O_2 consumption/O_2 delivery) decreased. Subsequently, Lodato[130] reported that when O_2 consumption and O_2 delivery were plotted in the conventional way, as ordinate and abscissa, respectively,

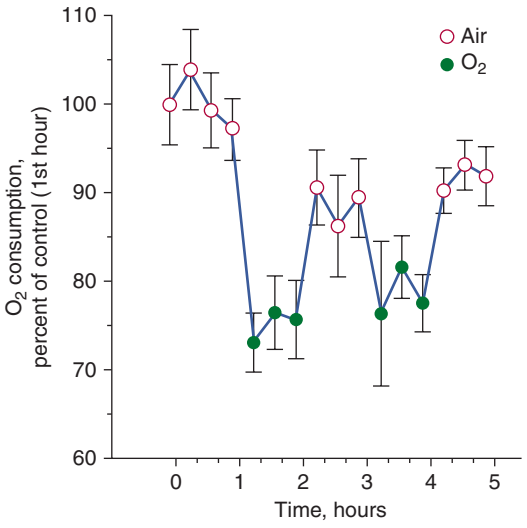

FIGURE 45-8 Time course of resting whole-body O_2 consumption as the inspired gas was alternated hourly between air (*open circles*) and O_2 breathing (hyperoxia; mean Pa_{O_2} = 475 torr) (*closed circles*) in six conscious dogs. Each point is expressed as percent of mean O_2 consumption (6.19 ± 0.65 mL O_2.min.$^{-1}$kg^{-1}) during control period (first hour). Paradoxical decrease in O_2 consumption during hyperoxia was fully developed by 20 minutes, was maintained for at least 1 hour, and was both reversible and reproducible. Mean of each 1-hour period was statistically significantly different from mean of its adjacent 1hour periods. (Used, with permission, from Lodato.[115])

hyperoxia produced a unique parallel shift downward in the O_2 consumption–O_2 delivery relationship (Fig. 45-9). Hyperoxia-induced decreases in O_2 consumption have also been reported in children with acyanotic congenital heart disease,[161] patients with sepsis,[158,159] cardiac-risk patients,[155] and patients during cardiopulmonary bypass.[153]

The mechanisms by which hyperoxia could induce such a decrease in O_2 consumption are obscure. The possibilities include[115] that hyperoxia may produce (a) systemic cellular O_2 toxicity, (b) a paradoxically inadequate O_2 supply ("hyperoxic hypoxia") at the microcirculatory level, owing to the diffuse systemic vasoconstriction,[165–168] or (c) a facultative decrease in O_2 demand, as has been demonstrated in mammals under certain physiologic challenges unrelated to hyperoxia.[169] Reinhart et al[159] investigated the second possibility. In patients with sepsis[159] and in stable patients with cardiac risk,[155] they infused the antioxidant *N*-acetylcysteine. They found that *N*-acetylcysteine attenuated the hyperoxia-induced decreases in both O_2 consumption (from 34% to only 11%) and gastric intramucosal pH (by tonometry, used as a marker of the adequacy of gastric O_2 supply).[159]

Pulmonary versus Systemic Cause of Death from Hyperoxia

Death in experimental animals exposed to prolonged hyperoxia is usually attributable to ARDS-like acute lung injury.[170,171] Hypoxemia, however, is generally absent. Matalon et al[171] found in sheep a terminal severe acute respiratory acidosis but supranormal Pa_{O_2} = 200 torr at death. Harabin et al[172] provided intriguing evidence that *systemic*, rather than pulmonary, O_2 toxicity may be the predominant cause of death. Dogs exposed continuously to 100% O_2 lived for a mean of 88 hours (3.7 days), but surprisingly, they maintained Pa_{O_2} at approximately 500 torr until shortly before death. Their brief preterminal course was characterized by a precipitous decrease in cardiac output and blood pressure accompanied by metabolic acidosis, all of which preceded the terminal deterioration in gas exchange. In fact, the acidosis (presumably lactic as seen terminally in hyperoxemic rabbits[173]) occurred in the face of supranormal Pa_{O_2} of 200 to 400 torr, indicating a systemic, or cardiovascular, rather than a pulmonary (hypoxemic) mechanism of their terminal deterioration.[172] Thus, these animals died clearly *with* lung injury but not so clearly *from* lung injury.

Further evidence of primary cardiovascular O_2 toxicity has been provided by Busing et al[174] (and others[11]), who described disseminated microscopic foci of myocardial necrosis (Fig. 45-10), especially in the subendocardium of the left ventricle, occurring in rabbits subjected to 60 hours (2.5 days) of 100% O_2. Hypoxemia from hyperoxic lung injury was excluded as the mechanism because the cardiac necrosis developed while the Pa_{O_2} was 300 to 400 torr, and, in fact, it preceded any morphologic pulmonary changes. Fracica et al[87,175] reported that baboons exposed to 100% O_2 for more than 80 hours (>3.3 days) had substantial deterioration in cardiac function without significant deterioration in oxygenation (mean Pa_{O_2} = 437 torr). These animals also showed focal areas of myocardial necrosis.[175] Robinson et al[176] studied several species of primates exposed to 100% O_2 for up to 14 days. Pa_{O_2} remained high (400 to 500 torr) until near death when it fell sharply and Pa_{CO_2} rose. The baboons, however, did have other clinical (increase respiratory effort) and pathologic evidence of severe lung injury. In contrast, the squirrel monkeys were surprisingly insensitive to pulmonary O_2 toxicity. They, too, died from the hyperoxic environment but of undetermined cause. Cardiac histopathologic examination was not reported.

Thus, it appears that experimental animals exposed to hyperoxia die primarily from systemic rather than pulmonary O_2 toxicity.

MECHANISMS OF OXYGEN TOXICITY

Formation of Reactive Oxygen Species

It is now generally accepted that the toxic effects of hyperoxia are the direct result of increased concentrations of highly reactive O_2-derived free radicals.[20,177–181] This extensive topic is now the subject of two recent monographs.[182,183] The "O_2-radical hypothesis" was first proposed in 1954 by Gerschman et al,[184] who suggested that hyperoxia-induced tissue injury and X-irradiation-induced tissue injury have as a common mechanism the production of reactive O_2 species

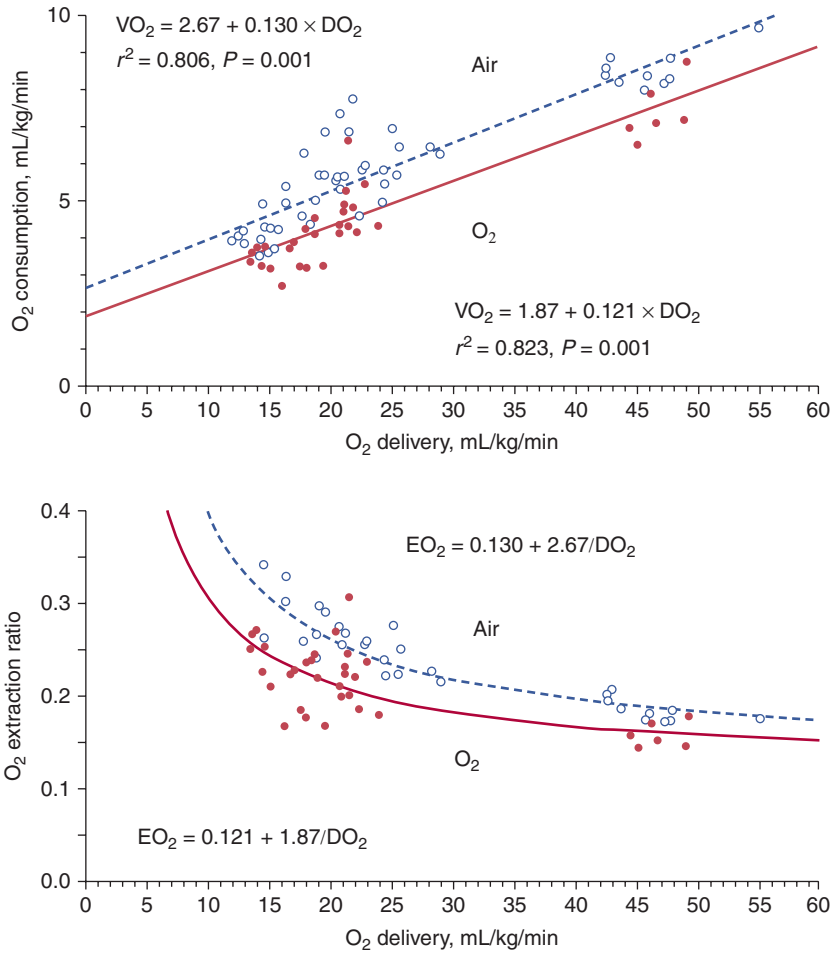

FIGURE 45-9 *Upper panel.* Relationship between O_2 consumption and O_2 delivery in six healthy, resting, conscious dogs for air (*open circles*) versus O_2 breathing (normobaric hyperoxia; *closed circles*). Each dog is represented by $n = 10$ independent determinations during air breathing and by $n = 6$ independent determinations during hyperoxia. Hyperoxia produced a unique parallel shift downward in the O_2 consumption–O_2 delivery relationship (see text). *Lower panel.* Oxygen extraction ratios corresponding to the data points in upper panel. (Used, with permission, from Lodato.[130])

in excess of the antioxidant defenses. Gerschman[185] pointed out that O_2 at 20% is potentially toxic and that its gradual accumulation in the atmosphere induced the evolution of cellular defense mechanisms.

The basic chemistry of reactive O_2 species has been extensively reviewed.[186–190] Molecular O_2 itself is generally nontoxic and only modestly reactive. When it is chemically reduced by the sequential addition of electrons (e^-), however, it forms partially reduced reactive O_2 species (ROS), as follows:

$$O_2 \xrightarrow{e^-} O_2^- \xrightarrow{e^- + 2H} H_2O_2 \xrightarrow{e^- + H} OH\cdot \xrightarrow{e^- + H} H_2O$$

where O_2^- is superoxide anion radical, H_2O_2 is hydrogen peroxide, and OH· is the hydroxyl radical. Superoxide is only modestly reactive. It can, however, yield the very highly reactive hydroxyl radical. Alternatively, superoxide can react with nitric oxide (NO), also a free radical, forming the very highly reactive peroxynitrite anion, $ONOO^-$. Of the ROS, the hydroxyl radical is by far the most reactive, reacting with all known biomolecules so rapidly that it acts only locally where it is produced.[187] In contrast, O_2^- and H_2O_2 can travel some distance and enter cells, H_2O_2 by simple diffusion across the cell membrane and O_2^- via anion channels.[189,191] The high reactivities of ROS and reactive nitrogen species (RNS) such as NO and peroxynitrite are the result of their very high affinity for additional electrons. This extreme electron affinity causes these agents to rapidly pull an electron from the nearest available molecule, resulting in oxidative damage to nearby lipids, proteins, and DNA. This oxidant damage is manifested by lipid peroxidation, enzyme inhibition, and DNA strand breakage, which can lead ultimately to loss of cell integrity and cell death.

The sources of ROS are many (Fig. 45-11). In the normal processes of cellular metabolism, ROS are produced at basal rates. Superoxide radical can be generated by both enzymatic and nonenzymatic (autooxidation) reactions. The major source of ROS in the lung is the mitochondrial electron-transport chain, during the production of adenosine 5′ triphosphate via oxidative phosphorylation.[190] The fate of nearly all O_2 taken up by the body is four-electron catalytic

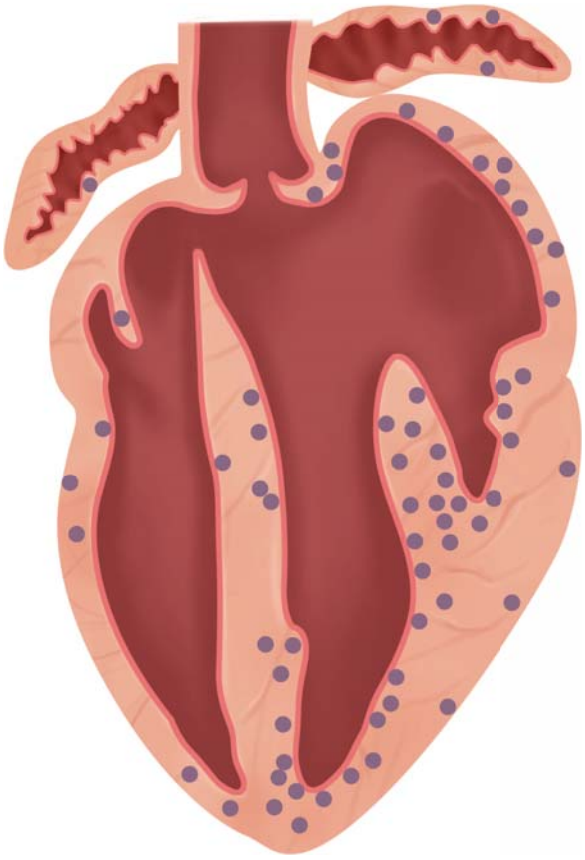

FIGURE 45-10 Distribution of disseminated microscopic foci of myocardial necrosis seen in rabbits exposed to 100% O_2 (normobaric hyperoxia) for more than 60 hours, as illustrated by a schematic longitudinal section through all chambers of the heart. All four chambers were affected, but the subendocardium of the left ventricle, including the papillary muscle and the septum, were the most vulnerable. The arterial O_2 tension was consistently greater than 300 torr, indicating that hypoxemia (from possible hyperoxic lung injury) was not the mechanism of the necrotizing cardiomyopathy. (From Busing CM, Kreinsen U, Buhler F, Bleyl U. Light and electron microscopic examinations of experimentally produced heart muscle necroses following normobaric hyperoxia. *Virchows Arch A Pathol Anat Histol.* 1975;366:137–147. With kind permission from Springer Science and Business Media.)

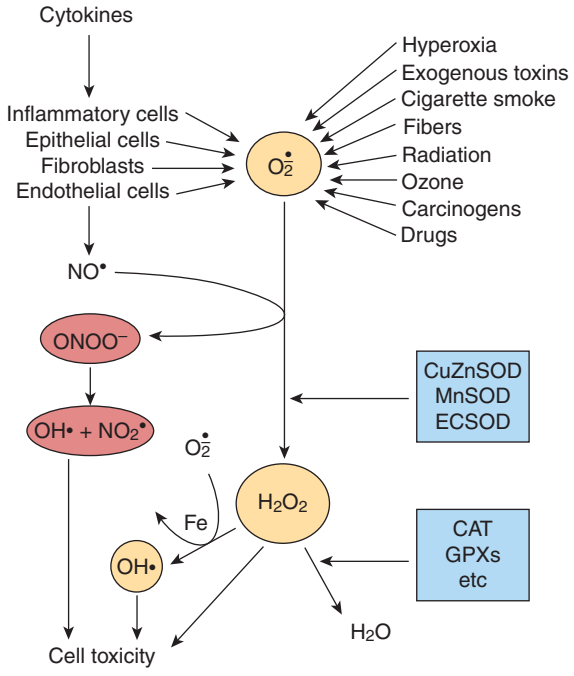

FIGURE 45-11 Sources of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in the lung. Both inflammation (*upper left*) and exogenous toxins (*upper right*), including hyperoxia, produce superoxide ($O_2^{\cdot}$), which can react with nitric oxide (NO) to produce peroxynitrite ($ONOO^-$) and other toxic RNS and ROS. Or, superoxide may be metabolized to hydrogen peroxide (H_2O_2), which may yield water (H_2O) or the toxic hydroxyl radical ($OH^{\cdot}$). See text for details. *CAT*, catalase, *GPx*, glutathione peroxidase, *SOD*, superoxide dismutase. (Reprinted with permission of the American Thoracic Society. Copyright © 2012 American Thoracic Society. From Kinnula VL, Crapo JD. Superoxide dismutases in the lung and human lung diseases. *Am J Respir Crit Care Med.* 2003;167(12):1600–1619. Official Journal of the American Thoracic Society.)

reduction by mitochondrial cytochrome *c* oxidase to form water. Normally, a tiny fraction (0.1% to 2%[189,192]) of the electron flow along this chain "leaks" off upstream of cytochrome oxidase, principally at the reduced form of nicotinamide adenine dinucleotide (NADH) dehydrogenase and ubiquinone (Fig. 45-12), and partially reduces O_2 to yield $O_2^{\cdot-}$.[178,193] The other major source of intracellular superoxide generation is the plasma membrane nicotinamide adenine dinucleotide phosphate (NADPH) oxidase.[163,194]

Under pathologic conditions, such as hyperoxia or inflammation, which may itself result from hyperoxic injury or from invading microorganisms, or other exogenous toxins (ozone, cigarette smoke, fibrogenic material, ionizing radiation, paraquat, or cytotoxic drugs), the production of both ROS and RNS is increased (see Fig. 45-11).[179,186–190] One hundred percent O_2 results in a 10-fold to 15-fold increase in mitochondrial H_2O_2 production.[195,196]

Inflammation results in increased production of ROS and RNS by release of proinflammatory chemokines and cytokines, which recruit neutrophils and other inflammatory cells (see Fig. 45-11). These proinflammatory stimuli also activate the membrane-bound NADPH-oxidase complex, which generates large amounts of superoxide,[189] manifested as the "respiratory burst" of neutrophils and macrophages (Fig. 45-13). Inflammation also upregulates inducible nitric oxide synthase, which produces great quantities of NO from L-arginine.[197] Thus, as above, superoxide and NO may react to yield the very highly reactive peroxynitrite anion, $ONOO^-$, which may be the most important species responsible for the incapacitation of microorganisms.[187] Inducible nitric oxide synthase can also generate superoxide.[198] An additional enzymatic pathway to increased ROS and RNS, particularly following ischemia, is via xanthine dehydrogenase.[189]

Superoxide radical, produced by any of the several pathways above, is converted to hydrogen peroxide by both spontaneous and enzymatic dismutation. Hydrogen peroxide, in turn, can be further reduced by transition metals to generate the hydroxyl radical. The metal ion-dependent

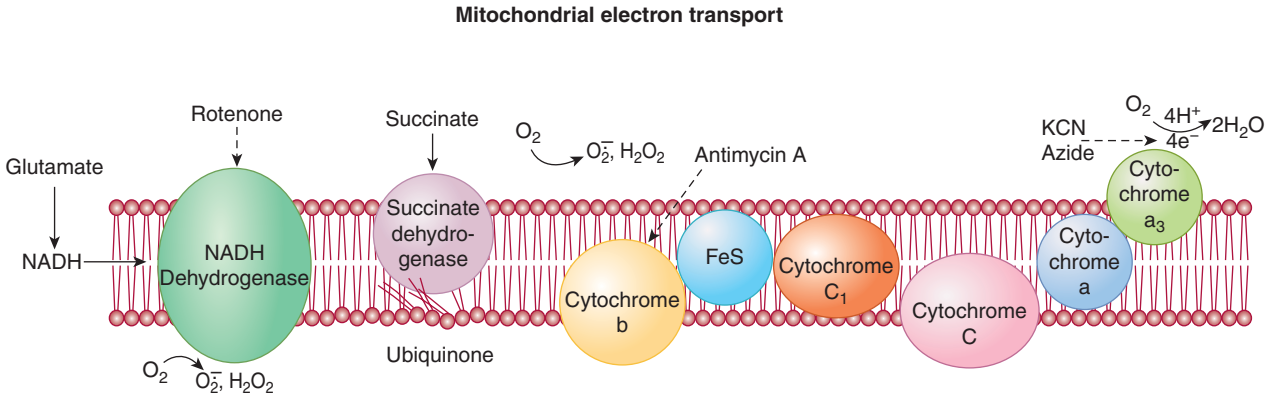

FIGURE 45-12 Generation of reactive oxygen species (ROS) in the mitochondria. The major source of mitochondrial ROS is the electron transport chain located on the inner mitochondrial membrane. Ubiquinone is reduced in a one-electron transfer to form the ubisemiquinone radical, which is reoxidized by molecular oxygen (autooxidation) to form the superoxide radical (O_2^-); this reaction is the major source of mitochondrial superoxide radical, which serves as a precursor to hydrogen peroxide (H_2O_2) and the hydroxyl radical ($OH^\cdot$), as shown. The autooxidation of the reduced form of nicotinamide adenine dinucleotide (NADH) dehydrogenase (a member of the class of flavoproteins) by molecular O_2 is an additional but quantitatively less important source of mitochondrial superoxide radical and thus, hydrogen peroxide and the hydroxyl radical. Also shown are various electron transport inhibitors (*dashed arrows*) used to study mitochondrial sources of superoxide radical. (Reprinted, with permission, from Macmillan Publishers Ltd. From Freeman BA, Crapo JD. Biology of disease. Free radicals and tissue injury. *Lab. Invest.* 1982;47:412–426.)

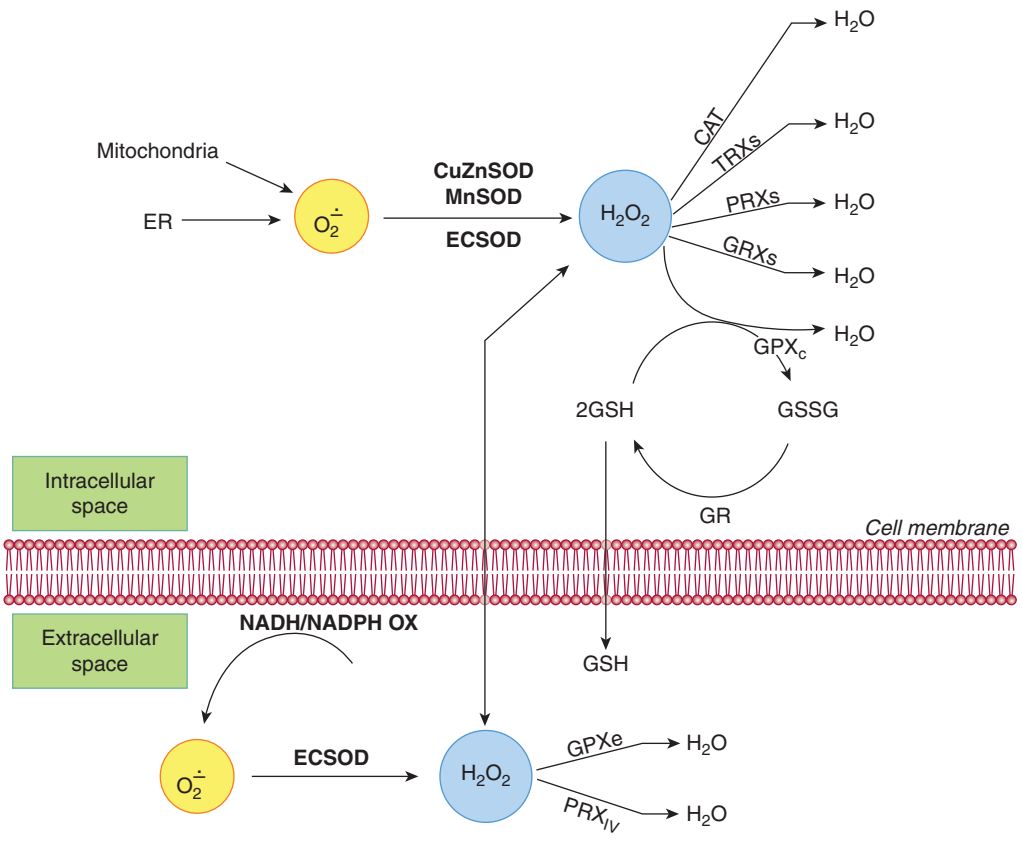

FIGURE 45-13 Major antioxidant pathways in the lung, intracellular and extracellular, scavenging superoxide (O_2^-) and hydrogen peroxide (H_2O_2). See text for details. *CAT*, catalase; *ER*, endoplasmic reticulum; *GPXc*, intracellular glutathione peroxidase; *GPXe*, extracellular glutathione peroxidase; *GRXs*, glutaredoxins; *GR*, glutathione reductase; *GSH*, reduced glutathione; *GSSG*, oxidized glutathione; *PRXs*, peroxiredoxins; SOD, superoxide dismutase; *TRXs*, thioredoxins. (Reprinted with permission of the American Thoracic Society. Copyright © 2012 American Thoracic Society. From Kinnula VL, Crapo JD. Superoxide dismutases in the lung and human lung diseases. *Am J Respir Crit Care Med.* 2003;167(12):1600–1619. Official Journal of the American Thoracic Society.)

formation of OH· from H_2O_2 is accelerated by O_2^- according to the metal-catalyzed Haber-Weiss reaction, which is referred to as the Fenton reaction if the metal is iron:[199]

$$O_2^- + Fe^{3+} \longrightarrow O_2 + Fe^{2+}$$

$$H_2O_2 + Fe^{2+} \longrightarrow OH^- + OH^- + Fe^{3+}$$

Cell Death by Hyperoxia: Apoptosis and Necrosis

Recently, attention has focused on the observation that the morphology of alveolar epithelial and endothelial cell death induced by hyperoxia, in vitro and in vivo, is both apoptotic and necrotic.[200–202] The importance of this observation is that it suggests that the degree hyperoxia-induced lung injury could be modulated by controlling apoptosis,[202,203] as has been shown in a model of ventilator-induced lung injury.[204] Budinger et al[203] showed in mice that oxidants generated in the mitochondria in response to hyperoxia activate the intrinsic cell death pathway by activating BAX and BAK. When activated, these two proteins create channels in the outer mitochondrial membrane, with release of cytochrome *c* and other pro-apoptotic proteins from the mitochondrial intermembrane space into the cytosol, leading to activation of the caspases, cell death, and lung injury[201,203] (see Fig. 45-14). The activity of the pro-apoptotic proteins BAX and BAK are, in turn, counterbalanced by the Bcl-2 family of antiapoptotic proteins, for example, Bcl-2 and A1.[201] The activity of these antiapoptotic proteins (specifically, A1) can be upregulated by cytokines (e.g., interleukin-11 and VEGF) and even hyperoxia itself[200,201] (Fig. 45-14), limiting the damage from hyperoxia. These observations provide a basis for potential therapy for hyperoxic lung injury.

Antioxidant Defense Mechanisms

Four antioxidant defense mechanisms exist in the cell[205]: (a) prevention of the formation of free radicals, (b) conversion of ROS to less-toxic species, (c) compartmentalization of ROS away from vital cellular structures (e.g., the binding of intracellular iron to ferritin to prevent its participation in the Haber-Weiss reaction), and (d) repair of molecular injury induced by ROS.

The primary cellular defense against ROS are enzymes that catalyze the removal of superoxide and hydrogen peroxide, namely, superoxide dismutase (SOD), catalase, and the enzymes of the glutathione redox cycle (see Fig. 45-13).[186,205] No enzyme-scavenging system exists for the hydroxyl radical.[189] Superoxide radical is converted by dismutation to hydrogen peroxide by SOD:

$$2O_2^- + 2H^+ \xrightarrow{\text{Superoxide Dismutase}} H_2O_2 + O_2$$

The lung contains three forms of SOD. These have been reviewed in detail.[186,188] The cytosolic form of SOD contains copper and zinc (CuZnSOD). The mitochondrial form contains manganese (MnSOD). An extracellular form (ECSOD) is concentrated in airway and vessel walls.[206]

Hydrogen peroxide is converted to water by the enzymes catalase (a hemoprotein) and glutathione peroxidase:[187]

$$2H_2O_2 \xrightarrow{\text{Catalase}} 2H_2O + O_2$$

Glutathione peroxidase is a selenium-dependent enzyme that inactivates both hydrogen peroxide and lipid peroxides. It is the key enzyme in the glutathione redox cycle (Fig. 45-15),[205] and requires the sulfhydryl-containing tripeptide glutathione (GSH; L-γ-glutamyl-L-cysteinyl-glycine) as a cosubstrate. The enzyme catalyzes the reaction that forms oxidized glutathione,[207] or glutathione disulfide (GSSG), according to,

$$H_2O_2 + 2GSH \xrightarrow{\text{Glutathione peroxidase}} GSSG + 2H_2O$$

or, in the case of lipid hydroperoxides,[205]

$$L\text{-}OOH + 2GSH \xrightarrow{\text{Glutathione peroxidase}} GSSG + L\text{-}OH + H_2O$$

GSSG is rapidly reduced back to GSH by the NADPH-dependent enzyme, glutathione reductase. NADPH is in turn restored from the oxidized form of nicotinamide adenine dinucleotide phosphate positive ($NADP^+$) by the hexose monophosphate shunt (see Fig. 45-12).[207]

Within the cell are several other antioxidants.[186,188] These include water-soluble cytoplasmic antioxidants (e.g., ascorbate [vitamin C]), and fat-soluble membrane-associated antioxidants (e.g., α-tocopherol [vitamin E]), beta-carotene, and ubiquinol. Vitamin E, one of the most important of the nonenzymatic antioxidants, partitions into and protects lipid membranes.[205] Vitamin E is particularly effective against O_2^-, OH·, and blocks propagation of lipid peroxidation by scavenging peroxy free radicals.[188]

The human lung expresses several other enzymes capable of inactivating H_2O_2,[186] including the thioredoxin–thioredoxin reductase system, thioredoxin peroxidases (peroxiredoxins), and glutaredoxins.[208–210]

Other nonenzymatic antioxidants include glutathione, surfactant protein D, albumin, and proteins that bind iron and copper (powerful promoters of oxidative damage) such as transferrin, ferritin, ceruloplasmin, and lactoferrin.[186] Others include urate and bilirubin.[190]

DIAGNOSIS AND MANAGEMENT OF PULMONARY OXYGEN TOXICITY

Diagnosis

At present, there is no clinically useful means of diagnosing pulmonary O_2 toxicity in patients. Such a diagnostic capability would be most useful is ARDS. Physiologic indexes of pulmonary function (e.g., decrements in vital capacity), require patient cooperation and specialized equipment. But their greatest limitation is that in patients

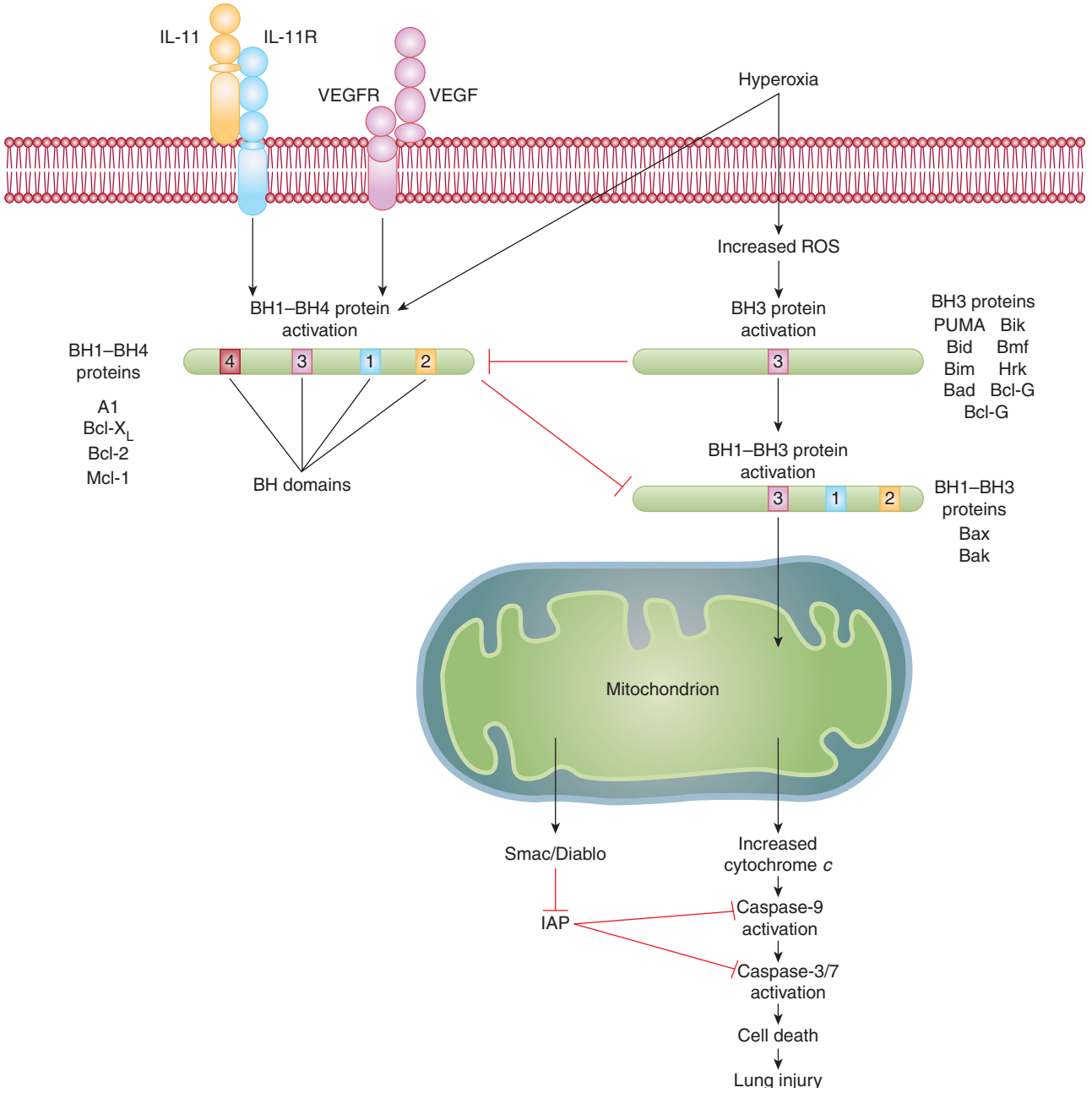

FIGURE 45-14 Schematic of the intrinsic or mitochondrial apoptosis pathway by which hyperoxia is postulated to cause cell death and lung injury. Cytokines, such as interleukin (IL)-11 and vascular endothelial growth factor (VEGF), and hyperoxia itself, upregulate the activity of A1, a member of the antiapoptotic Bcl-2 family of proteins. A1 downregulates the activity of the proapoptotic proteins BAX and BAK and thereby ameliorates the damage from hyperoxia. See text for details. *IAP*, inhibitors of apoptosis; *IL-11R*, interleukin-11 receptor; *PUMA*, p53 upregulated modulator of apoptosis; *ROS*, reactive oxygen species; *VEGFR*, vascular endothelial growth factor receptor. (Used, with permission, from Budinger and Sznajder.[201])

with ARDS such tests cannot distinguish between progressive O_2 toxicity and progression of the underlying cardiopulmonary condition. Chest radiographs also share this diagnostic limitation. Indexes of the lung's ability to metabolize biogenic amines (e.g., serotonin), polypeptides (e.g., by angiotensin-converting enzyme), and prostaglandins are sensitive in experimental animals but their use in critically ill patients is limited by their lack of specificity, dependence on capillary surface area and transit time, and the production by the injured lung of related compounds.[25] The pathology of pulmonary O_2 toxicity, diffuse alveolar damage, is a nonspecific (albeit clearly identifiable) pattern seen in ARDS from any cause. The sophisticated study by Montgomery et al,[80] which examined solute permeability of the lung, indexes of systemic toxicity, and pulmonary function, demonstrated that there is no better index

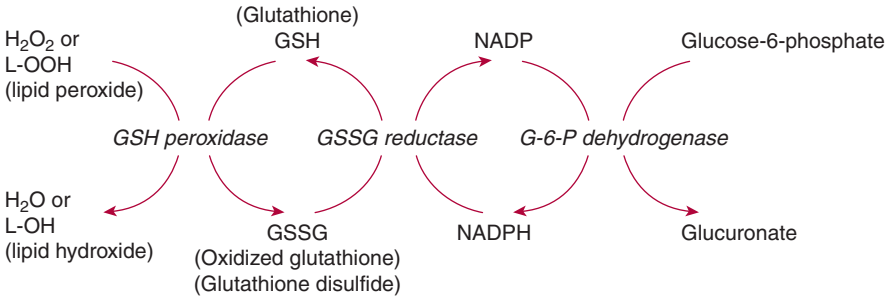

FIGURE 45-15 The glutathione (*GSH*) oxidation-reduction (redox) cycle and its pivotal role in the reduction of toxic intracellular hydroperoxides, including hydrogen peroxide and lipid peroxides. The key enzyme in the GSH redox cycle is *GSH peroxidase*, a predominantly cytosolic enzyme that requires reduced GSH as a substrate. Regeneration of reduced GSH by *GSSG reductase*, which is tightly bound to GSH peroxidase, requires nicotinamide adenine dinucleotide phosphate (NADPH), which is supplied by *G-6-P dehydrogenase* in the hexose monophosphate shunt.

of O_2 toxicity than the individual's subjective symptoms of retrosternal pain suggestive of acute tracheobronchitis. Studies such as theirs suggest that critical care physicians should maintain a heightened awareness and seek out such symptoms in patients on high levels of O_2 and include the possibility of pulmonary O_2 toxicity in the differential diagnosis of chest pain in such patients.

Exogenous Antioxidant Therapy for the Lung

The many approaches that have been taken in efforts to increase pulmonary antioxidant capacity have been reviewed.[188–190,211] The major antioxidant strategies that have been evaluated for the lung include: (a) exogenous administration of normal intracellular enzymatic antioxidants, such as SOD, catalase, and GSH; (b) administration of synthetic antioxidant mimetics; (c) pharmacologic inhibition of free radical generating systems, such as by the iron chelator deferoxamine; (d) supplementation with nonenzyme antioxidants, such as vitamin E, *N*-acetylcysteine, and dietary supplementation with polyunsaturated fatty acid; and (e) agents to prevent the neutrophil-mediated amplification of the hyperoxic injury. All these approaches have been tried in vitro or in animal models, but only a few have been tried in human patients.

Adenovirus-mediated overexpression of MnSOD in mice protects against hyperoxia-induced acute lung injury and lethality[203] and overexpressing ECSOD increases tolerance to hyperoxia.[212,213] In adult baboons exposed to 96 hours of 100% O_2, aerosolized recombinant human (rh) MnSOD improved oxygenation and alveolar epithelial histology, and decreased lung edema.[214,215] Because in these latter reports the MnSOD was found extracellularly, Asikainen and White[190] speculated that the beneficial effect of rhMnSOD may have been scavenging ROS generated by activated inflammatory cells. In premature human infants, intratracheal rhCuZnSOD did not change the 28-day mortality or the incidence bronchopulmonary dysplasia.[216,217] Among the surviving infants, however, those who had been treated with rhCuZnSOD had less frequent acute respiratory events (asthma medication requirements, emergency department visits, and hospitalizations) over the first year of life.[217]

Synthetic SOD-mimetic (catalytic) antioxidants have been studied,[188,190] particularly the metalloporphyrins. They are highly active, stable, potentially nontoxic, and protect against ROS-mediated lung injury in experimental models.[190] They scavenge superoxide, hydrogen peroxide, and peroxynitrite, and inhibit lipid peroxidation.[218] In a fetal baboon model of bronchopulmonary dysplasia, the catalytic antioxidant metalloporphyrin AEOL 10113, given by continuous intravenous infusion, improved histology and proinflammatory mediators, but not oxygenation.[111]

A number of studies have been carried out in effort to enhance the GSH-dependent antioxidant capacity of the lung. *N*-acetylcysteine readily crosses into cells and, by undergoing deacetylation, forms cysteine, the rate-limiting amino acid in GSH biosynthesis. *N*-acetylcysteine acts both by directly reducing O_2^-, H_2O_2, OH·, and HOCl (hypochlorous acid), and by supporting GSH synthesis.[219] Its clinical use is well established in the treatment of acetaminophen-induced hepatotoxicity.[220] In animal studies,[221–226] *N*-acetylcysteine protects against oxidant lung injury. In human studies, however, disappointingly, a half dozen clinical trials of *N*-acetylcysteine in critically ill patients with acute lung injury, ARDS, or multiple organ failure have failed to show benefit in survival or oxygenation.[227–231] In 1998, a clinical trial with procysteine in patients with acute lung injury or ARDS was stopped for lack of efficacy.[232] In very-low-birth-weight infants, supplementation of selenium (required for glutathione peroxidase) also failed to improve outcome.[233]

Lisofylline, an antiinflammatory compound that modulates the metabolism of lipids, including the proinflammatory linoleic acid, showed promise in preclinical studies but failed to show beneficial effects in a randomized controlled trial of 235 patients with acute lung injury or ARDS.[234]

Clinical trials of vitamin E supplementation failed to prevent bronchopulmonary dysplasia in premature newborns[235] or hyperoxic lung injury in neonates.[236] In contrast, vitamin A supplementation slightly decreased the incidence of bronchopulmonary dysplasia in extremely-low-birth-weight

infants.[237] In adult critically ill surgical patients, the combination of vitamins E and C reduced the incidence of organ failure and length of stay in the intensive care unit.[238]

Newborn rats have increased survival during hyperoxic challenge after dietary supplementation with polyunsaturated fatty acid (PUFA), including n-6 PUFA (linoleic and arachidonic acid, from safflower oil),[239] n-3 PUFA (eicosapentaenoic and docosahexaenoic acid; from fish oil),[240] and enteral Intralipid (commercial combination n-6 and n-3 PUFA; from soybean oil).[241] In ARDS, the combination of vitamins E and C plus fish oil (eicosapentaenoic acid) and borage oil (γ-linolenic acid) improved pulmonary neutrophil recruitment, gas exchange, requirement for mechanical ventilation, length of intensive care unit stay, and number of new organ failures.[242] A retrospective analysis of a subset of only forty-three of these patients[243] reported that the twenty-one treated patients had decreased levels of interleukin-8, leukotriene B_4, and neutrophils in bronchoalveolar lavage fluid, and decreased alveolar–capillary membrane permeability. A more recent randomized controlled trial in 100 patients with acute lung injury, reported that, compared to standard diet alone, adding eicosapentaenoic acid plus γ-linolenic acid and antioxidants improved oxygenation, compliance, and time on mechanical ventilation, but not mortality.[244] In a randomized controlled trial of 165 mechanically ventilated patients with severe sepsis, this same dietary intervention improved oxygenation, time on mechanical ventilation, occurrence of new organ dysfunctions, time in the intensive care unit, and mortality.[245] More recently, the ARDS Network OMEGA trial of enteral omega-3 (N-3) fatty acids, γ-linolenic acid, and antioxidants was stopped for futility after enrolling 272 acute lung injury patients, with a 60-day adjusted mortality of 24.6% versus 17.9% in control patients.[246]

In premature baboons the iron chelator deferoxamine to prevent hyperoxic lung injury (by inhibiting iron-catalyzed ROS generation) resulted in rapid cardiovascular collapse and death (<42 hours) in all animals.[247]

Another approach at lung protection from hyperoxic injury is to block neutrophil accumulation in the lung and thereby block further amplification and propagation of ROS-mediated injury.[188] Such blockade can be achieved by antibodies directed against cytokine-induced neutrophil chemoattractant-1 (CINC-1), which is the major rat neutrophil chemoattractant cytokine, or chemokine.[248] This antibody, given intraperitoneally in a newborn-rat model of bronchopulmonary dysplasia, prevented neutrophil influx and preserved lung compliance, alveolar development, and lung cell proliferation.[248] Neutrophil influx can also be prevented by blocking the receptor, CXCR2, through which the chemokines act. In the same rat model, Auten et al[249] showed that a competitive antagonist (SB-265610, a nonpeptide) of this chemokine receptor also prevented hyperoxia-induced neutrophil accumulation. Recent studies also show that other chemokines, including interleukin-8 and monocyte chemoattractant protein-1, play important roles in neutrophil attraction to the lung[188,250] and are potential therapeutic targets. Mercer and Crapo[188] pointed out that the neutrophil-blocking approach and the ECSOD-enhancement approach appear to be complementary. That is, ECSOD enhancement protects against direct oxidant injury and neutrophil blockade prevents injury in areas not well protected by the enhanced ECSOD.

Several other experimental approaches have been investigated and reviewed in detail by Asikainen and White,[190] including catalytic antibodies, lazaroids, and novel approaches involving transcription factors, signaling pathways, DNA repair mechanisms, and growth factors. Despite their promise, none has yet been shown to be effective in humans.

Induction of Tolerance to Hyperoxia

In 1978, Frank et al[251] made the fortuitous discovery that endotoxin fully protected rats from hyperoxic morbidity and mortality. Similar results had been reported earlier following other toxic insults to the lung, including oleic acid,[252] α-naphthylthiourea,[253] and diphosgene,[78] all of which were reported to increase survival on subsequent exposure to hyperoxia. Frank et al[251] also showed that endotoxin induced increases in SOD, catalase, and glutathione peroxidase. They speculated that in patients with acute respiratory failure ("for example… hyaline membrane disease," or infant respiratory distress syndrome), coincident gram-negative infection may modulate the toxic effects of therapeutic hyperoxia.[251]

In animals, other challenges that are protective against the lethality of subsequent exposure to hyperoxia include sublethal hyperoxia,[254,255] hypoxia (in the absence of hypercarbia),[256,257] and the combination of tumor necrosis factor-α and interleukin-1.[258] Tumor necrosis factor-α and interleukin-1 are proinflammatory cytokines that mediate much of the pathophysiology of endotoxin.[197,259,260] In rats the protective effects of each of these pretreatments can be explained by the induction of SOD, catalase, and glutathione peroxidase.[251,254,257,261] The protective effect, however, may also occur in the absence of antioxidant enzyme induction. In the study by White et al,[261] the induction of the antioxidant enzymes induced by pretreatment with tumor necrosis factor-α plus interleukin-1 occurred relatively late (after 72 hours), after all control rats had already died. These authors suggested that the mechanisms of the lung protection may include, in addition to enzyme induction, the recruitment to the lung of more resistant cell lines.[261] Baker et al[255] showed that the protective effect of preexposure to sublethal hyperoxia in adult rabbits, unlike that in neonatal rabbits[262] and rats, is not accompanied by an increase in antioxidant enzymes; it may be explained, instead, by the observed increase in endogenous surfactant induced by the preexposure to hyperoxia.[255] More recently, additional mechanisms to explain the ameliorating effects on lung injury of cytokines or preexposure to hyperoxia have been provided by He et al[200] (see Fig. 45-14 and "Cell Death by Hyperoxia: Apoptosis and Necrosis" above).

The clinical relevance of these observations is obvious. Critically ill patients with acute respiratory failure are commonly exposed to such "pretreatments," namely, hyperoxia, hypoxia, endotoxin, and (endogenous) tumor necrosis factor-α and interleukin-1. Additionally, as part of routine nutritional support, these patients commonly receive nutritional supplementation with polyunsaturated fatty acid, as discussed above.

Exogenous Surfactant Administration

Surfactant is discussed in detail in Chapter 60 and is reviewed elsewhere.[263,264] Endogenous surfactant is a complex mixture of approximately 85% to 90% phospholipids, 7% to 10% apoproteins (surfactant proteins A, B, C, and D), and 4% to 7% neutral lipids.[263] Its primary function is to reduce the otherwise high liquid-gas surface tension within the alveoli and thereby decrease their tendency to collapse. Hyperoxia impairs surfactant function.[265] Both ROS and RNS degrade surfactant, particularly the surfactant proteins, but the damage from RNS, especially peroxynitrite, appears more important.[263] In most species, despite its impairment of surfactant function, hyperoxia also induces surfactant synthesis.[255,266,267] Endogenous surfactant has intrinsic antioxidant activity,[268,269] can enhance intracellular antioxidant enzyme content,[268] and in animal models, protects from hyperoxic lung injury and death.[64,268,270]

Exogenous surfactants vary significantly in their composition.[264] They also have antioxidant activity[271] and in animal models, protect against hyperoxic lung injury and death.[271–274] After administration of exogenous surfactant (Curosurf), human preterm infants with respiratory distress syndrome show enhanced SOD and catalase activity in the tracheobronchial secretions.[275]

Exogenous surfactant therapy is now standard in neonatal intensive care units.[264,276] A number of clinical trials in young patients have reported beneficial outcomes in newborns with respiratory distress syndrome,[276–280] in infants with acute respiratory failure caused by respiratory syncytial virus,[281] and in children with hypoxemic acute respiratory failure.[282] In contrast, in adult patients with ARDS, the results have been disappointing.[264] A trial of 725 adult patients with sepsis-induced ARDS using surfactant (Exosurf) found no benefit.[283,284] The failure of this trial may be related in part to differences in both the surfactant constitutions and the delivery systems, between the neonatal-pediatric trials and the adult trials.[264] Very recently, a trial of recombinant surfactant protein C-based surfactant in 843 adult patients with severe direct lung injury again showed no clinical benefit, perhaps related to insufficient surface activity.[285,286]

Minimization of Oxygen Toxicity in the Intensive Care Unit

Ironically, in several ways the disease process of ARDS itself would seem to provide some degree of protection against hyperoxic injury. First, the alveolar epithelial and endothelial cells in the areas of shunt (presumably the areas of greatest injury) have, by definition, relatively low values of P_{O_2}, similar to the P_{O_2} of the mixed venous blood, and thus are not directly exposed to hyperoxia. Second, in ARDS the systemic circulation is also protected from hyperoxia because, by definition, this syndrome is characterized by systemic arterial hypoxemia. Third, the pathophysiology of ARDS and its management include exposure to hyperoxia, hypoxia, endogenous cytokines such as tumor necrosis factor-α and interleukin-1,[287,288] and, commonly, endotoxin.[287,288] However, as discussed above, prior exposure to each of these agents induces in animals tolerance and protection against future exposure to hyperoxia. Thus, patients who survive the initial insult of ARDS may be better able to withstand ongoing hyperoxic exposure. Fourth, the intraalveolar hemorrhage and exudation of plasma that is characteristic of ARDS (see discussion of pathology above) provides erythrocytes rich in antioxidant enzyme capacity, as noted above, and plasma proteins with substantial antioxidant activities. In fact, bronchoalveolar lavage fluid from ARDS patients possesses greater antioxidant activity than bronchoalveolar lavage fluid from normal subjects, largely as a result of the plasma proteins transferrin and ceruloplasmin.[289]

Once the possibility of pulmonary O_2 toxicity is considered (generally in an ARDS patient requiring $FI_{O_2} \geq 0.60$ for >24 to 48 hours), the only accepted treatment clinically at present is to reduce the FI_{O_2} to lowest level consistent with adequate systemic oxygenation. This goal should be approached by first minimizing excess O_2 demand (e.g., secondary to fever, infection, anxiety, pain, or "fighting the ventilator" with the judicious use of antipyretics,[290] antimicrobials, sedatives, analgesics, or neuromuscular blocking agents,[291] respectively). Second, one should optimize all other determinants of systemic oxygenation, such as hemoglobin concentration, by using a restrictive strategy of red blood cell transfusion,[292,293] and overall respiratory and cardiovascular status.[294]

As discussed in detail in other chapters, the best principles and practice of mechanical ventilation should be applied. These would include optimizing positive end-expiratory pressure, tidal volume, and plateau pressure using an open-lung or lung-protective ventilation strategy,[2] consideration of alternative modes of ventilation (e.g., high-frequency ventilation), prone ventilation,[295] inhaled NO, extracorporeal membrane oxygenation, and so on.

Complicating conditions interfering with oxygenation should be meticulously sought out and treated. These conditions may include superimposed nosocomial pneumonia, excessive secretions, bronchospasm, occult pneumothorax and other parenchymal ventilator-induced lung injury, inadvertent intubation of a mainstem bronchus, occult large posterior pleural effusions, cardiopulmonary shunts unrelated to parenchymal lung injury (e.g., patent foramen ovale[296]), pulmonary emboli, cor pulmonale, low cardiac output, and hydrostatic-pressure pulmonary edema (elevated pulmonary arterial wedge pressure). Hydrostatic-pressure pulmonary edema should be minimized by adopting a conservative

strategy of fluid management[297] and considering, in the hypoproteinemic patient, albumin plus furosemide therapy, which can improve fluid balance, oxygenation, and hemodynamics.[298] Inotropic agents (e.g., dobutamine) should be considered as a possible means of decreasing the pulmonary arterial wedge pressure (and thus the hydrostatic gradient for pulmonary edema formation) while maintaining or increasing cardiac output. Supranormal cardiac indices, however, should be avoided.[299,300]

After the above concerns have been adequately addressed, the FI_{O_2} should be adjusted to the lowest value required to maintain the arterial saturation within an acceptable range (e.g., 88% to 95%[2]). (Mountain climbers tolerate Pa_{O_2} of 28 torr for brief periods[301] and Sa_{O_2} of 73% to 85% for at least 4 days including with exercise.[302,303]) Although the treatment of ARDS is largely supportive, treatment should, of course, be given for the underlying disease that may have produced the ARDS, particularly, if it is infection. In especially difficult patients with ARDS and refractory hypoxemia requiring sustained high levels of inspired O_2, the clinician may be faced with the very difficult task of choosing among (a) accepting a lower level of arterial oxygenation, (b) increasing the already high airway pressures and risking ventilator-induced lung injury, and (c) continuing or even increasing the already high FI_{O_2}. In these very difficult cases it seems prudent to keep in mind that, based on information to date, the known immediate risks of systemic hypoxemia or ventilator-induced lung injury are clearly more established and devastating than the potential future risk of hyperoxia-induced lung injury. That is, the priorities should be, in order of their vital importance: (a) maintenance of arterial oxygenation; (b) avoidance of ventilator-induced lung injury; and (only then) (c) avoidance of high inspired O_2 fractions.

IMPORTANT UNKNOWNS AND THE FUTURE

The most important unknown is the optimum inspired O_2 fraction to use in ARDS. Remarkably, the answer is still unknown more than four decades after ARDS was defined.[304] Other unknowns concern the relationship between O_2 toxicity and ventilator-induced lung injury. These two entities have in common that both are a concern in acute respiratory failure, both share mechanisms of injury, and both initiate their injury in the lung but cause death from systemic multiorgan organ failure more than from their pulmonary injury. Future work should resolve their relative importance in acute lung injury: Are they independent or synergistic forces? Will therapy for one also be therapeutic for the other? In ARDS would there be further benefit in keeping the FI_{O_2} higher than usually done (e.g., near 100%) and thereby allowing use of an even more aggressive lung-protective strategy (that is, even lower tidal volumes and plateau pressures than those targeted in the ARDS Network trial)?[2] Future research should resolve how optimally to trade off the risks of hypoxemia, ventilator-induced lung injury, and O_2 toxicity. This trade-off will be facilitated when more specific markers of O_2 toxicity become available.

The degree to which patients with ARDS have induction of tolerance to hyperoxia (by preexisting hyperoxia, hypoxia, endotoxin, and cytokines; see above) is unknown. This induction could be manipulated to optimize a patient's antioxidant defenses. The potential benefit of combining two or more complementary therapies, for example, neutrophil blocking plus ECSOD enhancement,[188] are yet to be explored. Novel therapies, like activated protein C, which has been successful uniquely in severe sepsis,[305] give hope that similar results can be achieved in ARDS and O_2 toxicity. Other proposed novel approaches involve transcription factors, signaling pathways, DNA repair mechanisms, and growth factors.[190] One of the most promising and recent approaches is to directly inhibit activation of the oxidant-mediated intrinsic apoptotic pathway of cell death (see Fig. 45-14).[200–203]

SUMMARY AND CONCLUSION

More than two centuries after his discovery of O_2, Priestley seems remarkably prescient regarding oxygen's medical and toxic potential. O_2 is now recognized as lifesaving in patient conditions ranging from ambulatory to critically ill. The enormous expansion of knowledge about its biochemistry, physiology, and toxicology has relevance throughout all of biology. Continuing growth in our understanding of this "vital air" of Lavoisier is vital to continuing improvement in the care and safety of patients.

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PNEUMONIA IN THE VENTILATOR-DEPENDENT PATIENT

Jean E. Chastre
Charles-Edouard Luyt
Jean-Yves Fagon

Ventilator-associated pneumonia (VAP) is the most frequent intensive care unit (ICU)-acquired infection among patients receiving mechanical ventilation.[1] In contrast to infections of other frequently involved organs (e.g., urinary tract and skin), for which mortality is low, ranging from 1% to 4%, the mortality rate for VAP, defined as pneumonia occurring more than 48 hours after endotracheal intubation and initiation of mechanical ventilation, ranges from 20% to 50% and can even be higher in some specific settings or when lung infection is caused by high-risk pathogens.[1–3] Although the attributable mortality rate for VAP is still debated, it has been shown that these infections prolong both the duration of ventilation and the duration of ICU stay.[1,2] Approximately 50% of all antibiotics prescribed in an ICU are administered for respiratory tract infections.[4] Because several studies have shown that appropriate antimicrobial treatment of patients with VAP significantly improves outcome, more rapid identification of infected patients and accurate selection of antimicrobial agents represent important clinical goals.[2] Consensus, however, on appropriate diagnostic, therapeutic, and preventive strategies for VAP has yet to be reached. In this chapter, we summarize published studies on epidemiology, diagnosis, treatment, and prevention of nosocomial pulmonary infection in critically ill patients mechanically ventilated in the ICU, and present our experience with this infection.

EPIDEMIOLOGY

Accurate data on the epidemiology of VAP are limited by the lack of standardized criteria for its diagnosis. Conceptually, VAP is defined as an inflammation of the lung parenchyma caused by infectious agents not present or incubating at the

time mechanical ventilation was started. Despite the clarity of this conception, the past three decades have witnessed the appearance of numerous operational definitions, none of which is universally accepted. Even definitions based on histopathologic findings at autopsy may fail to find consensus or provide certainty. Pneumonia in focal areas of a lobe may be missed, microbiologic studies may be negative despite of presence of inflammation in the lung, and pathologists may disagree on the findings.[5] The absence of a "reference standard" continues to fuel controversy about the adequacy and relevance of many studies in this field.

Incidence of Ventilator-Associated Pneumonia

The exact incidence varies widely depending on the case definition of pneumonia and the population being evaluated.[6–10] All studies, however, have confirmed that nosocomial pneumonia is considerably more frequent in ventilated patients than in other ICU patients, with an incidence increasing by as much as sixfold to 20-fold in this subset of patients.[11,12] VAP occurs in 9% to 27% of all intubated patients and its incidence increases with duration of ventilation.[10,13] The risk of VAP is highest early in the course of hospital stay and is estimated to be 3% per day during the first 5 days of ventilation, 2% per day during days 5 to 10 of ventilation, and 1% per day beginning from day 11.[13] Because most mechanical ventilation is short term, approximately half of all episodes of VAP occur within the first 4 days of mechanical ventilation. In a large epidemiologic study, independent predictors of VAP retained by multivariable analysis were a primary admitting diagnosis of burns, trauma, central nervous system disease, respiratory disease, cardiac disease, mechanical ventilation during the preceding 24 hours, witnessed aspiration, and use of paralytic agents. Exposure to antibiotics conferred protection, but this effect was attenuated over time.[13] According to four studies, the VAP rate was higher in patients with acute respiratory distress syndrome (ARDS) than other ventilated patients, affecting between 34% and more than 70% of patients with ARDS and often leading to the development of sepsis, multiorgan failure, and death.[14–17]

Mortality, Morbidity, and Cost

Mechanically ventilated patients in the ICU with VAP appear to have a twofold to 10-fold higher risk of death as compared with patients without pneumonia. Although these statistics indicate that VAP can be lethal, previous studies have not demonstrated clearly that pneumonia is responsible for the higher mortality rate of these patients.[18] It is often difficult to determine whether ICU patients with severe underlying illness would have survived if VAP had not occurred. VAP, however, has been recognized in several case-controlled studies or studies using multivariate analysis as an important prognostic factor for different groups of critically ill patients.[18–23]

Other factors beyond the simple development of VAP, such as the severity of the disease, the responsible pathogens, or the appropriateness of initial treatment, may be more important determinants of outcome for patients in whom pneumonia develops.[24] Indeed, it may be that VAP increases mortality only in the subset of patients with intermediate severity of illness,[23] when initial treatment is inappropriate,[25–32] and/or in patients with VAP caused by high-risk pathogens, such as *Pseudomonas aeruginosa*.[24,33] Patients with very low severity and early onset pneumonia caused by organisms such as *Haemophilus influenzae* or *Streptococcus pneumoniae* have excellent prognoses with or without VAP, whereas very ill patients with late-onset VAP, occurring while they are in a quasi-terminal state, would be unlikely to survive. Using a multistate progressive disability model that appropriately handled VAP as a time-dependent event in a high-quality database of 2873 mechanically ventilated patients, Nguile-Makao et al showed that VAP attributable mortality was 8.1% overall, varying widely with case mix, severity at admission, time to VAP onset, and severity of organ dysfunction at VAP onset.[24] These results are consistent with the 10.6% value obtained in five German ICUs using also a multistate model progressive disability model.[34]

It is impossible to evaluate precisely the morbidity and excess costs associated with VAP. All studies, however, have shown clearly that patients with VAP have prolonged duration of mechanical ventilation and lengthened ICU and hospital stay as compared with patients who do not have VAP.[1,2,35,36] Summarizing available data, VAP appears to extend the ICU stay by at least 4 to 6 days, with the attributable ICU length of stay being longer for medical than surgical patients and for patients infected with "high-risk" as opposed to "low-risk" organisms.[37] The prolonged hospitalization of patients with VAP underscores the considerable financial burden imposed on the health care system by the development of VAP.[10,35,36,38–41]

Etiologic Agents

Microorganisms responsible for VAP differ according to the population of ICU patients, the durations of hospital and ICU stays, and the specific diagnostic method(s) used to establish the responsible pathogens. A number of studies have shown that gram-negative bacilli cause many of the respiratory infections in this setting.[1,2,42,43] The data from twenty-four studies conducted on ventilated patients, for whom bacteriologic studies were restricted to uncontaminated specimens obtained using a protected specimen brush (PSB) or bronchoalveolar lavage (BAL), confirmed these results: gram-negative bacilli represented 58% of recovered organisms (Table 46-1).[1] The predominant gram-negative bacilli were *P. aeruginosa* and *Acinetobacter* spp., followed by *Proteus* spp., *Escherichia coli*, *Klebsiella* spp., and *H. influenzae*. A relatively high rate of gram-positive pneumonias was also reported in those studies, with *Staphylococcus aureus*

TABLE 46-1: ETIOLOGY OF VENTILATOR-ASSOCIATED PNEUMONIA AS DOCUMENTED BY BRONCHOSCOPIC TECHNIQUES IN 24 STUDIES FOR A TOTAL OF 1689 EPISODES AND 2490 PATHOGENS

Pathogen	Frequency (%)
Pseudomonas aeruginosa	24.4
Acinetobacter spp.	7.9
Stenotrophomonas maltophilia	1.7
Enterobacteriaceae[a]	14.1
Haemophilus spp.	9.8
Staphylococcus aureus[b]	20.4
Streptococcus spp.	8.0
Streptococcus pneumoniae	4.1
Coagulase-negative staphylococci	1.4
Neisseria spp.	2.6
Anaerobes	0.9
Fungi	0.9
Others (<1% each)[c]	3.8

[a]Distribution when specified: *Klebsiella* spp., 15.6%; *Escherichia coli*, 24.1%; *Proteus* spp., 22.3%; *Enterobacter* spp., 18.8%; *Serratia* spp., 12.1%; *Citrobacter* spp., 5.0%; *Hafnia alvei*, 2.1%.

[b]Distribution when specified: Methicillin-resistant *Staphylococcus aureus* (MRSA), 55.7%; methicillin-susceptible *Staphylococcus aureus* (MSSA), 44.3%.

[c]Including *Corynebacterium* spp.; *Moraxella* spp.; and *Enterococcus* spp.

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involved in more than 20% of the cases.[42] Many episodes of VAP are caused by multiple pathogens.[1,44]

Underlying diseases may predispose patients to infection with specific organisms. Patients with chronic obstructive pulmonary disease are at increased risk for *H. influenzae, Moraxella catarrhalis,* or *S. pneumoniae* infections; cystic fibrosis increases the risk of *P. aeruginosa* and/or *S. aureus* infections, while trauma and neurologic disease increases the risk for *S. aureus* infection. Furthermore, the causative agent for pneumonia differs among ICU surgical populations, with 18% of the nosocomial pneumonias caused by *Haemophilus* or pneumococci, particularly in patients with trauma, but not in patients with malignancy or who underwent transplantation, abdominal, or cardiovascular surgery.[1,2]

Despite somewhat different definitions of early onset pneumonia, varying from onset of less than 3 days to less than 7 days, high rates of *H. influenzae, S. pneumoniae*, methicillin-susceptible *Staphylococcus aureus* (MSSA) or susceptible Enterobacteriaceae were constantly found in early onset VAP, whereas *P. aeruginosa*, *Acinetobacter* spp., methicillin-resistant *Staphylococcus aureus* (MRSA), and multiresistant gram-negative bacilli were significantly more frequent in late-onset VAP.[1] The different pattern of distribution of etiologic agents between early- and late-onset VAP is linked to prior antimicrobial therapy in many patients with late-onset VAP. When multivariate analysis was used to identify risk factors for VAP caused by potentially drug-resistant bacteria such as MRSA, *P. aeruginosa, Acinetobacter baumannii*, and/or *Stenotrophomonas maltophilia* in 135 consecutive episodes of VAP, only three variables remained significant: mechanical ventilation duration of longer than 7 days before onset of VAP, prior antibiotic use, and prior use of broad-spectrum drugs (third-generation cephalosporins, fluoroquinolones, and/or imipenem).[45] Not all studies have confirmed this distribution pattern, and in some studies the most common pathogens associated with early onset VAP were *P. aeruginosa*, MRSA, and *Enterobacter* spp., with similar pathogens associated with late-onset VAP.[46,47] These findings might be explained in part by prior hospitalization and the use of antibiotics before transfer to the ICU.

The incidence of multiresistant pathogens is also closely linked to local factors and varies widely from one institution to another. Consequently, each ICU has to continuously collect meticulous epidemiologic data.[48] Clinicians must clearly be aware of the common microorganisms associated with both early-onset and late-onset VAP in their own hospitals so as to avoid the administration of initial inadequate antimicrobial therapy.

Legionella species, anaerobes, and even *Pneumocystis jiroveci* should be mentioned as potential causative agents, but these microbes are not commonly found when pneumonia is acquired during mechanical ventilation. Herpesviridae, namely herpes simplex virus, can be detected in the lower respiratory tracts of 5% to 64% of ICU patients, depending on the population and the diagnostic method used. In most cases, herpes simplex virus recovery from lower respiratory tract samples of nonimmunocompromised ventilated patients corresponds to viral contamination from the mouth and/or throat. For some patients, however, real herpes simplex virus bronchopneumonitis can develop, and it can evolve into ARDS and/or facilitate the occurrence of bacterial superinfection.[49–51] Cytomegalovirus-induced pneumonia is a rare event in ventilated patients. As for herpes simplex virus bronchopneumonitis, it is impossible to know whether cytomegalovirus detection in the lower respiratory tract is merely a marker of disease severity or signals real disease with its own morbidity and mortality.[52–55]

Isolation of fungi, most frequently *Candida* species, at significant concentrations poses interpretative problems. Invasive disease has been reported in VAP but yeasts are isolated more frequently from respiratory tract specimens in the absence of apparent disease, even when retrieved at high concentrations from bronchoscopic specimens.[56–60] Thus, based on current data, the presence of yeasts in respiratory secretions obtained from nonimmunosuppressed ventilated patients usually indicates colonization rather than infection of the respiratory tract and does not justify by itself a specific antifungal therapy. Evidence of lung tissue invasion is needed for making the diagnosis of *Candida* pneumonia in such a setting. Interactions, however, between *Candida* and bacteria, particularly *Pseudomonas*, have been reported, and colonization of the respiratory tract by yeasts may predispose to bacterial VAP.[61–64]

By examining currently available data, the clinical significance of anaerobes in the pathogenesis and outcome of VAP remains unclear except as etiologic agents in patients with necrotizing pneumonitis, lung abscess, or pleuropulmonary infections. Anaerobic infection and coverage with antibiotics, such as clindamycin or metronidazole, should probably also be considered for patients with respiratory secretions documenting numerous extracellular and intracellular microorganisms after Gram staining in the absence of positive cultures for aerobic pathogens.

PATHOGENESIS AND PREDISPOSING FACTORS

Pneumonia results from microbial invasion of the normally sterile lower respiratory tract and lung parenchyma caused by either a defect in host defenses, a challenge by a particularly virulent microorganism, or an overwhelming inoculum. The normal human respiratory tract possesses a variety of defense mechanisms that protect the lung from infection. Examples include anatomic barriers, such as the glottis and larynx; cough reflexes; tracheobronchial secretions; mucociliary lining; cell-mediated and humoral immunity; and a dual phagocytic system that involves both alveolar macrophages and neutrophils.[1] When these coordinated components function properly, invading microbes are eliminated and clinical disease is avoided. When these defenses are impaired, however, or if they are overcome by virtue of a high inoculum of organisms or organisms of unusual virulence, pneumonitis may result.

As suggested by the infrequent association of VAP with bacteremia, most of these infections appear to result from aspiration of potential pathogens that have colonized the mucosal surfaces of the oropharyngeal airways. Intubation of the patient not only compromises the natural barrier between the oropharynx and trachea, but may also facilitate the entry of bacteria into the lung by pooling and leakage of contaminated secretions around the endotracheal tube cuff.[65] This phenomenon occurs in most intubated patients, whose supine position may facilitate its occurrence. In previously healthy, newly hospitalized patients, normal mouth flora or pathogens associated with community-acquired pneumonia may predominate. In sicker patients who have been hospitalized more than 5 days, gram-negative bacilli and *S. aureus* frequently colonize the upper airway.[66]

Uncommonly, VAP may arise in other ways. Observed "macroaspirations" of gastric material initiate the process in some patients. Allowing condensates in ventilator tubing to drain into the patient's airway may have the same effect. Fiber-optic bronchoscopy, tracheal suctioning, or manual ventilation with contaminated equipment may also bring pathogens to the lower respiratory tract. More recently, concerns have focused on the potential role of contaminated inline medication nebulizers, but these devices are infrequently associated with VAP.

Risk factors for tracheobronchial colonization with gram-negative bacilli appear to be the same as those that favor pneumonia and include more severe illness, longer hospitalization, prior or concomitant use of antibiotics, malnutrition, intubation, azotemia, and underlying pulmonary disease.[67] Experimental investigations have linked some of these risk factors to changes in adherence of gram-negative bacilli to respiratory epithelial cells. Although formerly attributed to losses of cell-surface fibronectin, these changes in adherence more likely reflect alterations of cell-surface carbohydrates. Bacterial adhesins and prior antimicrobial therapy appear to facilitate the process. Interestingly, Enterobacteriaceae usually appear in the oropharynx first, whereas *P. aeruginosa* more often appears first in the trachea.[68]

Other sources of pathogens causing VAP include the paranasal sinuses, dental plaque, and the subglottic area between the true vocal cords and the endotracheal tube cuff. Not all authors agree that the gastropulmonary route of infection is truly operative in ICU patients.[69] Progression of colonization from the stomach to the upper respiratory tract with subsequent episodes of VAP could not be demonstrated in several studies and efforts to eliminate the gastric reservoir with antimicrobial therapy without decontaminating the oropharyngeal cavity have generally failed to prevent VAP.[69–71] In fact, there is more than one potential pathway for colonization of the oropharynx and trachea in such a setting, including fecal–oral cross-infection on the hands of health care personnel, and contaminated respiratory therapy equipment. Patient-care activities, such as bathing, oral care, tracheal suctioning, enteral feeding, and the tube manipulations, provide ample opportunities for transmission of pathogens when infection-control practices are substandard.[72]

Risk Factors

Risk factors provide information on the probability of lung infection developing in individuals and populations. Thus, they may contribute to the elaboration of effective preventive strategies by indicating which patients might be most likely to benefit from prophylaxis against pneumonia. Table 46-2 summarizes the independent factors for VAP that were identified by multivariate analyses in selected studies.[13,25,38,73–80]

SURGERY

Postsurgical patients are at increased risk for VAP. In a 1981 report, the pneumonia rate during the postoperative period was 17%.[81] Those authors stated that the development of pneumonia was closely associated with preoperative markers of severity of the underlying disease, such as low serum albumin concentration and a high score on the American Society of Anesthesiologists preanesthesia physical status classification. A history of smoking, longer preoperative stays, longer surgical procedures and thoracic or upper abdominal surgery were also significant risk factors for postsurgical pneumonia. Another study comparing adult

TABLE 46-2: INDEPENDENT FACTORS FOR VENTILATOR-ASSOCIATED PNEUMONIA IDENTIFIED BY MULTIVARIATE ANALYSIS

Host Factors	Intervention Factors
Serum albumin <2.2 g/dL	H_2 blockers ± antacids
Age ≥ 60 years	Paralytic agents, continuous intravenous Sedation
ARDS	
COPD, pulmonary disease	>4 units of blood products
Coma or impaired consciousness	Intracranial pressure monitoring
Burns, trauma	MV >2 days
Organ failure	Positive end-expiratory pressure
Severity of illness	Frequent ventilator-circuit changes
Large-volume gastric aspiration	Reintubation
Gastric colonization and pH	Nasogastric tube
Upper respiratory tract colonization	Supine head position
Sinusitis	Transport out of the ICU
	Prior antibiotic or no antibiotic therapy[a]
	Other factor: Season: fall, winter

Abbreviations: ARDS, acute respiratory distress syndrome; *COPD*, chronic obstructive pulmonary disease; ICU, intensive care unit; *MV*, mechanical ventilation.

[a]See text for explanations.

ICU populations demonstrated that postoperative patients had consistently higher rates of nosocomial pneumonia than did medical ICU patients, with a risk ratio of 2.2.[79] Multiple regression analysis was performed to identify independent predictors of nosocomial pneumonia in the two groups; for surgical ICU patients, mechanical ventilation (>2 days) and Acute Physiology and Chronic Health Evaluation (APACHE) score were retained by the model; for the medical ICU population, only mechanical ventilation (>2 days) remained significant. It has been suggested that different surgical ICU patient populations may have different risks for nosocomial pneumonia: Cardiothoracic surgery and trauma (particularly head trauma) patients were more likely to develop VAP than medical or other types of surgical patients.[13]

ANTIMICROBIAL AGENTS

The use of antibiotics in the hospital setting is associated with an increased risk of nosocomial pneumonia and selection of resistant pathogens.[22,25,45,66,82–85] In a cohort study of 320 patients, prior antibiotic administration was identified by logistic regression analysis to be one of the four variables independently associated with VAP along with organ failure, age greater than 60 years, and the patient's head positioning (i.e., flat on the patient's back or supine vs. head and thorax raised 30 degrees to 40 degrees or semirecumbent).[22] Other investigators, however, found that antibiotic administration during the first 8 days was associated with a lower risk of early onset VAP.[86] For example, Sirvent et al showed that a single dose of a first-generation cephalosporin given prophylactically was associated with a lower rate of early-onset VAP in patients with structural coma.[87] Moreover, multiple logistic regression analysis of risk factors for VAP in 358 medical ICU patients identified the absence of antimicrobial therapy as one of the factors independently associated with VAP onset.[88] Finally, the results of the multicenter Canadian study on the incidence of and risk factors for VAP indicated that antibiotic treatment conferred protection against VAP.[13] This apparent protective effect of antibiotics disappears after 2 to 3 weeks, suggesting that a higher risk of VAP cannot be excluded beyond this point. Thus, risk factors for VAP change over time, thereby explaining why they differ from one series to another.

STRESS-ULCER PROPHYLAXIS

In theory, patients receiving stress-ulcer prophylaxis that does not change gastric acidity, such as sucralfate, should have lower rates of gastric bacterial colonization and, consequently, a lower risk for nosocomial pneumonia, than those receiving antacids or H_2 blockers.[89–90]

According to meta-analyses of the efficacy of stress-ulcer prophylaxis in ICU patients, respiratory tract infections were significantly less frequent in patients treated with sucralfate than those receiving antacids or H_2 blockers.[91,92] This conclusion, however, was not fully confirmed in a very large, multicenter, randomized, blinded, placebo-controlled trial that compared sucralfate suspension (1 g every 6 hours) with the H_2-receptor antagonist ranitidine (50 mg every 8 hours) for the prevention of upper gastrointestinal bleeding in 1200 ventilated patients.[93] Clinically relevant gastrointestinal bleeding developed in ten of the 596 (1.7%) patients receiving ranitidine, as compared with twenty-three of the 604 (3.8%) receiving sucralfate (relative risk [RR], 0.44; 95% confidence interval [CI], 0.21 to 0.92; $p = 0.02$). In the ranitidine group, 114 of 596 (19.1%) patients had VAP, as diagnosed by an adjudication committee using a modified version of the Centers for Disease Control and Prevention criteria, versus ninety-eight of 604 (16.2%) in the sucralfate group (RR, 1.18; 95% CI, 0.92 to 1.51; $p = 0.19$). VAP, however, occurred significantly less frequently in patients receiving sucralfate when the diagnosis of pneumonia was based on Memphis VAP Consensus Conference criteria (if there was radiographic evidence of abscess and a positive needle aspirate, or histologic proof of pneumonia at biopsy or autopsy) ($p = 0.03$).[93]

Sucralfate appears to have a small protective effect against VAP because stress-ulcer prophylactic medications that raise the gastric pH might themselves increase the incidence of pneumonia.[94,95] This contention is supported by direct comparisons of trials of H_2-receptor antagonists versus no prophylaxis, which showed a trend toward higher pneumonia rates among the patients receiving H_2-receptor antagonists (odds ratio [OR], 1.25; 95% CI, 0.78 to 2.00).[91] Furthermore, the comparative effects of sucralfate and no prophylaxis are

unclear. Among 226 patients enrolled in two randomized trials, those receiving sucralfate tended to develop pneumonia more frequently than those given no prophylaxis (OR, 2.11; 95% CI, 0.82 to 5.44).[96,97]

ENDOTRACHEAL TUBE, REINTUBATION, AND TRACHEOTOMY

The presence of an endotracheal tube by itself circumvents host defenses, causes local trauma and inflammation, and increases the probability of aspiration of nosocomial pathogens from the oropharynx around the cuff. Scanning electron microscopy of 25 endotracheal tubes revealed that 96% had partial bacterial colonization and 84% were completely coated with bacteria in a biofilm or glycocalyx.[98] The authors hypothesized that bacterial aggregates in biofilm dislodged during suctioning might not be killed by antibiotics or effectively cleared by host immune defenses. Clearly, the type of endotracheal tube may also influence the likelihood of aspiration. Use of low-volume, high-pressure endotracheal cuffs reduced the rate to 56% and the advent of high-volume, low-pressure cuffs further lowered it to 20%.[99] Leakage around the cuff allows secretions pooled above the cuff to enter the trachea; this mechanism, recently confirmed, underlines the importance of maintaining adequate intracuff pressure for preventing VAP.[100]

In addition to the presence of endotracheal tubes, reintubation is, per se, a risk factor for VAP.[101] This finding probably reflects an increased risk of aspiration of colonized oropharyngeal secretions into the lower airways by patients with subglottic dysfunction or impaired consciousness after several days of intubation. Another explanation is direct aspiration of gastric contents into the lower airways, particularly when a nasogastric tube is kept in place after extubation.

Some investigators postulated that early tracheotomy could lower VAP rate because it can permit easier oral hygiene and bronchopulmonary toilet or less time spent deeply sedated.[102] Such benefit, however, was not confirmed in other studies, including two large recent randomized trials having systematically evaluated this issue.[103–106]

NASOGASTRIC TUBE, ENTERAL FEEDING, AND POSITION OF THE PATIENT

Almost all ventilated patients have a nasogastric tube inserted to evacuate gastric and enteral secretions, prevent gastric distension, and/or provide nutritional support. The nasogastric tube is not generally considered to be a potential risk factor for VAP, but it may increase oropharyngeal colonization, cause stagnation of oropharyngeal secretions, and increase reflux and the risk of aspiration. A multivariate analysis retained the presence of a nasogastric tube as one of the three independent risk factors for nosocomial pneumonia based on a series of 203 patients admitted to the ICU for 72 hours or more.[77]

Early initiation of enteral feeding is generally regarded as beneficial in critically ill patients, but it may increase the risk of gastric colonization, gastroesophageal reflux, aspiration, and pneumonia.[107,108] The aspiration rate generally varies as a function of differences in the patient population, neurologic function, type of feeding tube, location of the feeding port, and method of evaluating aspiration. Clinical impressions and preliminary data suggest that postpyloric or jejunal feeding entails less risk of aspiration and may therefore be associated with fewer infectious complications than gastric feeding, although this point remains controversial.[109,110] Nonetheless, aspiration can easily occur should the feeding tube be inadvertently dislodged. A retrospective study of non–critically ill adult patients showed a 40% rate of accidental feeding tube dislodgment, but all the patients whose tube was dislodged were confused or disoriented or had altered awareness, as is frequently observed in ICU patients.[111]

Maintaining ventilated patients with a nasogastric tube in place in a supine position is also a risk factor for aspiration of gastric contents into the lower airways. When radioactive material was injected through a nasogastric tube directly into the stomach of nineteen ventilated patients, the mean radioactive counts in endobronchial secretions were higher in a time-dependent fashion in samples obtained from patients in a supine position than in those obtained from patients in a semirecumbent position.[112] The same microorganisms were isolated from the stomach, pharynx, and endobronchial samples of 32% of the specimens taken while patients were lying supine. The same investigators conducted a randomized trial comparing semirecumbent and supine positions.[113] The trial, which included eighty-six intubated and ventilated patients, was stopped after the planned interim analysis because the frequency and the risk of VAP were significantly lower for the semirecumbent group. These findings were indirectly confirmed by the demonstration that the head position of the supine patient during the first 24 hours of mechanical ventilation was an independent risk factor for acquiring VAP.[22] To what degree of elevation, however, the head of bed should be targeted remains controversial.[114–117]

RESPIRATORY EQUIPMENT

Ventilators with humidifying cascades often have high levels of tubing colonization and condensate formation that may also be risk factors for pneumonia. The rate of condensate formation in the ventilator circuit is linked to the temperature difference between the inspiratory-phase gas and the ambient temperature, and may be as high as 20 to 40 mL/hour.[118,119] Examination of condensate colonization in twenty circuits detected a median level of 2.0×10^5 organisms/mL, and 73% of the fifty-two gram-negative isolates present in the patients' sputum samples were subsequently isolated from condensates.[119] Because most of the tubing colonization was derived from the patients' secretions, the highest bacterial counts were present near the endotracheal tube. Simple procedures, such as turning the patient or raising the bed rail, may accidentally spill contaminated condensate directly into the patient's tracheobronchial tree.[120] Inoculation of large amounts of fluid with high bacterial concentrations is an excellent way to overwhelm pulmonary defense mechanisms and cause pneumonia. Heating ventilator tubing markedly

lowers the rate of condensate formation, but heated circuits are often nondisposable and are expensive. Inline devices with one-way valves to collect the condensate are probably the easiest way to handle this problem; they must be correctly positioned into disposable circuits and emptied regularly.

To decrease condensation and moisture accumulation in ventilator circuits, several studies have investigated the use of heat–moisture exchangers in place of conventional heated-water humidification systems. Slightly lower VAP rates were observed in four studies and a significant difference in a fifth study, suggesting that heat–moisture exchangers are at least comparable to heated humidifiers and may be associated with lower VAP rates than heated humidifiers.[121–125] Changing the heat–moisture exchangers every 48 hours did not affect ventilator circuit colonization and the authors concluded that the cost of mechanical ventilation might be substantially reduced without any detriment to the patient by prolonging the time between heat–moisture exchangers changes from 24 to 48 hours.[126] Furthermore, using heat–moisture exchangers may decrease the nurses' workload (no need to refill cascades, to void water traps on circuits, and so on), decrease the number of septic procedures (it was clearly shown that respiratory tubing condensates must be handled as an infectious waste), and reduce the cost of mechanical ventilation, especially when used for prolonged periods without change. Because some observational studies, however, have documented an increased resistive load and a larger dead space associated with exchangers,[127,128] their use should be discouraged in patients with ARDS ventilated with a low tidal volume and in patients with chronic obstructive pulmonary disease during the weaning period, if pressure support, and not T-piece trials, are used.

There is no apparent advantage to changing ventilator circuits frequently for VAP prevention. This holds true whether circuits are changed every 2 days or every 7 days compared with no change at all, and whether they are changed weekly as opposed to three times per week.[129–131] A policy of no circuit changes or infrequent circuit changes is simple to implement and the costs are likely lower than those generated by regular, frequent circuit changes; thus, such a policy is strongly recommended by the 1997 Centers for Disease Control and Prevention guidelines and other guidelines.[132–134]

SINUSITIS

While many studies have compared the risk of nosocomial sinusitis as a function of the intubation method used and the associated risk of VAP, only a few were adequately powered to give a clear answer. In one study of 300 patients who required mechanical ventilation for at least 7 days and were randomly assigned to undergo nasotracheal or orotracheal intubation, computed tomographic evidence of sinusitis was observed slightly more frequently in the nasal than oral endotracheal group ($p = 0.08$), but this difference disappeared when only bacteriologically confirmed sinusitis was considered.[135]

The rate of infectious maxillary sinusitis and its clinical relevance were also prospectively studied in 162 consecutive critically ill patients, who had been intubated and ventilated for 1 hour to 12 days before enrollment.[136] All had a paranasal computed tomography scan within 48 hours of admission, which was used to divide them into three groups (no, moderate, or severe sinusitis), according to the radiologic appearance of the maxillary sinuses. Patients who had no sinusitis at admission ($n = 40$) were randomized to receive endotracheal and gastric tubes via the nasal or oral route and, based on radiologic images, respective sinusitis rates were 96% and 23% ($p < 0.03$); yet, no differences in the rates of infectious sinusitis were documented according to the intubation route. VAP, however, was more common in patients with infectious sinusitis, with 67% of them developing lung infection in the days following the diagnosis of sinusitis.[136] Therefore, although it seems clear that infectious sinusitis is a risk factor for VAP, no studies have yet been able to definitively demonstrate that orotracheal intubation decreases the infectious sinusitis rate compared to nasotracheal intubation. Thus, no firm recommendations on the best route of intubation to prevent VAP can be advanced.

INTRAHOSPITAL PATIENT TRANSPORT

A prospective cohort study conducted in 531 ventilated patients evaluated the impact of transporting the patient out of the ICU to other sites within the hospital.[137] Results showed that 52% of the patients had to be moved at least once, for a total of 993 transports, and that 24% of the transported patients developed VAP compared with 4% of the patients confined to the ICU ($p < 0.001$). Multiple logistic regression analysis confirmed that transport out of the ICU was independently associated with VAP (OR = 3.8; $p < 0.001$).

DIAGNOSIS

VAP is typically suspected when a patient has new or progressive radiographic infiltrates and clinical findings suggesting infection, such as the new onset of fever, purulent sputum, leukocytosis, increased minute ventilation, and/or a decline in arterial oxygenation. Because interpretation of chest radiographs is difficult, particularly in patients with prior abnormalities, such as ARDS, it is also mandatory to consider the diagnosis of VAP in ventilated patients who clinically deteriorate, and/or in whom vasopressors should be increased to maintain blood pressure, even in the absence of a clear-cut progression of the radiographic abnormalities.

The systemic signs of infection, however, such as fever, tachycardia, and leukocytosis, are nonspecific findings that can be caused by any condition that releases cytokines. In trauma and other surgical patients, fever and leukocytosis should prompt the physician to suspect infection, but during the early posttraumatic or postoperative period (i.e., during the first 72 hours), these findings usually are not conclusive. Later, fever and leukocytosis are more likely to be caused by pulmonary or nonpulmonary (vascular catheter infection, gastrointestinal infection, urinary tract infection, sinusitis, or wound infection) infections, but even then, other events associated with an inflammatory response (e.g., devascularized tissue, open

wounds, pulmonary edema, and/or infarction) can be responsible for these findings. Although the plain (usually portable) chest roentgenogram remains an important component in the evaluation of ventilated patients with suspected pneumonia, it is most helpful when it is normal and rules out pneumonia. When infiltrates are evident, the particular pattern is of limited value for differentiating among cardiogenic pulmonary edema, noncardiogenic pulmonary edema, pulmonary contusion, atelectasis (or collapse), and pneumonia, even when using computed tomographic scanning.[8,17,138–142] Because the tracheobronchial tree of mechanically ventilated patients is frequently rapidly colonized by potential pathogens, the presence of bacteria at that level is not a sufficient argument to diagnose true lung infection, which constitutes another major obstacle for the diagnosis of VAP.[8,143]

In 1991, a composite clinical score, the clinical pulmonary infection score (CPIS) was proposed, based on seven variables (temperature, blood leukocyte count, volume and purulence of tracheal secretions, oxygenation, pulmonary radiography, and semiquantitative culture of tracheal aspirate) accorded 0, 1, or 2 points.[144] This scoring system, however, is quite tedious to calculate and difficult to use in clinical practice, because several variables, such as progression of pulmonary infiltrates and results of semiquantitative cultures of tracheal secretions, can lead to different calculations depending on the observer.[145] Furthermore, its value was not validated in several subsequent prospective studies, especially in patients with bilateral pulmonary infiltrates.[146–154]

Thus, as soon as a ventilated patient is suspected of developing pneumonia, a more complete diagnostic workup should be undertaken, targeting two objectives. The first objective is the immediate recognition of a true VAP or of an extrapulmonary bacterial infection, so as to start effective antibiotics against the microorganisms responsible for infection as soon as possible.[1,2] Numerous studies indicate that failure to initiate prompt appropriate antimicrobial treatment in this setting is a major risk factor for an increased morbidity and mortality.[155–163] The second objective is to avoid overusing antibiotics in patients with only proximal airways colonization and no ongoing bacterial infection. Epidemiologic investigations have clearly demonstrated that indiscriminate use of antimicrobial agents in ICU patients may have immediate and long-term consequences, which contribute to emergence of multiresistant pathogens and increase the risk of serious superinfections.[164–169] This risk is not limited to one patient. Instead, the risk of colonization or infection by multidrug-resistant strains is increased in patients throughout the ICU and even the entire hospital. Virtually all reports emphasize that better antibiotic control programs to limit bacterial resistance are urgently needed in ICUs, and that patients without true infection should not receive antimicrobial treatment.[164]

To reach these objectives, all diagnostic strategies should follow three consecutive steps: (a) obtaining a respiratory tract sample (from proximal or distal airways) for microscopy and culture (qualitative, semiquantitative, or quantitative) before introduction of new antibiotics; (b) immediately starting empiric antimicrobial treatment, unless there are both a negative microscopy and no signs of severe sepsis; and (c) reevaluating treatment on day 2 or 3, based on microbiologic cultures results and clinical outcome.[1,2]

Qualitative Cultures of Endotracheal Aspirates

The first option is to use a clinical strategy and to treat every patient clinically suspected of having a pulmonary infection with new antibiotics (even when the likelihood of infection is low), arguing that several studies showed that immediate initiation of appropriate antibiotics was associated with reduced mortality.[28,32,157,170–175] Using this strategy, all patients suspected of having VAP are treated with new antibiotics after having obtaining an endotracheal aspirate for microscopy and qualitative culture. The selection of appropriate empirical therapy is based on risk factors and local microbiologic and resistance patterns, and involves qualitative testing to identify possible pathogens. The initial antimicrobial therapy is adjusted according to culture results and clinical response (Fig. 46-1). Antimicrobial treatment is discontinued if and only if the following three criteria are fulfilled on day 3: (a) clinical diagnosis of VAP is unlikely (there are no definite infiltrates found on chest radiography at follow-up and no more than one of the three following findings are present: temperature higher than 38.3°C [100.9°F], leukocytosis or leukopenia, and purulent tracheobronchial secretions) or an alternative noninfectious diagnosis is confirmed;

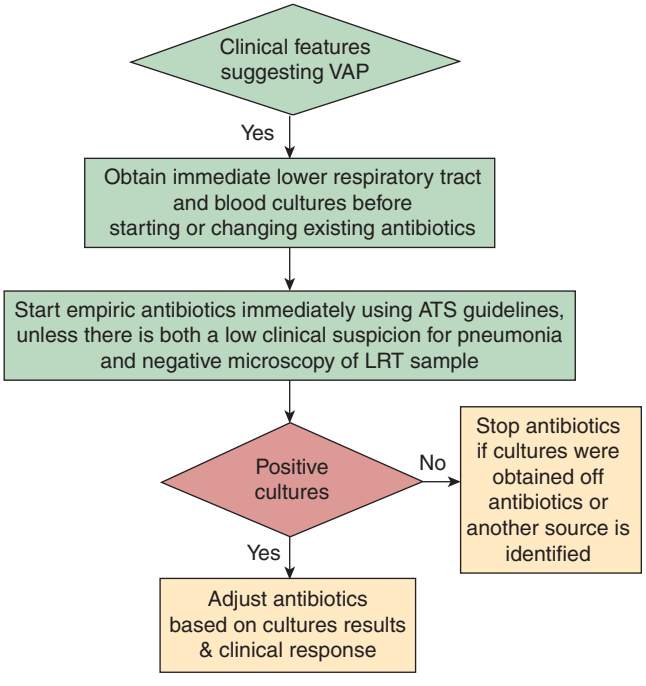

FIGURE 46-1 Diagnostic and therapeutic strategy applied to patients managed with the "clinical" strategy. *ATS*, American Thoracic Society; *LRT*, lower respiratory tract; *VAP*, ventilator-associated pneumonia.

(b) tracheobronchial aspirate culture results are nonsignificant; and (c) severe sepsis or shock are not present.[176]

This clinical approach has two undisputable advantages: first, no specialized microbiologic techniques are required, and, second, the risk of missing a patient who needs antimicrobial treatment is minimal when all suspected patients are treated with new antibiotics. Because, however, tracheobronchial aspirate culture results are rarely negative secondary to the high rate of proximal airways colonization observed in patients receiving mechanical ventilation, discontinuation of antibiotics on day 3 is difficult to perform, leading to antibiotic overuse in many ICU patients. Qualitative endotracheal aspirate cultures contribute indisputably to the diagnosis of VAP only when they are completely negative for a patient with no modification of prior antimicrobial treatment. In such a case, the negative-predictive value is very high and the probability of the patient having pneumonia is close to zero.[5] This is why some investigators have proposed to replace qualitative cultures of endotracheal aspirates by semiquantitative or quantitative cultures of the same specimens.[177]

Quantitative Cultures of Endotracheal Aspirates

Several studies using quantitative culture techniques suggest that endotracheal aspirate cultures may have an acceptable overall diagnostic accuracy, similar to that of several other more invasive techniques.[177] Not all studies, however, have confirmed this conclusion. To assess the reliability of that method, bronchoscopy with PSB and BAL was used to study fifty-seven episodes of suspected lung infection in thirty-nine ventilator-dependent patients with no recent changes of antimicrobial therapy.[178] The operating characteristics of endotracheal aspirate cultures were calculated over a range of cutoff values (from 10^3 to 10^7 colony-forming units [CFU]/mL); the threshold of 10^6 CFU/mL appeared to be the most accurate, with a sensitivity of 68% and a specificity of 84%. When this threshold was applied to the study population, however, almost one-third of the patients with pneumonia were not identified. Furthermore, only 40% of microorganisms cultured in endotracheal aspirate samples coincided with those obtained from PSB specimens. Other authors have emphasized that, although quantitative endotracheal aspirate cultures can correctly identify patients with pneumonia, microbiologic results cannot be used to infer which microorganisms present in the trachea are really present in the lungs. In a study comparing quantitative endotracheal aspirate culture results to postmortem quantitative lung biopsy cultures, only 53% of the microorganisms isolated from the former samples at concentrations greater than 10^7 CFU/mL were also found in the latter cultures.[179]

The inherent advantage of quantitative cultures of endotracheal aspirates is that they are more specific, permitting the discontinuation of antibiotics in more patients than when using only qualitative cultures. But it must be kept in mind that this technique has several potential pitfalls. First, many patients may not be identified using the cutoff value of 10^6 CFU/mL. Second, as soon as a lower threshold is used, specificity declines sharply and overtreatment becomes a problem. Finally, selecting antimicrobial therapy solely on the basis of endotracheal aspirate culture results can lead to either unnecessary antibiotic therapy or overtreatment with broad-spectrum antimicrobial agents.

The "Singh" Strategy

Another option when using the clinical approach is to follow the strategy described by Singh et al, in which decisions regarding initial antibiotic therapy are based on CPIS, a clinical score constructed from seven variables.[180] Patients with CPIS greater than 6 are treated as having VAP with antibiotics for 10 to 21 days, and antibiotics are discontinued after 3 days if the CPIS is 6 or less (Fig. 46-2). Such an approach avoids prolonged treatment of patients who have a low likelihood of infection, while allowing immediate treatment of patients who are more likely to have VAP.

Two conditions must be fulfilled when using this strategy. First, the selection of initial antimicrobial therapy should be based on the most common microbes responsible for VAP at each institution. For example, ciprofloxacin would not be the right choice in hospitals with a high prevalence of MRSA infections. Second, physicians should reevaluate antimicrobial treatment on day 3, when susceptibility patterns of the microorganism(s) recovered from pulmonary secretions are available, so as to select treatment with a narrower spectrum antibiotic.

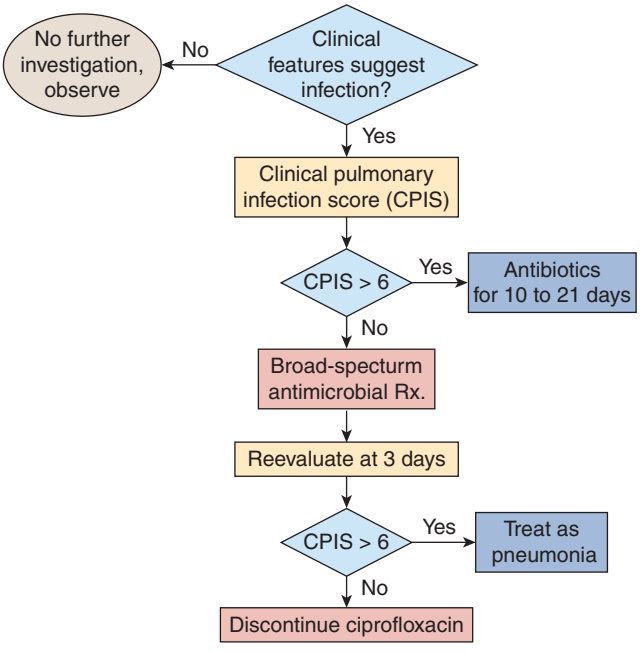

FIGURE 46-2 Diagnostic and therapeutic strategy applied to patients managed with the strategy proposed by Singh et al.[180]

Quantitative Cultures of Distal Specimens Obtained by Bronchoscopy

This strategy uses quantitative cultures of lower respiratory secretions (BAL or PSB collected with a bronchoscope) to define both the presence of pneumonia and the etiologic pathogen(s). Pathogens are present in inflammatory secretions of the lower respiratory tract at concentrations of at least 10^5 to 10^6 CFU/mL, whereas contaminants are generally present at less than 10^4 CFU/mL.[181] The diagnostic thresholds proposed for PSB and BAL are based on this concept. Because PSB collects between 0.001 and 0.01 mL of secretions, the presence of greater than 10^3 bacteria in the originally diluted sample (1 mL) actually represents 10^5 to 10^6 CFU/mL of pulmonary secretions. Similarly, 10^4 CFU/mL for BAL, which collects 1 mL of secretions in 10 to 100 mL of effluent, represents 10^5 to 10^6 CFU/mL.[182–184] Using this strategy, therapeutic decisions are tightly protocolized, using the results of direct examination of distal pulmonary samples and results of quantitative cultures in deciding whether to start antibiotic therapy, which pathogens are responsible for infection, which antimicrobial agents to use, and whether to continue therapy (Fig. 46-3).

One major technical problem with all bronchoscopic techniques is proper selection of the sampling area in the tracheobronchial tree. Almost all intubated patients have purulent-looking secretions and the secretions first seen may represent those aspirated from another site into gravity-dependent airways or from upper-airway secretions aspirated around the endotracheal tube. Usually, the sampling area is selected based on the location of infiltrate on chest radiograph or the segment visualized during bronchoscopy as having purulent secretions.[185] Collection of secretions in the lower trachea or mainstem bronchi, which may represent recently aspirated secretions around the endotracheal tube cuff, should be avoided. In patients with diffuse pulmonary infiltrates or minimal changes in a previously abnormal chest

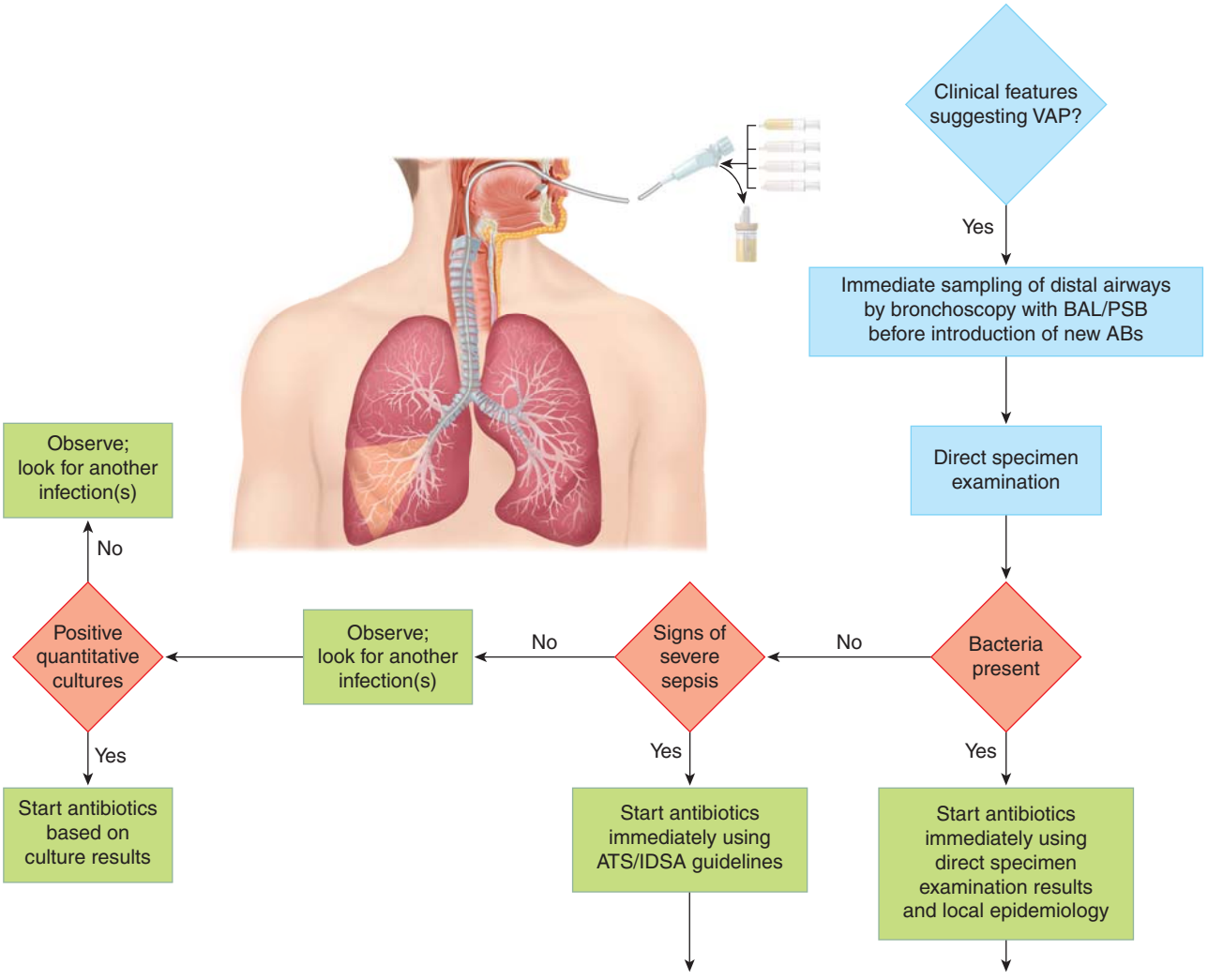

FIGURE 46-3 Diagnostic and therapeutic strategy applied to patients managed with the "invasive" strategy. *AB*, antibiotic; *ATS*, American Thoracic Society; *BAL*, bronchoalveolar lavage; *IDSA*, Infectious Disease Society of America; *PSB*, protector specimen brush; *VAP*, ventilator-associated pneumonia.

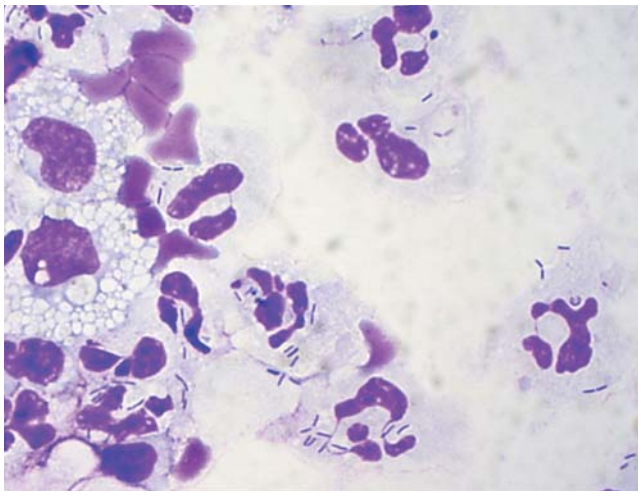

FIGURE 46-4 Light micrograph of cells recovered by BAL from a patient with *Pseudomonas aeruginosa* pneumonia (Diff-Quick stain).

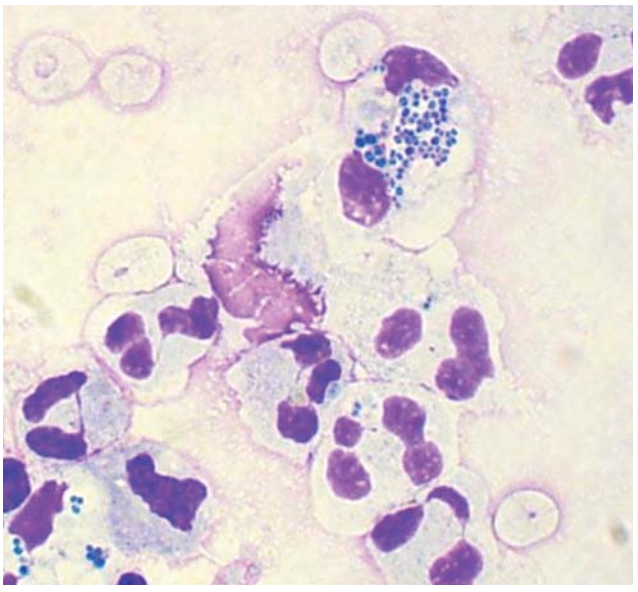

FIGURE 46-5 Light micrograph of cells recovered by BAL from a patient with *Staphylococcus aureus* pneumonia (Diff-Quick stain).

radiograph, determining the correct airway to sample may be difficult. In these cases, sampling should be directed to the area where endobronchial abnormalities are maximal.[186] In case of doubt, and because autopsy studies indicate that VAP frequently involves the posterior portion of the right lower lobe, this area should probably be sampled as a priority.[187] Although bilateral sampling in the immunosuppressed host with diffuse infiltrates has been advocated, there is no convincing evidence that multiple specimens are more accurate than single specimens for diagnosing nosocomial bacterial pneumonia in ventilated patients.

Because BAL harvests of cells and secretions from a large area of the lung and specimens can be microscopically examined immediately after the procedure to detect the presence or absence of intracellular or extracellular bacteria in the lower respiratory tract, it is particularly well suited to provide rapid identification of patients with pneumonia (Figs. 46-4 and 46-5).[183,188–193] Assessment of the degree of qualitative agreement between Gram stains of BAL fluid and PSB quantitative cultures for a series of fifty-one patients with VAP, however, showed correspondence to be complete for 51%, partial for 39%, and nonexistent for 10% of the cases.[190]

Many groups have investigated the value of quantitative BAL culture for the diagnosis of pneumonia in ICU patients.[183,194,195] When the results of the eleven studies evaluating BAL fluids from a total of 435 ICU patients with nosocomial pneumonia were pooled, overall accuracy was very close to that of PSB: The Q value was 0.84 (Q represents the intersection between the summary receiver operating characteristics curve and a diagonal from the upper-left corner to the lower-right corner of the receiver operating characteristics space).[194] Similar conclusions were drawn in another meta-analysis, which pooled the results of twenty-three studies: Sensitivity and specificity of BAL were 73% ± 18% and 82% ± 19%, respectively.[195] When analysis in these studies was restricted to patients without prior antibiotics or when only lung tissue cultures were used as the reference standard, results of bronchoscopic techniques pneumonia were much better: Sensitivity was always greater than 80%.

Other studies confirm the accuracy of bronchoscopic techniques for diagnosing nosocomial pneumonia. In a study evaluating spontaneous lung infections occurring in ventilated baboons with permeability pulmonary edema, Johanson et al found excellent correlation between the bacterial content of lung tissue and results of quantitative culture of lavage fluid.[196] BAL recovered 74% of all species present in lung tissue, including 100% of species present at a concentration equal to or greater than 10^4 CFU/g of tissue. Similarly, in twenty ventilated patients who had not developed pneumonia before the terminal phase of disease and who had no recent changes in antimicrobial therapy, Chastre et al found that bronchoscopic BAL specimens obtained just after death identified 90% of all species present in the lung, with a strong correlation between the results of quantitative cultures of both specimens.[183] These findings confirm that bronchoscopic BAL samples very reliably identify, both qualitatively and quantitatively, microorganisms present in lung segments, even when the pneumonia develops as a superinfection in a patient already receiving antimicrobial treatment for several days.

Values within 1 $\log_{10}$ of the cutoff must, however, be interpreted cautiously, and bronchoscopy should be repeated in symptomatic patients with a negative ($<10^4$ CFU/mL) result.[197] Many technical factors, including medium and adequacy of incubation, and antibiotic or other toxic components, may influence results. Reproducibility of PSB sampling has been recently evaluated by three groups.[198–200] Although in vitro repeatability was excellent and in vivo qualitative recovery 100%, quantitative results were more variable. In 14% to 17% of patients, results of replicate samples fell on both sides of the 10^3 CFU/mL threshold, and results varied

by more than 1 $\log_{10}$ in 59% to 67% of samples.[198–200] This variability is presumably related to both the irregular distribution of organisms in secretions and the very small volume actually sampled by PSB. As with all diagnostic tests, borderline PSB and/or BAL quantitative culture results should be interpreted cautiously, and the clinical circumstances should be considered before reaching any therapeutic decision.

The most compelling argument for invasive techniques coupled with quantitative cultures of PSB or BAL specimens is that they can reduce excessive antibiotic use. There is little disagreement that the clinical diagnosis of nosocomial pneumonia is overly sensitive and leads to the unnecessary use of broad-spectrum antibiotics. Because bronchoscopic techniques may be more specific, their use would reduce antibiotic pressure in the ICU, thereby limiting the emergence of drug-resistant strains and the attendant increased risks of superinfection.[22,201] When culture results are available, BAL and/or PSB techniques facilitate precise identification of the offending organisms and their susceptibility patterns. Such data are invaluable for optimal antibiotic selection in patients with a true VAP. They also increase the confidence and comfort level of health care workers in managing patients with suspected nosocomial pneumonia.[202] The more targeted use of antibiotics also could reduce overall costs, despite the expense of bronchoscopy and quantitative cultures, and minimize antibiotic-related toxicity. This is particularly true in patients who have late-onset VAP, in whom expensive combination therapy is commonly recommended. A conservative cost analysis in a trauma ICU suggested that the discontinuation of antibiotics upon the return of negative bronchoscopic quantitative culture results could lead to a savings of more than $1700 per patient suspected of VAP.[203]

Finally, a major benefit of a negative bronchoscopy is to direct attention away from the lungs as the source of fever. Many hospitalized patients with negative bronchoscopic cultures have other potential sites of infection that can be identified via a simple diagnostic protocol. In fifty patients with suspected VAP who underwent a systematic diagnostic protocol designed to identify all potential causes of fever and pulmonary densities, Meduri et al confirmed that lung infection was present in only 42% of cases; the frequent occurrence of multiple infectious and noninfectious processes justifies a systematic search for the source of fever in this setting.[141] Delay in diagnosis or definitive treatment of the true site of infection may lead to prolonged antibiotic therapy, more antibiotic-associated complications, and induction of further organ dysfunction.[204]

Quantitative Cultures of Distal Specimens Obtained without Bronchoscopy

At least fifteen studies have described a variety of nonbronchoscopic techniques using various types of endobronchial catheters for sampling distal lower respiratory tract secretions; globally, results have been similar to those obtained with bronchoscopy.[205] Compared to conventional PSB and/or BAL, nonbronchoscopic techniques are less invasive, can be performed by clinicians not qualified to perform bronchoscopy, have lower initial costs than bronchoscopy, avoid potential contamination by the bronchoscopic channel, are associated with less compromise of gas exchange during the procedure, and can be performed even in patients intubated with small endotracheal tubes. Disadvantages include the potential sampling errors inherent in a blind technique and the lack of airway visualization. Although autopsy studies indicate that pneumonia in ventilator-dependent patients has often spread into every pulmonary lobe and predominantly involves the posterior portion of the lower lobes, several clinical studies on ventilated patients with pneumonia contradict those findings, as some patients had sterile cultures of PSB specimens from the noninvolved lung.[17,206] Furthermore, although the authors of most studies concluded that the sensitivities of nonbronchoscopic and bronchoscopic techniques were comparable, the overall concordance was only approximately 80%, emphasizing that, in some patients, the diagnosis could be missed by a blind technique, especially in the case of pneumonia involving the left lung.[17]

Patients Already Receiving Antimicrobial Therapy

Performing microbiologic cultures of pulmonary secretions for diagnostic purposes after initiation of new antibiotic therapy in patients suspected of having developed VAP leads to a high rate of false-negative results, regardless of the method of obtaining the secretions. In fact, all microbiologic techniques are of limited value in patients with a recent infiltrate who have received new antibiotics, even if they have received the new antibiotics for less than 24 hours. A negative finding could indicate that the patient has been successfully treated for pneumonia and the bacteria are eradicated, or that the patient had no lung infection to begin with. Using both PSB and BAL, Souweine et al prospectively investigated sixty-three episodes of suspected VAP.[207] If patients had been treated with antibiotics but did not have a recent change in antibiotic class, sensitivity of PSB and BAL culture (83% and 77%, respectively) were similar to the sensitivities achieved in patients not being treated with antibiotics. In other words, prior therapy did not reduce the yield of diagnostic testing among patients receiving current antibiotics given to treat a prior infection. Conversely, if therapy was recent, sensitivity of invasive diagnostic methods, using traditional thresholds, was only 38% with BAL and 40% with PSB.[207] These two clinical situations should be clearly distinguished before interpreting the results of pulmonary secretion cultures, irrespective of how they were obtained. In the second situation, when the patient receives new antibiotics after the appearance of signs suggesting VAP, no conclusion concerning the presence or absence of pneumonia can be drawn if culture results are negative.[207–209] Pulmonary secretions therefore need to be obtained before starting new antibiotics, as is the case for all types of microbiologic samples.

Use of Procalcitonin and Other Biologic Markers

Procalcitonin (PCT), a 116-amino-acid peptide that is one of the precursors of the hormone calcitonin, has been described as a good diagnostic marker of bacterial infection in patients with community-acquired infections, especially in patients with lower respiratory tract infection.[210–213] Moreover, several interventional trials have shown that PCT could be used to start or to postpone antibiotic treatment in community-acquired lower respiratory tract infections.[214–218] In patients with nosocomial infections, and particularly in patients with VAP, its usefulness as a diagnostic marker is more doubtful.[219–223] There are several reasons to explain why PCT is not a good diagnostic marker in patients with suspected VAP. First, pneumonia may be a localized infection; thus, as for other localized infections, PCT can be synthesized locally without systemic release, explaining its low serum level or apparent decrease in patients with true pulmonary infections. Second, ICU patients may suffer from previous severe sepsis or septic shock, multiorgan failure, or may have developed a systemic inflammatory response syndrome after surgery or trauma, conditions known to increase blood level of biomarkers including PCT in the absence of infection.[222] Thus, a high level of PCT the day VAP is suspected is not useful, because it is not possible to distinguish an elevation caused by a previous noninfectious condition from an elevation caused by an active infection. Third, it is known that a time lag of 24 to 48 hours can exist between bacterial infection onset and peak PCT release, and that may also explain the apparent low level of PCT on the day of VAP onset. Incorporating PCT values in clinical score (such as CPIS) did not improve its diagnostic value.[221,222]

The soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) molecule is known to be specifically released during several infectious processes.[224] Although it was apparently a reliable marker of pneumonia, especially VAP, more recent studies obtained contradictory findings, thereby raising doubt as to its usefulness for VAP diagnosis.[220,225–227] Pending additional studies, and because this marker is not routinely available, sTREM-1 is not recommended as an indicator to guide antibiotic use in such situations.

Gram-negative bacilli cause more than 80% of VAP episodes and are associated with high mortality. Because gram-negative bacilli pneumonia might be diagnosed more rapidly by endotoxin measurement in BAL fluid, several investigators tested this hypothesis.[228–231] Applying a threshold of greater than 5 endotoxin units (EU/mL) in BAL fluid yielded the best operating characteristics for gram-negative bacilli pneumonia diagnosis (100% sensitivity; 75% specificity; area under the receiver operating characteristics curve: 0.88) in a series of sixty-three hospitalized adults suspected of having lung infection.[229] Three other studies confirmed the potential contribution of this tool.[228,230,231] These findings suggest that endotoxin determination in BAL fluid might become an acceptable adjunct for the rapid diagnosis of gram-negative bacilli pneumonia in the near future, when it will be available at bedside.

Summary of the Evidence

Aside from decision-analysis studies[232,233] and a single retrospective study,[202] five trials have used a randomized scheme to assess the effect of a diagnostic strategy on antibiotic use and outcome in patients suspected of having VAP.[26,27,234–236] In three randomized studies conducted in Spain, no differences in mortality and morbidity were found when either invasive (PSB and/or BAL) or noninvasive (quantitative endotracheal aspirate cultures) techniques were used to diagnose VAP.[26,27,234] These studies were relatively small, ranging from fifty-one to eighty-eight patients. Antibiotics were continued in all patients despite negative cultures, thereby offsetting the potential advantage of the specific diagnostic test in patients with suspected VAP. Several prospective studies have concluded that antibiotics can be stopped in patients with negative quantitative cultures, without adversely affecting the recurrence of pneumonia and mortality.[188,237,238]

In a French study in which 413 patients were randomized, those receiving bacteriologic management using BAL and/or PSB had a lower mortality rate on day 14, lower sepsis-related organ failure assessment scores on days 3 and 7, and less antibiotic use.[235] Pertinently, twenty-two nonpulmonary infections were diagnosed in the bacteriologic strategy group and only five in the clinical strategy group, suggesting that overdiagnosis of VAP can lead to errors in identifying nonpulmonary infections. A randomized trial conducted by the Canadian Critical Care Trials Group investigated the effect of different diagnostic approaches on outcomes of 740 patients suspected of having VAP.[236] There was no difference in the 28-day mortality rate in patients in whom BAL was used versus those in whom endotracheal aspiration was used as the diagnostic strategy. The BAL group and the endotracheal aspiration group also had similar rates of targeted antibiotic therapy on day 6, days alive without antibiotics, and maximum organ-dysfunction scores. Unfortunately, information about how the decision algorithms were followed in the two diagnostic arms once cultures were available was not provided, raising uncertainties about how de-escalation of antibiotic therapy was pursued in patients with negative BAL cultures. Obviously, the potential benefit of using a diagnostic tool such as BAL for safely restricting unnecessary antimicrobial therapy in such a setting can only be obtained when decisions regarding antibiotics are closely linked to bacteriologic results, including both direct examination and cultures of respiratory specimens.

Our personal bias is that use of bronchoscopic techniques to obtain PSB and BAL specimens from an affected area of the lung in ventilated patients with signs suggestive of pneumonia enables the formulation of a therapeutic strategy superior to that based exclusively on clinical evaluation. Bronchoscopic techniques, when performed before the introduction of new antibiotics, enable physicians to identify most patients who need immediate treatment, and help select optimal therapy in a safe and well-tolerated manner. These techniques also avoid resorting to broad-spectrum coverage of all patients who develop a clinical suspicion of infection.[239] The full impact

of this decision tree on patient outcome remains controversial.[235,236] Yet, being able to withhold antimicrobial treatment from some patients without infection may constitute a distinct advantage in the long-term: It minimizes the emergence of resistant microorganisms in the ICU and redirects the search for another (the true) infection site.

In patients with clinical evidence of severe sepsis and rapid worsening organ dysfunction, hypoperfusion, or hypotension, or patients with a very high pretest probability of disease, the initiation of antibiotic therapy should not be delayed while awaiting bronchoscopy. Patients should be given immediate antibiotics. In this situation, simple nonbronchoscopic procedures find their best justification, allowing distal pulmonary secretions to be obtained on a 24-hour basis, just before starting new antimicrobial therapy.

Despite broad experience with PSB and BAL, it remains unclear which should be used. Most investigators prefer BAL over PSB to diagnose bacterial pneumonia, because BAL (a) has a slightly higher sensitivity to identify VAP-causative microorganisms, (b) enables better selection of an empiric antimicrobial treatment before culture results are available, based on microscopically examined cytocentrifuged preparations, (c) is less dangerous for many critically ill patients, (d) is less costly, and (e) may provide useful clues for the diagnosis of other types of infections. Nevertheless, a very small return on BAL may contain only diluted material from the bronchial rather than alveolar level, and thus give rise to false-negative results, particularly in patients with very severe chronic obstructive pulmonary disease. In these patients, the value of BAL is greatly diminished and PSB is preferred.[184]

When bronchoscopy is not available, we recommend replacing bronchoscopy in the algorithm in Figure 46-3 by one of the simplified nonbronchoscopic diagnostic techniques, or following the strategy described by Singh et al (see Figure 46-3). Such an approach avoids prolonged treatment of patients with a low likelihood of infection, while allowing immediate treatment of patients with VAP.

TREATMENT

Antimicrobial therapy of patients with VAP is a two-stage process. The first stage involves administering broad-spectrum antibiotics to avoid inappropriate treatment in patients with true bacterial pneumonia.[2] The second stage focuses on trying to achieve this objective without overusing and abusing antibiotics. In general, the first goal can be accomplished by identifying patients with pneumonia in a rapid fashion and starting therapy with an empirical regimen that is likely to be accurate. This requires that the choice be driven by anticipation of the likely etiologic pathogens, modified by knowledge of local patterns of antimicrobial resistance and local microbiology. The second goal involves combining a number of different steps, including stopping therapy in patients with a low probability of the disease, commitment to focus and narrow treatment once the etiologic agent is known, switching to monotherapy after day 3, and shortening duration of therapy to 7 to 8 days in most patients, as dictated by the patient's clinical response and information about the bacteriology.

Initial Therapy

Failure to initiate prompt appropriate and adequate therapy (the etiologic organism is sensitive to the therapeutic agent, the dose is optimal, and the correct route of administration is used) has been a consistent factor associated with increased mortality.[32,155–157] Because pathogens associated with inappropriate initial empiric antimicrobial therapy mostly include antibiotic-resistant microorganisms, such as *P. aeruginosa, Acinetobacter* spp., *Klebsiella pneumoniae*, *Enterobacter* spp., and MRSA, patients at risk for infection with these organisms should initially receive a combination of agents that can provide a very broad spectrum of coverage (Table 46-3).[2,173] Several observational studies have now confirmed that the

TABLE 46-3: INITIAL EMPIRIC THERAPY FOR VENTILATOR-ASSOCIATED PNEUMONIA IN PATIENTS WITH LATE-ONSET DISEASE OR RISK FACTORS FOR MULTIDRUG-RESISTANT PATHOGENS

Potential Pathogens	Combination Antibiotic Therapy
MDR Pathogens • *Pseudomonas aeruginosa* • *Klebsiella pneumoniae* (ESBL) • *Enterobacter* species • *Serratia marcescens* • *Acinetobacter* species	Antipseudomonal cephalosporin (cefepime, ceftazidime) *or* Antipseudomonal carbapenem (imipenem or meropenem or doripenem) *or* β-lactam, β-lactamase inhibitor (piperacillin-tazobactam) *plus* Antipseudomonal fluoroquinolone (ciprofloxacin or high-dose levofloxacin) *or* Aminoglycoside (amikacin, gentamicin, or tobramycin) *plus* Linezolid or vancomycin (if MRSA risk factors are present or there is a high incidence locally)
Methicillin-resistant *Staphylococcus aureus* (MRSA)	

Abbreviations: ESBL, extended-spectrum β-lactamase; *MDR*, multidrug resistant; *MRSA*, methicillin-resistant *Staphylococcus aureus.*

Source: Modified from Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med.* 2005;171:388–416, with permission.

use of a regimen that combines initially a broad-spectrum β-lactam with an aminoglycoside increases the proportion of patients appropriately treated as compared to monotherapy or to a regimen combining a β-lactam with a fluoroquinolone.[162,240–242] Only patients with early onset infection, mild or moderate disease severity, and no specific risk factors for multiresistant strains, such as prolonged duration of hospitalization (≥5 days), admission from a health care–related facility, recent prolonged antibiotic therapy, and specific local epidemiologic data, can be treated with a narrow-spectrum drug, such as a nonpseudomonal third-generation cephalosporin.[1,2,243]

When risk factors for multiresistant pathogens are present, the choice of agents should be based on local patterns of antimicrobial susceptibility and anticipated side effects. Having a current and frequently updated knowledge of local bacteriologic patterns can increase the likelihood that appropriate initial antibiotic treatment will be prescribed.[48] The choice should also take into account which therapies patients recently received (within the prior 2 weeks), striving not to repeat the same antimicrobial class, if possible.[244–246]

Use of endotracheal aspirate surveillance cultures two or three times weekly may also make it possible to increase the proportion of patients receiving initially appropriate antimicrobial therapy.[247–251] This strategy rests upon the observation that VAP caused by potentially multiresistant pathogens is typically preceded by colonization of the oropharynx and the proximal airways by the same strains. To be of clinical use in directing initial antibiotic therapy, surveillance cultures must be able to detect this colonization rapidly and with high sensitivity, as false-negative results would place the patient at risk for inappropriate therapy. Moreover, a focused antibiotic choice, with limitation of unnecessary broad-spectrum drugs, requires a low number of false-positive surveillance results. Patients with a prolonged hospital stay and numerous previous antibiotics will benefit the most. Thus, such a strategy can only be recommended when the local prevalence of multiresistant microorganisms is high, when current empirical therapy is suboptimal and cannot be easily increased through adaptation of a decision tree, and when the resources for the microbiologic workup are available.[248]

Stopping Therapy When the Diagnosis of Infection Becomes Unlikely

Because clinical signs of infection are nonspecific and can be caused by any condition associated with an inflammatory response, many more patients than necessary are initially treated with antibiotics. Thus, it is important to use serial clinical evaluations and microbiologic data to reevaluate therapy after 48 to 72 hours.[2,252]

The decision tree should contain an explicit statement that patients with a low probability of infection will be identified and therapy stopped when infection appears unlikely. The algorithm cannot be exactly the same for a "clinical" or an "invasive" strategy, depending on the general principles and microbiologic techniques on which the diagnostic strategy is constructed (see "Diagnosis" above). Using a "clinical strategy" in which all patients with clinically suspected pulmonary infection are treated with new antibiotics, even when the likelihood of infection is low, the decision whether to continue antibiotics or not on day 3 will be based essentially on a combination of clinical signs.[176] Briefly, antibiotics are discontinued if and only if the clinical diagnosis of VAP is unlikely (there are no definite infiltrates found on chest radiography at follow-up), tracheobronchial aspirate culture results are nonsignificant, and there is no severe sepsis or shock. Other decision trees for stopping antibiotics at 3 days can be constructed, for example, by incorporating results of serial levels of procalcitonin in the blood or sTREM-1 in bronchial secretions, but still require validation.[220,223,253]

The decision algorithm for withholding or withdrawing antibiotics using the "invasive strategy" is based on results of direct examination of distal pulmonary samples obtained by bronchoscopic or nonbronchoscopic BAL and results of quantitative cultures (see Fig. 46-3). Briefly, antibiotics are withheld in patients with no bacteria on gram-stained cytocentrifuged preparations and no signs of severe sepsis or septic shock; and discontinued when quantitative culture results are below the cutoff defining a positive result, except in patients with proven extrapulmonary infection and/or severe sepsis.[235] As demonstrated by several studies, patients managed with such a bacteriologic strategy receive fewer antibiotics, and more patients have all their antibiotics discontinued compared to the clinical strategy group, thereby confirming that the two strategies actually differed.[193,202,235,237,239] Future studies should, however, compare bronchoscopy against and in addition to a clinical strategy incorporating an explicit statement for stopping antibiotics in patients with a low probability of infection, for example using the algorithm described above or the CPIS score, as proposed by Singh et al.[146,176,180,254] Formal economic analysis is also required because prevention of resistance and better antibiotic control may result in cost savings. Whatever the diagnostic strategy used, each ICU team should monitor the adherence of their physicians to it and implement corrective measures, as needed.

Focusing Therapy Once the Agent of Infection is Identified

Once the results of respiratory tract and blood cultures become available, therapy can often be focused or narrowed, based on the identity of specific pathogens and their susceptibility to specific antibiotics, so as to avoid prolonged use of a broader spectrum of antibiotic therapy than is justified by the available information.[2,42,161,249,255–258] For many patients, including those with late-onset infection, therapy can be narrowed because an anticipated organism (such as *P. aeruginosa, Acinetobacter* spp., or MRSA) was not recovered or because

the organism isolated is sensitive to a narrower-spectrum antibiotic than used in the initial regimen. For example, vancomycin and linezolid should be stopped if no MRSA is identified, unless the patient is allergic to β-lactams and has developed an infection caused by a gram-positive microorganism.[249] Very broad-spectrum agents, such as carbapenems, piperacillin-tazobactam, and/or cefepime should also be restricted to patients with infection caused by pathogens only susceptible to these agents. In case of infection caused by a piperacillin-susceptible *P. aeruginosa* strain, antimicrobial treatment should be streamlined to this specific drug. Similarly, in the absence of an infection caused by a nonfermenting gram-negative bacilli or an extended-spectrum β-lactamase-producing Enterobacteriaceae, the β-lactam should be changed to a non-antipseudomonal antibiotic, such as ceftriaxone or cefotaxime. Clinicians must be aware, however, that emergence of stable, derepressed, resistant mutants may lead to treatment failure when third-generation cephalosporins are chosen in the case of infections caused by *Enterobacter, Citrobacter, Morganella morganii*, indole-positive *Proteus*, and *Serratia* spp., even if the isolate appears susceptible on initial testing.

Unfortunately, several studies have shown that although de-escalation was not associated with any adverse outcomes, it was not consistently performed in many ICUs.[259–263]

Optimizing Antimicrobial Therapy

Several published reports have demonstrated a relationship among serum concentrations of β-lactams or other antibiotics, the minimal inhibitory concentration (MIC) of the infecting organism, and the rate of bacterial eradication from respiratory secretions in patients with lung infection.[264–270] Consequently, clinical and bacteriologic outcomes can be improved by optimizing a therapeutic regimen according to pharmacokinetic–pharmacodynamic properties of the agent(s) selected for treatment.[161,265,271–278] Most investigators distinguish between antimicrobial agents that kill by a concentration-dependent mechanism (e.g., aminoglycosides and fluoroquinolones) from those that kill by a time-dependent mechanism (e.g., β-lactams and vancomycin). Multivariate analyses based on seventy-four acutely ill, mostly VAP patients, who were treated with intravenous ciprofloxacin (200 mg BID to 400 mg TID), demonstrated that the most important independent factor for probability of cure was a pharmacodynamic variable, that is, the 24-hour area under the concentration–time curve divided by the MIC (AUIC).[271] For AUIC less than 125, the probabilities of clinical and microbiologic cures were 42% and 26%, respectively; with AUIC greater than 125, the probabilities were 80% and 82%, respectively. Routine dosages of fourth-generation cephalosporins, carbapenems, and fluoroquinolones may not achieve the target AUICs for resistant gram-negative bacteria, such as *P. aeruginosa* and *Acinetobacter* spp. Higher dosing regimens and/or prolonged duration of infusion are frequently needed in that case.[264,265,279]

Pharmacokinetic-pharmacodynamic models have also been used to optimize aminoglycoside therapy for VAP caused by gram-negative bacilli, using the first measured maximum concentration of drug in serum (C_{max}).[272] Seventy-eight patients with VAP were analyzed, and the investigators reported an 89% success rate for temperature normalization by day 7 of therapy for C_{max}/MIC greater than 4.7, and an 86% success rate for leukocyte count normalization by day 7 of therapy for C_{max}/MIC greater than 4.5. Logistic regression analysis predicted a 90% probability of temperature and leukocyte count normalizations by day 7 if a C_{max}/MIC greater than 10 was achieved within the first 48 hours of aminoglycoside administration. Aggressive aminoglycoside doses immediately followed by pharmacokinetic monitoring for each patient would ensure that C_{max}/MIC target ratios are achieved early during therapy.

These findings confirm the need to adjust the target dose of antimicrobial agents (used in treating severe pulmonary infection) to an individual patient's pharmacokinetics and putative bacterial pathogens' susceptibilities. Altered pharmacokinetic secondary to increase in volume of distribution in critically ill patients can result in insufficient serum β-lactam concentrations when standard dosages are administered, emphasizing the need to carefully monitor peak and trough levels of antibiotics when treating resistant pathogens, such as gram-negative bacilli.[280–282] Development of a priori dosing algorithms based on MIC, patient creatinine clearance and weight, and the clinician-specified AUIC target might be a valid way to improve treatment of these patients, leading to a more precise approach than current guidelines for use of antimicrobial agents.[273–277]

Switching to Monotherapy at Days 3 to 5

The two most commonly cited reasons to use combination therapy for the duration of antibiotic treatment are to achieve synergy and to prevent the emergence of resistant strains. Synergy, however, has only been clearly documented to be valuable in vitro in the therapy of *P. aeruginosa* or other difficult-to-treat gram-negative bacilli and in patients with neutropenia[283] or bacteremic infection,[284,285] which is uncommon in hospital-acquired pneumonia or VAP. When combination therapy was evaluated in randomized controlled studies, its benefit was inconsistent or null, even when the results were pooled in a meta-analysis or the analysis was restricted to patients infected by *P. aeruginosa*.[286–293] Combination therapy did not prevent the emergence of resistance during therapy, but did lead to a significantly higher rate of nephrotoxicity. In a retrospective analysis of 115 episodes of *P. aeruginosa* bacteremia, the use of adequate combination antimicrobial therapy as empirical treatment until receipt of the sensitivity was associated with a better rate of survival at 30 days than the use of monotherapy.[294] Adequate combination antimicrobial therapy given as definitive treatment for *P. aeruginosa* bacteremia, however, did not improve the rate of survival compared to adequate definitive monotherapy.

Based on these data, therapy could be switched to monotherapy in most patients after 3 to 5 days, provided that initial therapy was appropriate, clinical course appears favorable, and that microbiologic data do not suggest a very difficult-to-treat microorganism, with a very high in vitro minimal inhibitory concentration, as it can be observed with some nonfermenting gram-negative bacilli.

Shortening Duration of Therapy

Efforts to reduce the duration of therapy for VAP are justified by studies of the natural history of the response to therapy. Dennesen et al demonstrated that when VAP was adequately treated, significant improvements were observed for all clinical parameters, generally within the first 6 days of antibiotics.[295] The consequence of prolonged therapy to 14 days or more was newly acquired colonization, especially with *P. aeruginosa* and Enterobacteriaceae, generally during the second week of therapy. These data support the premise that most patients with VAP, who receive appropriate antimicrobial therapy, have a good clinical response within the first 6 days.[295–297] Prolonged therapy simply leads to colonization with antibiotic-resistant bacteria, which may precede a recurrent episode of VAP.

Reducing duration of therapy in patients with VAP has led to good outcomes with less antibiotic use with a variety of different strategies. Singh et al used a modification of the CPIS scoring system to identify low-risk patients (CPIS ≤6) with suspected VAP who could be treated with 3 days of antibiotics as opposed to the conventional practice of 10 to 21 days of antibiotic therapy.[180] Patients receiving the shorter course of antibiotic therapy had better clinical outcomes than the patients receiving longer therapy, with fewer subsequent superinfections attributed to antibiotic-resistant pathogens, although many of these patients may not have had pneumonia. A multicenter, randomized, controlled trial demonstrated, in a large series of 413 patients with microbiologically proven VAP, that patients who received appropriate initial empiric therapy for 8 days had outcomes similar to patients who received therapy for 15 days.[298] A trend toward greater rates of relapse for short-duration therapy was seen if the etiologic agent was *P. aeruginosa* or *Acinetobacter* spp., but clinical outcomes were exactly the same. These results were recently confirmed by two other studies, including a prospective, randomized trial of 290 patients evaluating an antibiotic discontinuation policy.[254,299]

Based on these data, an 8-day regimen can probably be standard for patients with VAP. Possible exceptions to this recommendation include immunosuppressed patients, those whose initial antimicrobial treatment was not appropriate for the causative microorganism(s), and patients whose infection was caused by very difficult-to-treat microorganisms and had no improvement in clinical signs of infection.

Many clinicians, however, remain hesitant about prescribing fewer fixed days of antibiotics for patients with VAP, and would prefer to customize antibiotic duration based on the clinical course of the disease and/or using serial determinations of a biologic marker of infection, such as PCT. The rationale for using a biomarker to tailor antibiotic-treatment duration relies on the fact that the inflammatory response is most often proportional to infection severity.[212] When that response is absent or low, it might be logical to discontinue antibiotics earlier. Moreover, it is well known that PCT levels reflect the inflammatory response intensity and are related to outcome.[223,300,301] Thus, adapting antimicrobial treatment duration to PCT kinetics seems reasonable, and has been demonstrated as useful in several randomized trials targeting patients with acute respiratory infection, including five trials conducted in the ICU.[211,214–218,222,302–308]

Stolz et al randomized 101 patients with VAP to be managed with an antibiotic discontinuation strategy according to guidelines (control group) or to serum PCT concentrations.[304] In patients randomized in the PCT group, attending physicians were recommended to stop antibiotics when the PCT concentration was below 0.5 ng/m, or had decreased by more than 80% from the baseline value. Using this algorithm, the number of antibiotic-free days alive within 28 days after VAP diagnosis was significantly higher in the PCT group than in the control group (median [interquartile range], 13 days [2 to 21] vs. 9.5 days [1.5 to 17]). This reduction in antibiotic administration was not associated with a worse outcome, because ventilator-free days, ICU-free days, length of hospital stay, 28-day mortality, and hospital mortality rates were similar in the two groups.[304] Similar results were observed by Bouadma et al in the PRORATA (PROcalcitonin to Reduce Antibiotic Treatments in Acutely ill patients) trial, a randomized trial that included 621 ICU patients, of whom 141 had microbiologically proven VAP.[305] Using predefined algorithms to initiate or discontinue antibiotics according to serum PCT levels, the duration of antibiotic treatment for the first episode was significantly decreased in the seventy-five patients randomized in the PCT-guided group compared to the control group managed using international and local guidelines (7.3 ± 5.3 days vs. 9.4 ± 5.7 days, $p = 0.02$, respectively), with no detrimental effects on patients' outcome.[305]

Aerosolized Therapy

Because insufficient dosing of antibiotics at the site of infection in patients with VAP may lead to clinical and microbiologic failures, efforts to optimize pulmonary penetration of antimicrobial agents are warranted. Directly delivering the drug to the site of infection via aerosolization may represent a valid option, providing that this technique actually allows improved lung-tissue concentrations at the infected site. This mode of administration, by achieving high pulmonary antibiotic concentrations, could increase the antibacterial activity of concentration-dependent antibiotics, such as aminoglycosides, or restore the bactericidal activity of antibiotics in the case of infections caused by pathogens of impaired sensitivity. Furthermore, by limiting systemic exposure, it could also allow the administration of antibiotics

characterized by a high systemic toxicity, such as aminoglycosides and polymyxins.

Pooling the results of the five randomized controlled trials that examined the potential benefit of inhaled or endotracheally instilled antibiotics for the treatment of patients with hospital-acquired pneumonia or VAP, a statistically higher success rate was demonstrated in patients receiving antimicrobial agents via the respiratory tract.[309] No difference in mortality, however, could be documented and the meta-analysis was based on a very limited number of patients. It should also be noted that the bronchial deposition of aerosolized antibiotics might have rendered cultures of endotracheal samples falsely "negative," which could have artificially increased the rate of success in patients randomized to aerosolized or endotracheally instilled antibiotics, casting some doubt on the validity of the results.

Several recent studies, based on a new generation of nebulizers with improved technology, have renewed the interest in aerosolized antibiotic therapy for patients with VAP.[310–313] In anesthetized piglets on prolonged mechanical ventilation for a severe experimental *E. coli* bronchopneumonia, amikacin lung-tissue concentrations were markedly higher following aerosolization as compared to intravenous administration.[314] Seventy-one percent of lung segments were found sterile after two nebulizations and 25 hours of treatment, whereas cultures of lung segments were comparable in nontreated and intravenously treated animals. In a recent study using a new device with a vibrating plate and multiple apertures to produce an aerosol of amikacin conducted in sixty-nine patients with gram-negative bacilli VAP, the authors found that the nebulized drug was well distributed in the lung parenchyma, with high tracheal and alveolar levels but low serum concentration, below the renal toxicity threshold.[315] Moreover, aerosolized amikacin was well tolerated, without any severe adverse event, and patients who received amikacin twice daily required significantly less antibiotics than patients given placebo.[316]

Data on the impact of aerosolized antibiotics active against gram-positive bacteria are scarce. In a placebo-controlled trial, Palmer et al randomized forty-three patients with purulent tracheobronchitis and gram-stain-identified microorganisms to receive aerosolized antibiotics ($n = 19$) or placebo ($n = 24$).[311] The antibiotic was chosen according to tracheal aspirate gram-staining results (vancomycin for gram-positive, gentamicin for gram-negative). Antibiotic aerosolization led to faster resolution of clinical signs of pneumonia than placebo, fewer subsequent VAP episodes, less bacterial resistance and use of systemic antibiotics, and perhaps accelerated weaning from mechanical ventilation.[311]

Aerosolized polymyxin is also being used increasingly for treating patients with infections caused by multidrug-resistant gram-negative bacilli, mainly *A. baumannii* and *P. aeruginosa,* with mixed results.[312,313] In a randomized trial that included 100 patients with VAP caused by gram-negative bacilli (predominantly multidrug-resistant *A. baumannii* and/or *P. aeruginosa*), patients who were treated with a combination of systemic antibiotics and nebulized colistin had a higher rate of favorable microbiologic outcome than did patients who were treated with systemic antibiotics alone (microbiologic eradication or presumed eradication 61% vs. 38%), but there was no differences in clinical outcome (51% vs. 53%).[313] In a retrospective case-control study that included eighty-six patients with VAP caused by multidrug-resistant gram-negative bacilli (predominantly *A. baumannii*) treated with a combination of intravenous and aerosolized colistin compared with intravenous colistin alone, there was only a trend toward improved rates of clinical cure, pathogen eradication, and mortality in the patients who received aerosolized and intravenous colistin.[312]

Thus, although the results of recent investigations emphasize the potential contribution of aerosolized antibiotics to treat VAP as an efficient adjunctive therapy to intravenous antibiotics, the clinical impact of such a strategy has not yet been definitively established. At present, aerosolized antibiotics can only be recommended to treat patients with multidrug-resistant VAP, for which no effective intravenous antibiotics are available. Indisputably, large prospective trials are needed to evaluate the potential usefulness of this therapeutic modality.

PREVENTION

Because VAP is associated with increased morbidity, longer hospital stay, increased health care costs, and higher mortality rates, prevention is a major challenge for intensive care medicine.[2,317,318] A number of recommendations for the prevention of VAP are empiric rather than based on controlled observations, which make evaluation of the impact of such interventions difficult in this setting for several reasons: (a) the difficulty in obtaining an accurate diagnosis of VAP, that is, to distinguish patients with true infection from patients with tracheal colonization and/or other pathologic processes as only patients who develop true VAP are likely to benefit from preventive measures; (b) the difficulty of precisely determining the impact of prophylactic measure on the overall mortality of a general ICU population, that is, to identify preventable deaths, directly attributable to VAP, among all deaths occurring in a population of ventilated ICU patients; and (c) the difficulty of evaluating the consequences of a preventive measure on a potentially pathogenic mechanism, for example, to evaluate the exact role played by prevention or reduction of tracheal colonization in modifying the development of VAP.

Conventional Infection-Control Approaches

These measures should be the first step taken in any prevention program.[319] The design of the ICU has a direct effect on the potential for nosocomial infections. Adequate space and lighting, proper functioning of ventilation systems, and facilities for handwashing lead to lower infection rates.[320] It should, however, be kept in mind that physical upgrading of

the environment does not per se reduce the infection rate unless personnel attitude and practices are improved. In any ICU, one of the most important factors is the health care staff, including the number, quality, and motivation of medical, nursing, and ancillary members.[321] The team should include a sufficient number of nurses to minimize them moving from one patient to another and to avoid having them working under constant pressure.[322–325] The importance of personal cleanliness and attention to aseptic procedures must be emphasized at every possible opportunity. At the same time, unnecessarily rigid restrictions should be avoided.[326] The importance of personal cleanliness and attention to aseptic procedures must be emphasized at every opportunity. It is clear that careful monitoring, decontamination, and compliance with guidelines for the use of respiratory equipment all reduce the incidence of nosocomial pneumonia.[324] In particular, handwashing and handrubbing with alcohol-based solutions remain the most important components of effective infection control practices in the ICU.[132,324,327]

A bacterial monitoring policy facilitates the early recognition of colonization and infection and is associated with significant reductions in nosocomial infection rates.[328] The focal point for infection control activities in the ICU is a surveillance system designed to establish and maintain a database that describes endemic rates of nosocomial infection. Awareness of the endemic rates enables the recognition of the onset of an epidemic when infection rates rise above a calculated threshold.

Adoption of an antibiotic policy restricting the prescription of broad-spectrum agents and useless antibiotics is of major importance.[22,164,235,329] Better use of antibiotics in the ICU can be achieved by implementing strict guidelines, avoiding the treatment of patients who do not have bacterial infections, using narrow-spectrum antibiotics whenever possible, and reducing the duration of treatment. Similarly, transfusion of red blood cells and other allogenic blood products should follow a strict policy, because several studies have identified exposure to allogenic blood products as a risk factor for postoperative infection and pneumonia.[330–335] Some very simple, safe, inexpensive, and logical measures may have major effects on the frequency of VAP in ventilated patients. These include avoiding nasal insertion of endotracheal and gastric tubes, maintaining the endotracheal tube cuff pressure above 20 cm H_2O to prevent leakage of bacteria around the cuff into the lower respiratory tract, prompt reintubation of patients who are likely to fail extubation, removing tubing condensate, and providing adequate oral hygiene with tooth brushing.[101,119,136,336,337]

Specific Prophylaxis against Ventilator-Associated Pneumonia

Specific strategies aimed at reducing the duration of mechanical ventilation (a major risk factor for VAP), such as improved methods of sedation, use of protocols to facilitate and accelerate weaning, using low tidal volume and adequate levels of positive end-expiratory pressure, and use of intensive insulin therapy to control blood glucose should be considered as integral parts of any infection-control program.[338–343] All are based on the application of strict protocols. Noninvasive ventilation is an alternative approach to using artificial airways to avoid infectious complications and injury of the trachea in patients with acute respiratory failure. Many observational studies and seven randomized trials suggest that patients who tolerate noninvasive ventilation have a lower incidence of pneumonia than those tracheally intubated.[338,344–352]

Apart from protocols aimed at reducing the duration of mechanical ventilation, eight prophylactic approaches have been studied: semirecumbent positioning, oscillating and rotating beds, continuous or intermittent aspiration of subglottic secretions, ventilator circuits management, methods of enteral feeding, stress-ulcer prophylaxis, oral decontamination with antiseptics, and selective digestive decontamination.

SEMIRECUMBENT POSITIONING

Supine positioning is independently associated with the development of VAP.[22] Placing ventilated patients in a semirecumbent position to minimize reflux and aspiration of gastric contents is a simple measure, although some practical problems can occur in unstable patients. Only a few trials have evaluated the efficacy of semirecumbent positioning.[112–114,117,353–355] In a randomized trial based on a small number of patients, Drakulovic et al observed lower rates of both clinically suspected and bacteriologically confirmed VAP, and identified supine positioning as an independent risk factor for VAP with enteral nutrition, ventilation for 7 days or longer and a Glasgow coma score of less than 9 points. The feasibility and efficacy of this intervention in a larger patient population, however, remain unknown, all the more as its efficacy was not confirmed in a subsequent trial that included 221 ventilated patients or in a recent meta-analysis.[117,353] Raising the head of bed to 30 degrees or higher may also have some detrimental skin effects and may increase the incidence of pressure ulcer formation.[115] Pending additional studies, most experts currently recommend maintaining the head of the bed elevated to at least 20 degrees to 30 degrees in all ventilated patients who are hemodynamically stable, particularly when they are receiving enteral nutrition.[134,317,356–361]

OSCILLATING AND ROTATING BED

Immobility in critically ill patients treated with mechanical ventilation results in atelectasis, impaired secretions drainage, and potentially predisposes to pulmonary complications including VAP. Oscillating and rotating beds may help in preventing pneumonia.[317] Six randomized trials, which included mostly surgical and trauma patients, ventilated or not, and summarized in a meta-analysis by Choi and Nelson,[362] compared continuous lateral

rotational therapy with standard beds. The meta-analysis found a significant reduction in the risk for pneumonia, principally concerning early onset (<5 days) pneumonia and a decreased duration of ICU stay. Notably, the only randomized, controlled trial—not included in the meta-analysis—conducted on a general ICU population did not show any differences in pneumonia rates but showed a significantly shorter length of ICU stay.[363] Some adverse events have been described with these beds including disconnection of catheters or pressure ulceration; in addition, nursing care is potentially complicated with oscillating beds. Finally, despite the cost of such beds, cost-to-benefit analyses suggested favorable results, mainly caused by the reduction of ICU length of stay.

ORAL DECONTAMINATION WITH ANTISEPTICS

Topical application of chlorhexidine or other antiseptics to the oral mucosa may decrease respiratory pathogen colonization and secondary lung infection in ventilated patients. Randomized, controlled trials, however, have reported mixed results: Some showed little effect whereas others found a reduction in the incidence of VAP.[364–376] Combining the results of the seven randomized controlled trials that evaluated the potential efficacy of chlorhexidine, a 30% relative reduction in the risk of VAP was observed, but no effect of chlorhexidine on reduction of mortality or duration of mechanical ventilation could be demonstated.[377] The varying concentration of the chlorhexidine solutions used in these studies may have affected the results. In the study by Koeman et al,[369] a 2% solution of chlorhexidine was used, a much higher concentration than in the other published studies, most of which used a 0.12% or 0.2% solution; this may partially explain the benefit of chlorhexidine for reducing VAP in this study. Reported adverse effects of oral use of chlorhexidine include staining of the teeth, which is reversible with professional cleaning, and a transient abnormality of taste.[377] The optimal concentration, frequency of application, effect on promoting resistance among oropharyngeal flora, and cost-effectiveness of chlorhexidine should be addressed in future studies.

ASPIRATION OF SUBGLOTTIC SECRETIONS AND USE OF SPECIALIZED ENDOTRACHEAL TUBES

Repeated micro inhalations of colonized oropharyngeal (subglottic) secretions are the major mechanism of VAP. Continuous or intermittent suctioning of oropharyngeal secretions has been proposed as a means to avoid chronic aspiration of secretions through the tracheal cuff of intubated patients. Aspiration of subglottic secretions requires the use of specially designed endotracheal tube with a separate lumen that opens into the subglottic region. Thirteen randomized controlled trials have studied aspiration of subglottic secretions for the prevention of VAP for a total of 2442 randomized patients.[378–386] Of the thirteen studies, twelve reported a reduction in VAP rates in the subglottic secretion drainage arm. When the results were combined in a meta-analysis, the overall risk ratio for VAP was 0.55 (95% CI, 0.46 to 0.66; $p < .00001$) with no heterogeneity, and the use of subglottic secretion drainage was associated with reduced ICU length of stay, decreased duration of mechanical ventilation, and increased time to first episode of VAP.[386] No effect, however, on hospital or ICU mortality could be demonstrated.[386] Some experimental data in sheep and ICU patients suggest the possibility of tracheal damage with the use of this type of tube.[382,387,388]

Bacterial aggregates in biofilm dislodged during suctioning might not be eradicated by antibiotics or effectively cleared by host immune defenses, thereby constituting dangerous inoculums for the lung. Preliminary data obtained in animal models and from small randomized human studies support the hypothesis that an endotracheal tube coated externally and internally with a potent antiseptic product such as silver could have a sustained antimicrobial effect within the proximal airways and block biofilm formation at its surface.[389–394] Such a device was evaluated in a large, randomized, multicenter, single-blind trial by Kollef et al.[395] The authors conclude that the new device was able to lower the VAP frequency from 7.5% for the control group to 4.8% for the group receiving the silver-coated endotracheal tube. The silver-coated tube, however, did not reduce mortality rates, the duration of intubation, hospital length of stay, or the frequency or severity of adverse effects.

VENTILATOR CIRCUIT MANAGEMENT

Decreased frequency of ventilator circuit change, replacement of heated humidifiers by heat and moisture exchangers, decreased frequency of heat and moisture exchanger change, and closed suctioning systems have been tested for preventing VAP.[2,317,318,396] Four randomized trials of decreased frequency of ventilator circuit changes have been published. Changes every 2 days, 7 days, and no scheduled change did not find significant difference in the rate of VAP as summarized in a recent meta-analysis.[397] One meta-analysis summarized the results of five randomized, controlled trials which compared the effects of heated humidifiers and heat and moisture exchangers on the risk of VAP.[318] Only one of these five studies found a significant reduction of VAP rate with the use of heat and moisture exchangers.[125] Efficacy of both humidification strategies seems comparable. Two studies, however, reported increased rates of endotracheal tube occlusion with the use of heat and moisture exchangers; the increased resistive load can cause difficulties in ventilation and weaning in patients with severe acute respiratory distress syndrome—related to larger dead space. No other adverse effects were observed. No effect on mortality was reported. Finally, one study has evaluated the impact of less frequent changes (daily vs. every 5 days) in heat and moisture exchangers on the development of VAP.[398] No difference in the VAP rates was observed.

To avoid hypoxia, hypotension, and contamination of suction catheters entering the tracheal tube, investigators

have examined closed suctioning systems.[396,399–400] They either found a nonsignificantly lower prevalence of VAP for patients managed with the closed system compared to the open system, without any adverse effect,[400] or they found that its use was associated with an increased frequency of endotracheal colonization.[399] Closed-suction systems also failed to reduce cross-transmission and acquisition rates of the most relevant gram-negative bacteria in ICU patients in a prospective crossover study in which 1110 patients were enrolled.[396]

METHODS OF ENTERAL FEEDING

Nearly all ventilated patients have a nasogastric tube inserted to manage gastric and enteral secretions, prevent gastric distension, or provide nutritional support. A nasogastric tube may increase the risk for gastroesophageal reflux, aspiration, and VAP.[77] Four randomized, controlled trials have evaluated methods of enteral feeding aimed at preventing VAP: postpyloric or jejunal feeding (vs. gastric feeding), the use of motility agents (metoclopramide vs. placebo), acidification of feeding (with addition of hydrochloric acid), and intermittent (vs. continuous) feeding.[108,401,402] These studies did not find differences in incidence of VAP or mortality rates. Potentially serious adverse effects have been observed in patients receiving acidified feeding (gastrointestinal bleeding) or intermittent enteral feeding (increased gastric volume and lower volumes of feeding). Thus, to date, methods of enteral feeding aimed at reducing the incidence of VAP cannot be recommended for routine use.

STRESS-ULCER PROPHYLAXIS

Gastric colonization by potentially pathogenic organisms increases with decreasing gastric acidity.[403] Thus, medications that decrease gastric acidity (antacids, H_2 blockers, proton pump inhibitors) may increase organism counts and increase the risk of VAP. In contrast, medications that do not affect gastric acidity (sucralfate) may not increase this risk. Several meta-analyses of more than 20 randomized trials have evaluated the risk for VAP associated with the methods used to prevent gastrointestinal bleeding in critically ill patients.[91,92,404] The largest randomized trial comparing ranitidine to sucralfate showed that ranitidine was superior in preventing gastrointestinal bleeding and did not increase the risk of VAP.[93] Therefore, despite the potential advantage of sucralfate (potentially less VAP with more gastrointestinal-bleeding) over H_2 blockers (potentially more VAP with less gastrointestinal bleeding) in preventing VAP, stress-ulcer prophylaxis with H_2 blockers appears to be safe in patients who are at high risk for bleeding as well as VAP.[405] Although proton pump inhibitors are now widely used for gastric bleeding prophylaxis in the ICU, based on their potentially higher efficacy, their use is associated with similar rates of nosocomial pneumonia as H_2 blockers.[404,406–410]

SELECTIVE DIGESTIVE DECONTAMINATION

Selective decontamination of the digestive tract (SDD) includes a short course of systemic antibiotic therapy, such as cefotaxime, trimethoprim, or a fluoroquinolone, and topical administration of nonabsorbable antibiotics (usually an aminoglycoside, polymyxin B, and amphotericin) to the mouth and stomach, in order to eradicate potentially pathogenic bacteria and yeast that may cause infections.[411] Since the original study published by Stoutenbeck et al in 1984,[412] which demonstrated a decrease of the overall infection rate in patients receiving the SDD regimen, more than forty randomized, controlled trials, and eight meta-analyses have been published. All eight meta-analyses reported a significant reduction in the risk of VAP, and four reported a significant reduction in mortality.[86,413–416] Recently, three prospective, randomized, controlled trials, all performed in ICUs with low rates of antibiotic resistance, have been published that were large enough to show a significant survival benefit in SDD-treated patients.[417–419] All three were in favor of treatment with SDD, the largest and most recent one by De Smet et al demonstrating a relative decrease in 28-day mortality rate (OR 0.83,95% CI, 0.72 to 0.97) and an absolute survival benefit of 3.5%.[419]

In spite of these benefits, widespread use of SDD in ICU patients remains controversial. The major concern with use of SDD is that it probably needs to be used in nearly all patients in a given ICU, and this widespread use has been shown in some studies to promote the emergence of resistant bacteria, particularly gram-positives such as MRSA.[420–424] This is likely to be even a greater problem in ICUs with a high baseline rate of resistance.[317,318,425] In contrast to what was expected, however, most studies that have evaluated this issue showed a lower incidence of colonization with (multi)resistant bacteria in SDD-treated patients than in control patients.[418,426] In a single-center observational study from Germany, 5-year use of SDD was not associated with an increase of MRSA or aminoglycoside and β-lactam resistance in gram-negative bacteria.[427] Putative explanations why colonization with resistant microorganisms is lower after treatment with SDD include the almost invariable sensibility of gram-negative aerobic bacteria for the commonly used combination of polymyxin E and tobramycin, the fact that treatment with polymyxin E rarely induces resistance, the very high local concentrations in the bowel of the used antibiotics, and the lower rate of use of systemic antibiotics in SDD-treated patients.[428]

IMPLEMENTING A STRUCTURED PREVENTION POLICY

The application of consistent evidence-based interventions to prevent VAP has been highly variable from one ICU to another and often suboptimal.[429–430] Moreover, no single preventive measure can succeed alone, emphasizing the need to use multifaceted and multidisciplinary programs to prevent VAP. Such programs are frequently referred to

as "care bundles." A care bundle is a set of readily implementable interventions that are required to be undertaken for each patient on a regular basis.[431] The key goal is that every intervention must be implemented for every patient on every day of his or her stay in the ICU. Compliance is assessed for the bundle as a whole, so failure to complete even a single intervention means failure of the whole bundle at a particular assessment. The interventions need to be packaged in such a way that they are easy to assess for compliance, which usually means that no more than five interventions are included in each care bundle. The performance goal is to routinely achieve more than 95% compliance. Care bundles make it possible to introduce evidence-based preventive measures, including appropriate nurse staffing levels, hand hygiene with alcohol-based formulations, standardized weaning protocols and daily interruption of sedation, oral care with chlorhexidine, and keeping patients who receive enteral nutrition in a semirecumbent position.[252] All of these measures can be consistently applied to all patients in a coordinated way. The aim of care bundles is therefore only to facilitate and promote changes in patient care and encourage compliance with guidelines. Several studies using quasi-experimental designs confirmed the usefulness of this strategy for preventing VAP in the ICU.[134,355,432–444]

The lack of methodologic rigor of the reported studies, however, precludes any conclusive statements about "bundle care" effectiveness or cost-effectiveness. The exact set of key interventions that should be part of the "VAP-prevention bundle" is also not currently known as well as the optimal way for implementing it.[134,445–447] Successful VAP prevention requires an interdisciplinary team, educational interventions, system innovations, process indicator evaluation, and feedback to health care workers. As shown by a recent study, simply having a checklist available for reference without consideration of a robust implementation and adherence strategy is unlikely to maximize patient outcomes.[444] Whether this organization and data collection can be generalized to all ICUs remains to be determined, as well as the selection of the "optimal" bundle. In the meantime, clinical practice quality indicators must be developed in parallel with guidelines to check the adequacy between the two and to find solutions to improve guideline compliance.

In the United States, the Centers for Medicare and Medicaid Services has proposed stopping hospital reimbursements for care made necessary by preventable complications, including nosocomial infections, aiming for a zero-VAP rate.[448] Although this plan may have the desirable consequences of improving the quality of care, it also may penalize hospitals that admit high-risk patients and inadvertently encourage institutions to underreport VAP or to overuse antibiotics, thereby favoring dissemination of multidrug-resistant microorganisms. This possibility further underscores the need to carefully evaluate all new strategies potentially aimed at preventing VAP against what represents best clinical practices.

CONCLUSION

VAP is associated with mortality in excess of that caused by the underlying disease alone, particularly in case of infection caused by high-risk pathogens, such as *P. aeruginosa* and MRSA. The high level of bacterial resistance observed in patients who develop VAP limits the treatment options available to clinicians and encourages the use of antibiotic regimens combining several broad-spectrum drugs, even if the pretest probability of the disease is low, because initial inappropriate antimicrobial therapy has been linked to poor prognosis. Besides its economic impact, this practice of "spiralling empiricism" increasingly leads to the unnecessary administration of antibiotics in many ICU patients without true infection, paradoxically resulting in the emergence of infections caused by more antibiotic-resistant microorganisms that are, in turn, associated with increased rates of patient mortality and morbidity. Every possible effort should therefore be made to obtain, before new antibiotics are administered, reliable pulmonary specimens for direct microscope examination and cultures from each patient clinically suspected of having developed VAP. Because respiratory tract colonization of ICU patients is generally very complex, corresponding to a mix of self-colonization and cross-transmission, only a multifaceted and multidisciplinary preventive program can be effective.

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47

SINUS INFECTIONS IN THE VENTILATED PATIENT

Jean-Jacques Rouby
Qin Lu

Infection of paranasal sinus cavities is a well-recognized cause of fever in mechanically ventilated patients.[1–7] Easy to detect in maxillary sinuses, the infectious process also frequently involves ethmoid, frontal, and sphenoid sinuses[8] where the diagnosis is more difficult to establish.[9] Infectious sinusitis represents an important reservoir of bacteria[10] that may disseminate into the respiratory tract[11] and intracranially.[12] In contrast to community-acquired sinusitis, ventilator-associated sinusitis is often clinically silent in sedated critically ill patients and may be underdiagnosed if not systematically screened for in the presence of fever of unknown origin. In the absence of diagnosis and appropriate treatment, bacteremia,[2,5] ventilator-associated pneumonia,[13] and life-threatening complications, such as orbital infection,[14] meningitis, mastoiditis, cerebral abscess, or thrombosis of the sinus cavernosus, may result.[12] Early detection and treatment of infectious maxillary sinusitis significantly reduces the incidence of ventilator-associated pneumonia and may decrease intensive care mortality.[11]

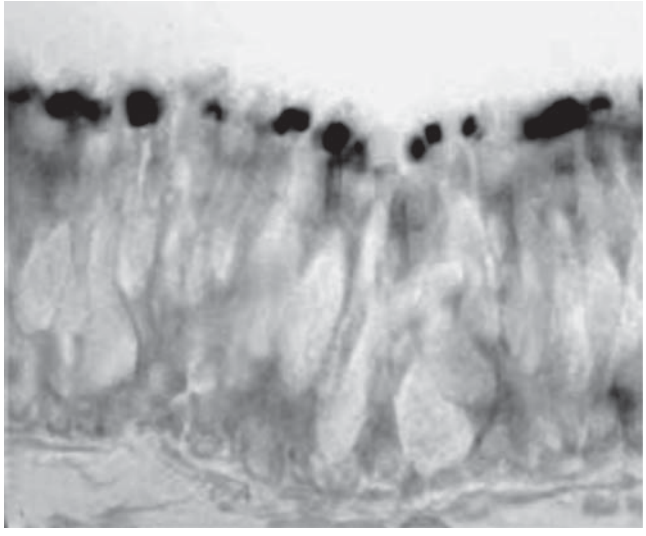
PHYSIOLOGY OF PARANASAL SINUSES

Classical Hypotheses

Located at the entry of the respiratory system, paranasal sinuses and the nose serve to humidify, filter, warm, and sense inspiratory gas.[15,16] A number of other presupposed physiologic roles have not yet received firm scientific confirmation.[17] Among them, the most popular are that paranasal sinuses help lighten the bones of the skull, improve the resonance of the voice, serve as a sound box for opera singers, increase the surface area of the olfactory membrane, serve as shock absorbers in mechanical impacts, protect against high pressure in the nasal region when sneezing, act as thermal insulators of the brain, and promote facial growth and architecture. More simply, paranasal sinuses might be considered as evolutionary relics or faults, whose form results from the influence of the forces created during the act of chewing.

Recent Hypothesis: The Role of the Regional Production of Nitric Oxide

Large amounts of nitric oxide are produced in human paranasal sinuses[18,19] and permanently released in the upper airways through the different ostia that link antral cavities to the nostrils.[20] As shown in Figure 47-1, an inducible form of nitric oxide synthetase is present in cilia and microvilli of the maxillary sinus epithelium of healthy volunteers.[18,19] Significant nitric oxide concentrations are also found in the exhaled gas of guinea pigs, pigs, rhesus monkeys, rats, rabbits, horses, and Asian elephants, all species possessing open paranasal sinuses.[20–24] Interestingly, seals and baboons, which do not have open paranasal sinuses, do not exhale nitric oxide,[25,26] thus confirming that pneumatic facial cavities play a critical role in the nasal production of nitric oxide in mammals. Humming, by accelerating gas exchange in sinus cavities, markedly increases exhaled nasal nitric oxide[27] whereas moderate exercise has an opposite effect.[28] Nitric oxide produced in the paranasal sinuses likely has an important role in host defense against inhaled pathogens, in the optimization of ventilation–perfusion ratios during normal breathing,[29] and in the regulation of ciliary motility.[30,31]



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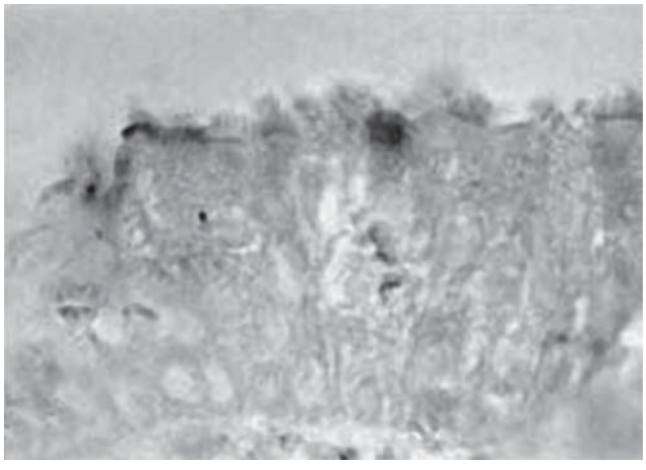


B

FIGURE 47-1 Immunoreactive sinus inducible nitric oxide synthetase distribution is represented in black on biopsy samples from maxillary sinus epithelium. In a healthy subject (**A**), a strong immunoreactivity is detected in the apical part of the ciliated epithelial cells near the surface. In a patient with radiographic maxillary sinusitis (**B**), the signal is weaker or absent. (Reprinted with permission of the American Thoracic Society. Copyright © 2012 American Thoracic Society. From Deja M, Busch T, Bachmann S, et al. Reduced nitric oxide in sinus epithelium of patients with radiologic maxillary sinusitis and sepsis. *Am J Respir Crit Care Med.* 2003;168:281–286. Official Journal of the American Thoracic Society.)

Each paranasal sinus communicates with the corresponding nostril by an ostium, which provides aeration of the antral cavity. Bacteria are present in nasal secretions covering the mucociliary epithelium and on the gingival mucosa and its crevices. Microorganisms may enter the maxillary cavity by the canine fossa and the inferior meatus. Paranasal sinuses, however, are normally sterile[32] as a result of two different protective mechanisms. First, the antral mucosa is covered with a protective mucus layer produced by goblet cells. Bacteria penetrating into the maxillary cavity are immediately enveloped by mucus and moved rapidly to the sinus ostium by respiratory cilia. Second, the antral concentrations of nitric oxide exert a bacteriostatic effect. Many pathogens are sensitive to nitric oxide in concentrations less than 1 part per million.[33–36] The antral concentrations of nitric oxide, produced by the maxillary epithelium, are equal to or greater than 2 parts per million and likely contribute to antral sterility.[32]

PATHOGENESIS AND PREDISPOSING FACTORS

Pathogenesis of radiographic sinusitis diagnosed in intubated and tracheostomized patients is incompletely understood.

Experimental Models

Rabbits have large and accessible nostrils and their sinuses show anatomical similarities to those of humans. In this species, sinuses consist of a number of cavities connected to each other and can be considered as one, called the maxillary sinus.[37] Historically, the first experimental model was created by opening the maxillary sinus through an anterior wall antrostomy, gluing and closing the natural ostium, and injecting bacterial strains directly supress "injected" into the maxillary cavity.[38] Although the model is extremely reliable for producing purulent sinusitis, it causes a traumatic injury that questions its relevance for human sinusitis. As a consequence, a rhinogenic model was proposed in the late 1990s and remains to date the reference:[39,40] a foreign body—an endotracheal tube,[41] a catheter,[42] or a sponge impregnated or not with bacteria[43]—is implanted into nostrils for a period

of time ranging from several days to several weeks. In the rhinogenic rabbit model, computed tomographic evidence of maxillary sinusitis is detected at the sixth day following foreign-body nasal placement.[43]

A number of lessons can be drawn from experimental studies. Direct or indirect obstruction of the ostia rapidly induces an acute sinus inflammation. The intranasal placement of a foreign body over several days results in purulent sinusitis, characterized by the accumulation of a thick and purulent discharge within the sinus cavity.[43] Initial histologic lesions are made of inflammation and exudation of maxillary mucosa; the number of goblet cells increases, augmenting mucus production and causing fluid accumulation within the cavity. Then, inflammatory polyp formation is observed,[41,43,44] associated with permanent loss of cilia, squamous metaplasia, and fibrosis.[43,45] The risk of sinusitis increases with the nasal catheterization period and the size of the intranasal catheter.[41,42] Relief of ostial obstruction promotes resolution of radiographic sinusitis within a few days,[46] whereas sinus inflammation persists for several weeks.[43] Over time, the fluid-filled maxillary cavity is contaminated[41] or infected[43] by species present in the adjacent nostril.[41] Surprisingly, bacteria impregnating the intranasal sponge are rarely found in the nasal cavity and are often replaced by bacteria belonging to the normal flora of the rabbit nostrils.[43,47]

Finally, the following sequence may lead to bacterial sinusitis. First, the presence of a nasal foreign body induces an ipsilateral inflammatory antral disease. Second, mucus accumulates within the antral cavity because of goblet cell proliferation, impairment of mucociliary clearance, and ostial obstruction. Third, the antral contents are contaminated and infected by microorganisms issued from the nostrils whose proliferation into the sinus cavity is facilitated by the lack of regional nitric oxide production.

Macroscopic and Microscopic Aspects of Sinusitis Complicating Mechanical Ventilation

Only a few studies have reported macroscopic and histologic disorders characterizing radiographic maxillary sinusitis in critically ill patients.[19,48–50] In thirty-three neurosurgical patients receiving prolonged mechanical ventilation with radiographic maxillary sinusitis, antroscopies were performed by the canine fossa route.[49] Most of radiographic maxillary sinusitis corresponded to "inflammatory" sinusitis, with the antral cavity filled with thin and transparent secretions and/or gelatinous and transparent mucus with a neutral smell. In a minority of patients, bacterial sinusitis was diagnosed as the presence of viscous and opaque pus with a foul smell. Both types of sinusitis were associated with varying mucosal reactions, ranging from pallid to vermilion edema with different degrees of transparency. Interestingly, in two patients with "inflammatory" sinusitis and one patient with bacterial sinusitis, maxillary mucosa was macroscopically normal. When present, mucosal edema always included the medial side with the ostial region.[49] Biopsy specimens of antral mucosa revealed various grades of inflammation. Acute inflammation involving the maxillary epithelium, the connective tissue, and the vessels with a massive infiltration by polymorphonuclear neutrophils was observed in patients with bacterial maxillary sinusitis. In patients with "inflammatory" sinusitis, mild inflammation was observed, characterized by a moderate cellular infiltration of the connective tissue with a massive infiltration of vessels by eosinophils.[48]

Predisposing Factors

FOREIGN BODIES WITHIN THE NOSTRILS

Several prospective and retrospective studies have shown that the occurrence of radiographic sinusitis has a higher incidence in the antrum adjacent to nasotracheal and nasogastric tubes than in the nonadjacent sinus.[3,4,6,7,51–62] The presence of a nasogastric tube for enteral feeding appears as an independent risk factor.[63] As in experimental sinusitis, the presence of a foreign body within the nostrils creates an ostial obstruction that initiates sinus inflammation and mucus accumulation within the sinus cavity. Confirming experimental data,[42] a large endotracheal tube induces radiographic sinusitis more frequently and faster than a small nasogastric tube.[55,58] In addition, the plastic nasotracheal tube is the site of biofilm formation for bacteria with adhesive capacity and enhanced pathogenicity:[64–66] microorganisms adhere to the internal and external surfaces of the endotracheal tube and some species exude an exopolysaccharide that acts as a slimelike adhesive.[67] Bacteria encased in this biofilm become partially resistant to the action of antimicrobials and host defences.[68,69] The bacterial proliferation around nasal foreign bodies forms a reservoir from which microorganisms penetrate into the antral cavity.[41]

SIZE OF THE MEATUS INFERIOR AND BODY POSITION

Ostial size, upon which drainage and ventilation of the sinus cavities depends, can markedly vary from one patient to another.[70] In humans, supine position is known to reduce ostial patency[71] by inducing swelling of the ostiomeatal complex.[72] A functional ostial area less than 5 mm^2 induces hypoventilation of the maxillary cavity, local hypoxia, decrease in mucosal blood flow, and predispose to maxillary sinusitis by impairing mucociliary clearance.[73]

SEPSIS

Generalized sepsis, well known for stimulating numerous tissue-inducible nitric oxide synthetases, inhibits the nitric oxide metabolic pathway at the maxillary level.[19] Autoinhaled nitric oxide plays an important antiinflammatory and antiviral role in colds.[74] Community-acquired, as well as ventilator-associated, sinusitis decreases exhaled nasal nitric oxide[19,75,76] by reducing its antral production (see Fig. 47-1).

Sepsis originating in other organs also markedly inhibits the antral production of nitric oxide through downregulation of inducible nitric oxide synthetase messenger ribonucleic acid.[19] The sepsis-induced reduction of antral nitric oxide concentrations contributes to impaired mucociliary clearance and decreased perfusion of the maxillary epithelium, both factors that facilitate infection of the maxillary cavity by impairing bacterial cleansing.[77]

EPIDEMIOLOGY AND COMPLICATIONS

Incidence

In critically ill patients, the reported incidence of radiographic sinusitis varies from 25% to 75%.[78] More than 80% of radiographic abnormalities of the maxillary sinuses are associated with radiographic abnormalities of the ethmoid, sphenoid, and frontal sinuses.[8,79] Variability in the estimated incidence stems from the many radiographic techniques used for diagnosis: Conventional radiography is much less accurate than computed tomography or maxillary ultrasound. After 12 hours of nasal endotracheal intubation and/or nasogastric tube placement, 38% of critically ill patients have computed tomographic evidence of radiographic maxillary sinusitis.[8] Among factors other than the presence of a foreign body in the nostrils, the supine position, head[63] and/or facial trauma,[51,53,80] allergy, and sepsis have been incriminated.[81] After 7 days, the incidence of radiographic maxillary sinusitis increases to 80%.[8] Infectious sinusitis is less frequent than radiographic sinusitis, occurring only in 20% to 30% of patients intubated longer than 7 days.[79] Its incidence is higher in nasotracheally than in orotracheally intubated patients.[8]

Nosocomial Sinusitis and Ventilator-Associated Pneumonia

A link between infectious maxillary sinusitis and bronchopneumonia has been established experimentally.[47,82] In critically ill patients, nosocomial sinusitis is considered a major cause of ventilator-associated pneumonia.[8,13,56,62] In a randomized study assessing a systematic search for sinusitis in nasotracheally ventilated patients, the incidence of ventilator-associated pneumonia was significantly higher in the control group than in the study group, where infectious maxillary sinusitis was systematically sought and treated, when confirmed, by sinus drainage and intravenous antibiotics.[11] In addition, the mortality rate significantly decreased from 46% in the control group to 36% in the study group. Although the association between nosocomial sinusitis and ventilator-associated pneumonia appears highly likely, the frequent discordance between microbiologic results from sinus and lower airway cultures[8,11] suggests that these two infections may also arise simultaneously and independently because of shared risk factors and diminished host defense for infection. A heavily contaminated nasopharynx may be the common bacterial reservoir from which sinuses and lungs are infected. Conversely, antral infection, characterized by high concentrations of microorganisms,[8] can also be a reservoir from which the oropharynx, the tracheobronchial tree, and the lung parenchyma are secondarily infected. Interestingly, concentrations of nitric oxide in the maxillary and nasal cavities markedly increase as infectious maxillary sinusitis is treated with antibiotics and sinus lavage.[83] The restoration of normal local concentrations of nitric oxide, by reestablishing maxillary ciliary function and immune defense, may help in preventing maxillary cavity superinfection and eliminating one of the risk factors for ventilator-associated pneumonia.

DIAGNOSIS

Clinical Diagnosis

Unlike clinical symptomatology of community-acquired maxillary sinusitis, clinical signs of ventilator-associated maxillary sinusitis are scarce and of limited specificity.[78] General signs of infection such as fever and leukocytosis have poor specificity. Mucopurulent nasal discharge is evocative but of limited sensitivity.[51] Frontal headache is often blunted by sedative drugs aimed at facilitating mechanical ventilation. As a consequence, ventilator-associated maxillary sinusitis cannot be reliably detected on clinical signs alone and should be systematically sought in the presence of fever of unknown origin.[4,11,84]

Radiographic Diagnosis

Rather than standard sinus radiography using the Blondeau's view performed in the upright position, sinus ultrasound is the first diagnostic tool for demonstrating community-acquired acute maxillary sinusitis in ambulatory and spontaneously breathing patients, and ventilator-associated maxillary sinusitis in ventilated patients lying in the supine position.[85,86]

COMPUTED TOMOGRAPHY SCAN

Paranasal computed tomography is the reference technique for establishing the diagnosis of radiographic sinusitis.[8,87–91] A low-dose computed tomography examination is preferred to avoid excessive radiation exposure.[91] Ten thin, noncontiguous computed tomography sections, using an initial interslice gap of 15 mm aimed at avoiding direct radiation to the eye lens (Fig. 47-2), should be performed. Such a technique decreases radiation exposure by more than 90% without seriously affecting the quality of the images (Fig. 47-3).

In ventilated patients, the computed tomographic image of a given paranasal sinus can be classified into

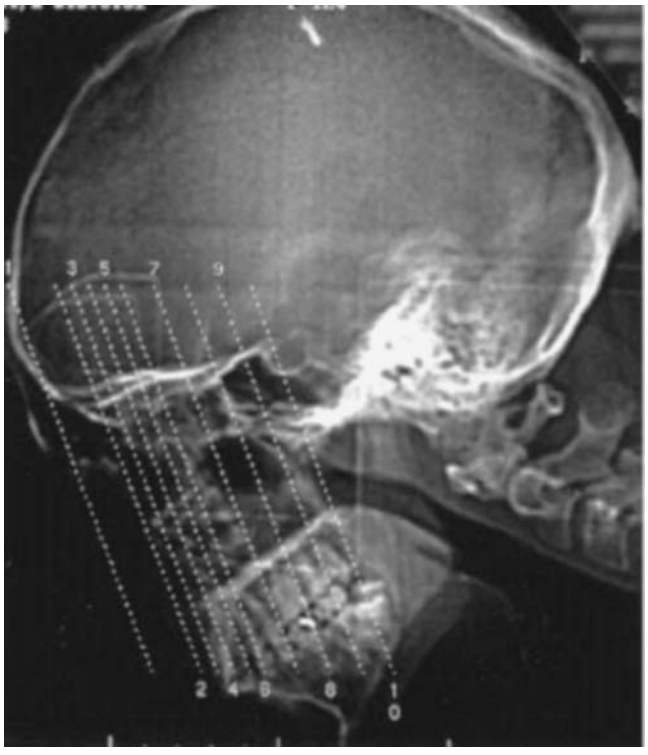


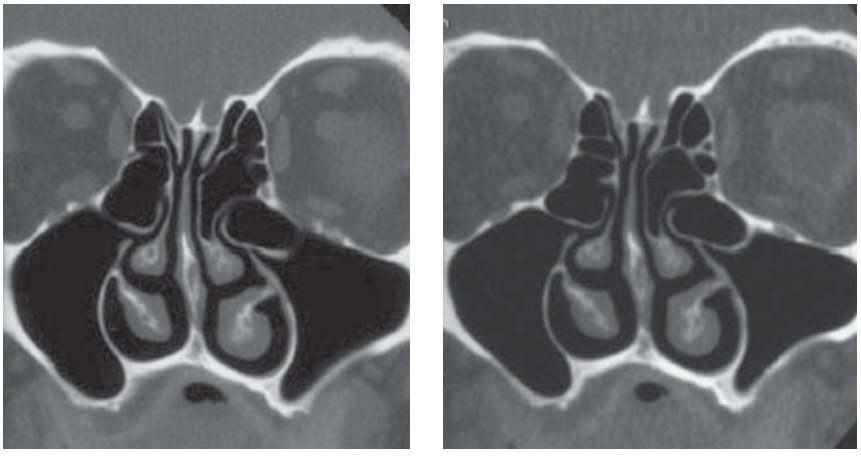
FIGURE 47-2 Scout view with different interslice gap between the 10 slices of the low-dose computed tomography protocol recommended for diagnosis of radiographic sinusitis. (Reproduced, with permission, from Hagtvedt T, Aalokken TM, Notthellen J, Kolbenstvedt A. A new low-dose CT examination compared with standard-dose CT in the diagnosis of acute sinusitis. *Eur Radiol.* 2003;13:976–980. With kind permission from Springer Science and Business Media.[91])

three categories:[8] normal (Fig. 47-4), mucosal thickening (Fig. 47-5), and radiographic maxillary sinusitis, characterized by a liquid content within the sinus cavity (Fig. 47-6). More than 80% of patients with radiographic abnormalities of maxillary sinuses have also abnormal frontal, ethmoid, and sphenoid sinuses. Conversely, only half of ventilated patients with normally aerated maxillary sinuses have radiographic abnormalities of frontal, ethmoid, and sphenoid sinuses.[8] An air–fluid level in the sinus cavity or the complete sinus opacification are evocative of infectious sinusitis and call for a bacteriologic confirmation. The significance of mucosal thickening in ventilated patients is incompletely understood. Very frequently, it represents an early stage of radiographic sinusitis.[8]

Although considered the gold standard, several limitations preclude the routine use of computed tomography for diagnosing ventilator-associated sinusitis. It requires transportation of ventilated patients outside the intensive care unit, a risky procedure.[92] It is costly and not easily repeatable. As a consequence, ultrasound techniques have been developed over the last 15 years and are currently considered an attractive alternative diagnostic tool.[61,88–90,93]

ULTRASOUND EXAMINATION OF MAXILLARY SINUSES

A-mode sinus ultrasound was proposed in the early 1990s for diagnosing radiographic maxillary sinusitis in ventilated patients.[61] At present, bedside B-mode ultrasound is considered as the reference technique.[88,89,93,94] The patient should be examined at the bedside in a semirecumbent position with a 3.5-MHz probe. The ultrasonic procedure should be performed in a transversal plane using different probe angulations, at the level of the front maxillary sinus wall, delineated by the lower orbital border, the nose, the upper maxilla, and the external cheekbone.[89] Image formation depends on the presence of fluid or mucosal thickening within the sinus cavity that transmits the ultrasonic beam to deep anatomic structures. When the posterior bony wall of the maxillary sinus becomes



A **B**

FIGURE 47-3 Standard-dose. (**A**) compared to low-dose (**B**) computed tomography images of normal ethmoid and maxillary sinuses obtained in a coronal plane through the ostiomeatal complex. (Reproduced, with permission, from Hagtvedt T, Aalokken TM, Notthellen J, et al. A new low-dose CT examination compared with standard-dose CT in the diagnosis of acute sinusitis. *Eur Radiol.* 2003;13:976–980. With kind permission from Springer Science and Business Media.)

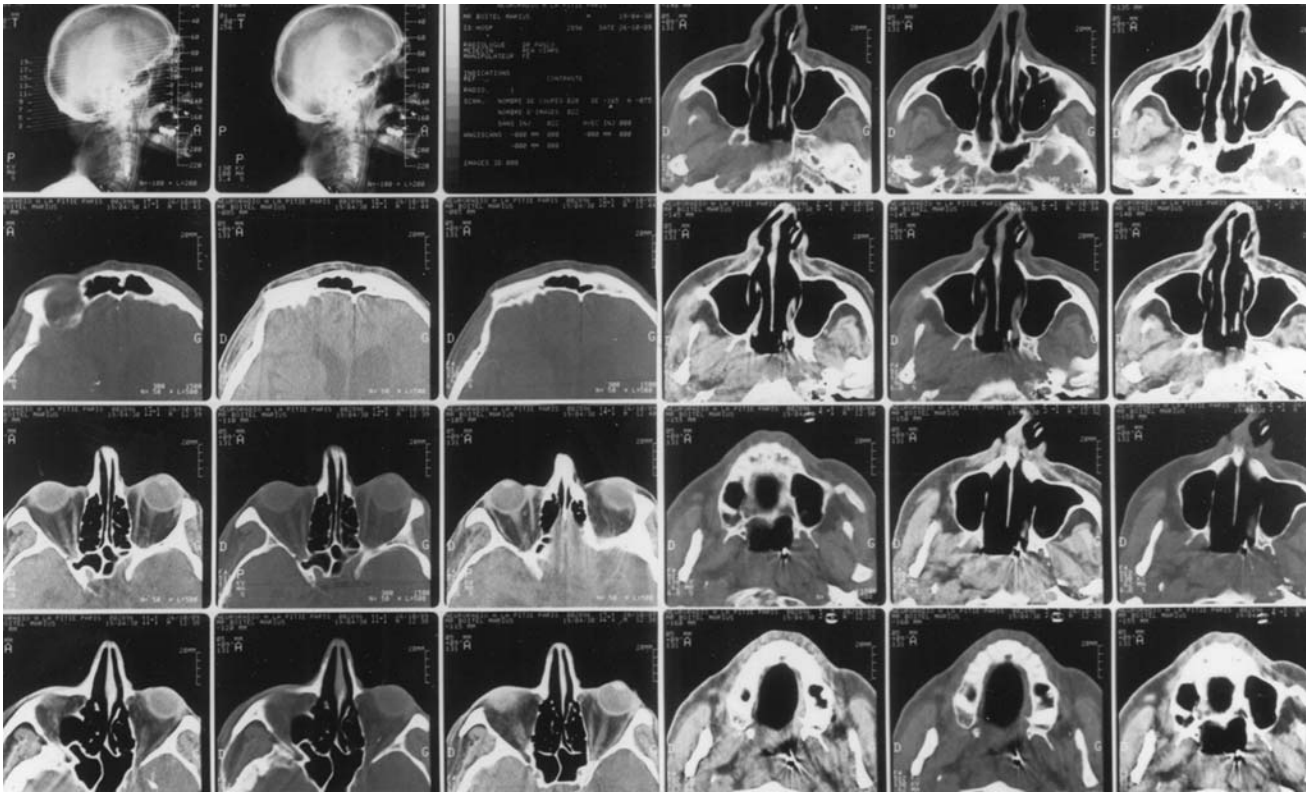


FIGURE 47-4 Normally aerated maxillary, ethmoid, sphenoid, and frontal sinuses in a ventilated patient with orotracheal intubation and the gastric tube positioned in the left nostril. (Reprinted with permission of the American Thoracic Society. Copyright © 2012 American Thoracic Society. From Rouby JJ, Laurent P, Gosnach M, et al. Risk factors and clinical relevance of nosocomial maxillary sinusitis in the critically ill. *Am J Respir Crit Care Med*. 1994;150:776–783. Official Journal of the American Thoracic Society.)

visible in part or completely, depending on the amount of gas present in the sinus cavity, a "sinusogram" is observed (Fig. 47-7).

In ventilated patients, the ultrasound image of the maxillary sinus can be classified into three categories:[89,93,94] absence of "sinusogram", partial "sinusogram", and complete "sinusogram" (Fig. 47-8). As shown in Figures 47-7 and 47-8, the absence of a "sinusogram" in a ventilated patient lying in the supine position may correspond either to an air–fluid level or to a normally aerated sinus. Repeating the ultrasound procedure in the half-sitting position, however, may reveal an incomplete "sinusogram", thereby asserting the diagnosis of radiographic maxillary sinusitis.[90,93] A partial "sinusogram" may indicate either mucosal thickening, simple inflammation of the sinus mucosa, or an air-fluid level. Note that in half the patients with complete opacification of the maxillary cavity on computed tomography exhibit a partial "sinusogram", resulting from the presence of small bubbles within the collection.[89] Repeating ultrasound in the supine position may facilitate the differentiation between mucosal thickening and true maxillary sinusitis.[93] The disappearance of the partial "sinusogram" in the supine position is evocative of an air–fluid level, characteristic of radiographic maxillary sinusitis. In contrast, the persistence of a partial "sinusogram" in the supine position is strongly suggestive of mucosal thickening.

If radiographic doubt persists and clinical signs are evocative of infectious maxillary sinusitis, a paranasal computed tomography scan should be performed. A complete "sinusogram" is always related to a true radiographic maxillary sinusitis and requires antral puncture in the presence of fever of unknown origin. Based on these recommendations, bedside maxillary ultrasound has a sensitivity of 100% and a specificity of 97% for diagnosing radiographic maxillary sinusitis in intubated patients undergoing mechanical ventilation.[90] An important limitation of bedside maxillary ultrasound is that it does not provide any reliable information on frontal, ethmoid, and sphenoid sinuses.

Microbiologic Diagnosis

DIAGNOSTIC CRITERIA FOR INFECTIOUS MAXILLARY SINUSITIS

Infectious maxillary sinusitis has to be clearly differentiated from radiographic maxillary sinusitis. The latter corresponds to fluid accumulation within the antral cavity, the liquid

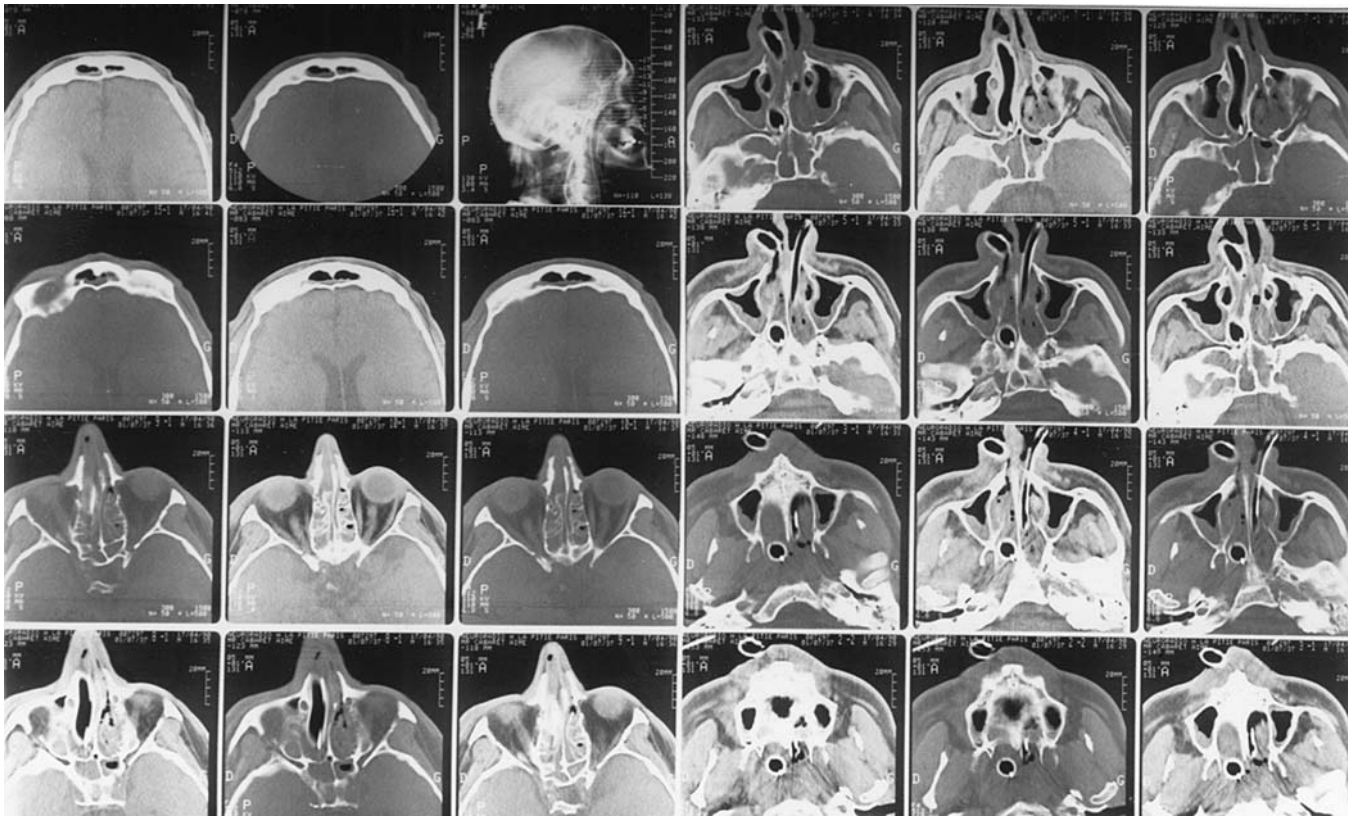


FIGURE 47-5 Computed tomography scan showing mucosal thickening of the right and left maxillary and frontal sinuses, and of the left ethmoid and sphenoid sinuses, associated with complete opacification of the right ethmoid and sphenoid sinuses in a ventilated patient with right nasotracheal intubation and a gastric tube positioned in the left nostril. On a second paranasal computed tomography scan, performed 1 week later without changing the initial position of the endotracheal and gastric tubes, complete opacification of the maxillary, ethmoid, and sphenoid sinuses was observed with a persistent mucosal thickening of both frontal sinuses. (Reprinted with permission of the American Thoracic Society. Copyright © 2012 American Thoracic Society. From Rouby JJ, Laurent P, Gosnach M, et al. Risk factors and clinical relevance of nosocomial maxillary sinusitis in the critically ill. 1994;150:776–783. Official Journal of the American Thoracic Society.)

being either mucus or pus. Infectious sinusitis is defined by the presence of pus in the maxillary cavity and requires cellular and bacterial analysis of the sinus contents. Therefore, antral puncture is indispensable for an accurate diagnosis. Examination of the sinus contents is impossible for frontal and ethmoid sinuses. It requires an easy-to-perform antral puncture for the maxillary sinus and a highly specialized endoscopic puncture for the sphenoid sinus. Maxillary puncture can be performed either by the transnasal or the canine fossa routes.

The transnasal and canine fossa approaches are exposed to massive bacterial contamination issued from the nostrils and gingiva, which are heavily contaminated by nosocomial microorganisms in critically ill patients. The presence of a foreign body in the nose further increases the bacterial burden and seriously complicates the process of nasal decontamination.[8] After a meticulous and time-consuming disinfection of the nasal cavities, only 50% of the nostrils are sterile and 11% remain heavily contaminated.[8] As a result, transnasal puncture of the maxillary sinus carries a significant risk of introducing bacteria into the antral cavity and overestimating the likelihood of infectious sinusitis.[81] As a consequence, a rigid protocol should be followed when performing a transnasal puncture and strict diagnostic criteria required for establishing the diagnosis. After a careful and prolonged disinfection of the nasal cavity using a povidone-iodine or a chlorhexidine alcohol solution,[8,95] a nasal swab is performed to assess the efficacy of nasal disinfection. Then transnasal puncture is performed using an Albertini trocar placed below the inferior turbinate, and sinus contents are directly aspirated before any lavage. The recovered fluid is then examined, using cell and quantitative bacterial analysis preceded by a Gram stain. In addition, the nasal swab is analyzed using a semiquantitative bacteriologic analysis. The diagnosis of infectious sinusitis requires fulfillment of the following criteria: more than five altered polymorphonuclear leukocytes per oil immersion field and a positive culture with a bacterial concentration equal to or greater than 10^3 colony-forming units (CFU)/mL in the case of negative nasal swab, or equal to or greater than 10^4 CFU/mL in the case of positive nasal swab.[8]

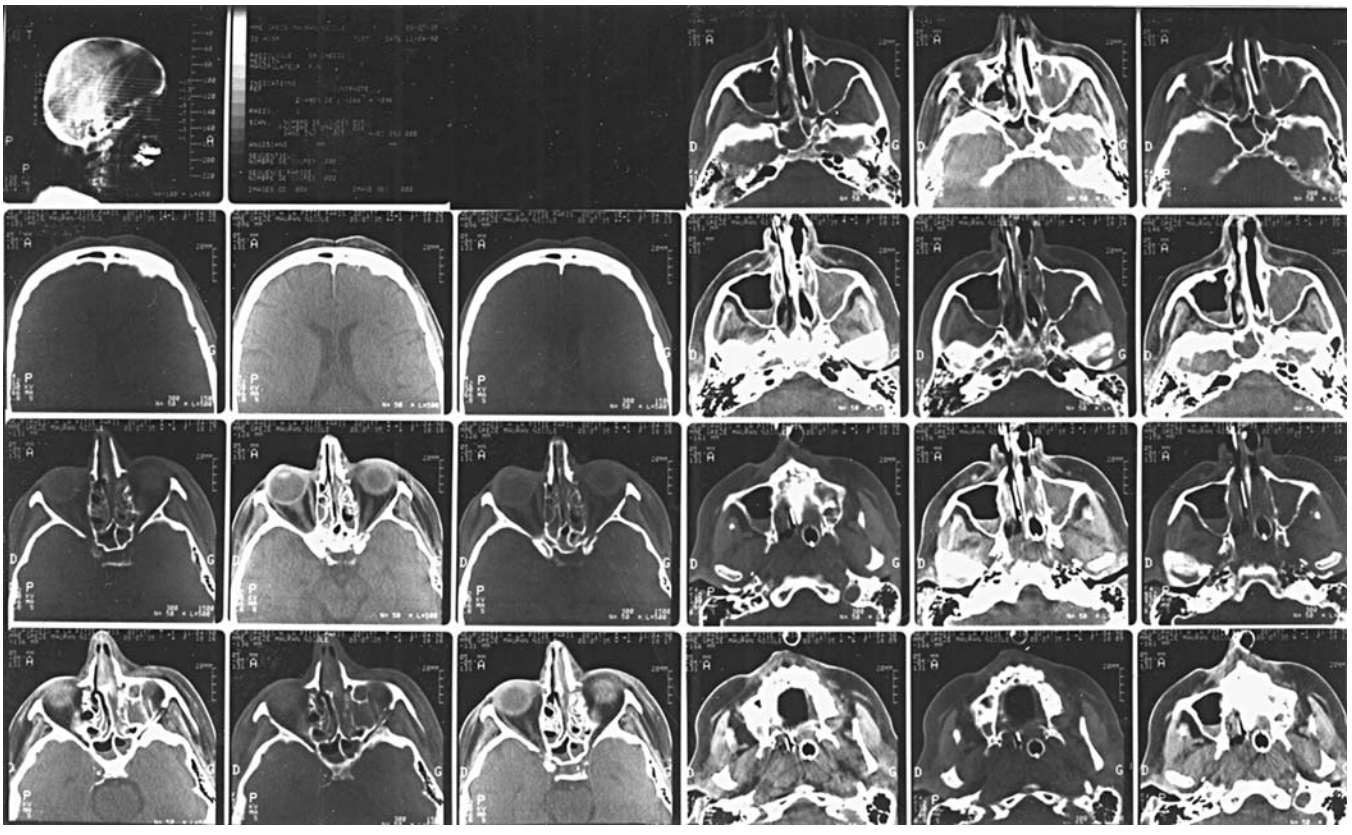


FIGURE 47-6 Typical aspect of radiographic maxillary sinusitis in a ventilated patient with left nasotracheal intubation and a right nasogastric tube. The left maxillary sinus exhibits complete opacification, whereas the right maxillary sinus exhibits a characteristic air–fluid level. Mucosal thickening can be seen in both ethmoid sinuses and the left frontal sinus. Both sphenoid sinuses exhibit air–fluid levels, whereas the right frontal sinus is normally aerated. (Reprinted with permission of the American Thoracic Society. Copyright © 2012 American Thoracic Society. From Rouby JJ, Laurent P, Gosnach M, et al. Risk factors and clinical relevance of nosocomial maxillary sinusitis in the critically ill. *Am J Respir Crit Care Med.* 1994;150:776–783. Official Journal of the American Thoracic Society.)

MICROBIOLOGY OF VENTILATOR-ASSOCIATED MAXILLARY SINUSITIS

Community-acquired maxillary sinusitis is predominantly caused by *Streptococcus pneumoniae, Moraxella catarrhalis,* and *Haemophilus influenzae*. In contrast, the most frequent microorganisms recovered in ventilated adult patients with infectious maxillary sinusitis, are gram-negative bacteria such as Enterobacteriaceae species, gram-positive cocci such as staphylococci or streptococci, anaerobes, and yeasts.[8,11,81,95–97] Very frequently, infection of the antral cavity is polymicrobial.[8,62,79,84] Anaerobes are the causative pathogens in more than 60% of cases of infectious maxillary sinusitis, either in association with aerobic species or alone.[98]

In adult patients, the most common anaerobes infecting the antral cavity are *Prevotella* species and *Fusobacterium nucleatum*, all bacteria that belong to the commensal nasal flora and are known to produce β-lactamases, which reduces their sensitivity to antibiotics.[98] Similar findings have been reported in ventilated children with nosocomial sinusitis: Aerobes were present in only 40% of the patients, anaerobes in only 25% of the patients, and mixed aerobic and anaerobic flora in 35% of the patients.[97] The predominant aerobes were *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Escherichia coli*, and *Klebsiella pneumoniae*. The predominant anaerobes were *Peptostreptococcus* species, *Prevotella* species, and *Fusobacterium* species.

Anaerobes are more commonly isolated from sinus aspirate samples obtained after prolonged mechanical ventilation.[97] The high incidence of anaerobes and their underestimation by classic means of bacterial examination probably explain the high number of purulent antral secretions remaining sterile on culture.[84] The presence of a nasal foreign body (endotracheal or gastric tube) markedly increases bacterial colonization of the ipsilateral middle meatus.[84] In Figure 47-9, a logical approach, including diagnostic criteria, is proposed for establishing the diagnosis of infectious maxillary sinusitis.

TREATMENT

Prevention of Ventilator-Associated Sinusitis

Although some of the published data on the prevention of sinus infection in ventilated patients are conflicting,[8,56,61,62] the following measures can be recommended for reducing

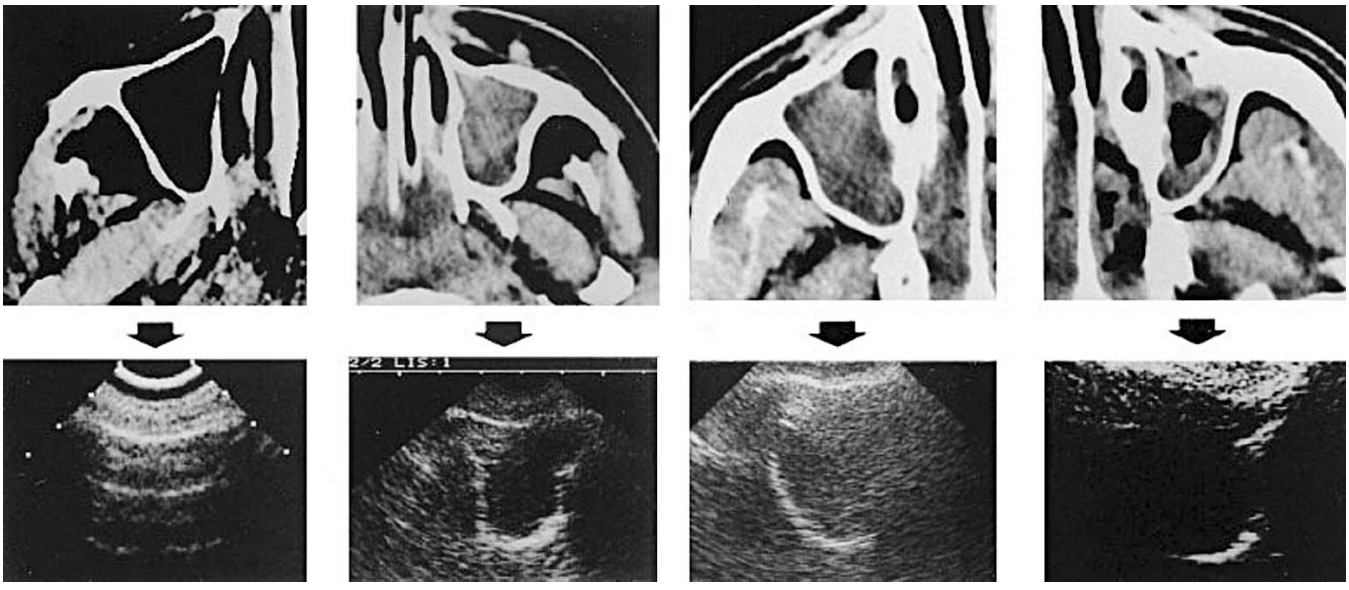


FIGURE 47-7 Normal versus pathologic ultrasound pattern. Computed tomography sections of maxillary sinuses are in the upper row with their corresponding ultrasound pattern in the lower row. *From left to right:* normal pattern—total opacity of the left maxillary sinus (the internal, posterior, and external walls of the sinus are visible, giving a complete "sinusogram"); 90% air–fluid level of the right maxillary sinus (the internal wall is not visualized, giving an incomplete "sinusogram"); and mucosal thickening of the left maxillary sinus (the internal wall is not visible and the external wall is ill-defined, giving a partial "sinusogram"). (Reproduced, with permission, from Lichtenstein D, Biderman P, Meziere G, et al. The "sinuso-gram", a real-time ultrasound sign of maxillary sinusitis. *Intensive Care Med.* 1998;24:1057–1061. With kind permission from Springer Science and Business Media.)

the incidence of ventilator-associated sinusitis. First, nasotracheal intubation and nasogastric tubes should be avoided. Most prospective studies that have examined the influence of nasotracheal intubation on ventilator-associated sinusitis have shown an increased incidence of maxillary sinusitis in nasotracheally intubated patients.[8,56,61] On the other hand, in a randomized single-center study that included 300 ventilated patients, there was no statistically significant difference in the occurrence of ventilator-associated sinusitis between patients intubated via the nasal versus the oral route. A trend ($p = 0.08$), however, suggested less sinusitis in the orotracheal group.[62] Second, the nostrils should remain free of foreign bodies and be regularly cleaned of nasal secretions that tend to accumulate. In a randomized open-label study performed in 79 patients with multiple trauma, the combination of locally applied nasal α-adrenergic and

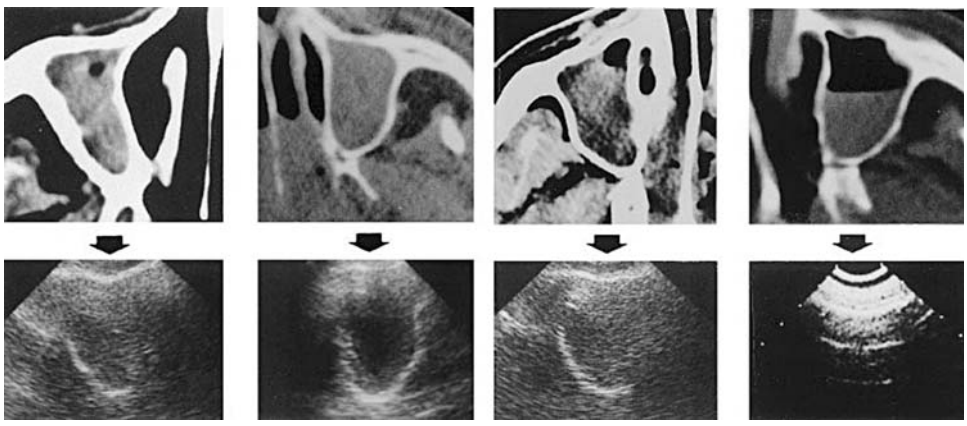


FIGURE 47-8 Different abnormal ultrasound patterns. Computed tomography sections of maxillary sinuses are in the upper row with their corresponding ultrasound pattern in the lower row. *From the left to the right:* total opacity of the right maxillary sinus with a small anterior air bubble (the external wall is visible and the internal wall is not visible, giving an incomplete "sinusogram"); total opacity of the left maxillary sinus (the internal, posterior, and external walls of the sinus are visible, giving a complete "sinusogram"); 90% air–fluid level of the right maxillary sinus (the internal wall is not visualized, giving an incomplete "sinusogram"); and 50% air–fluid level of the left maxillary sinus (the walls are not visible, giving an acoustic barrier, and thus no "sinusogram"). (Reproduced, with permission, from Lichtenstein D, Biderman P, Meziere G, et al. The "sinuso-gram", a real-time ultrasound sign of maxillary sinusitis. *Intensive Care Med.* 1998;24:1057–1061. With kind permission from Springer Science and Business Media.)

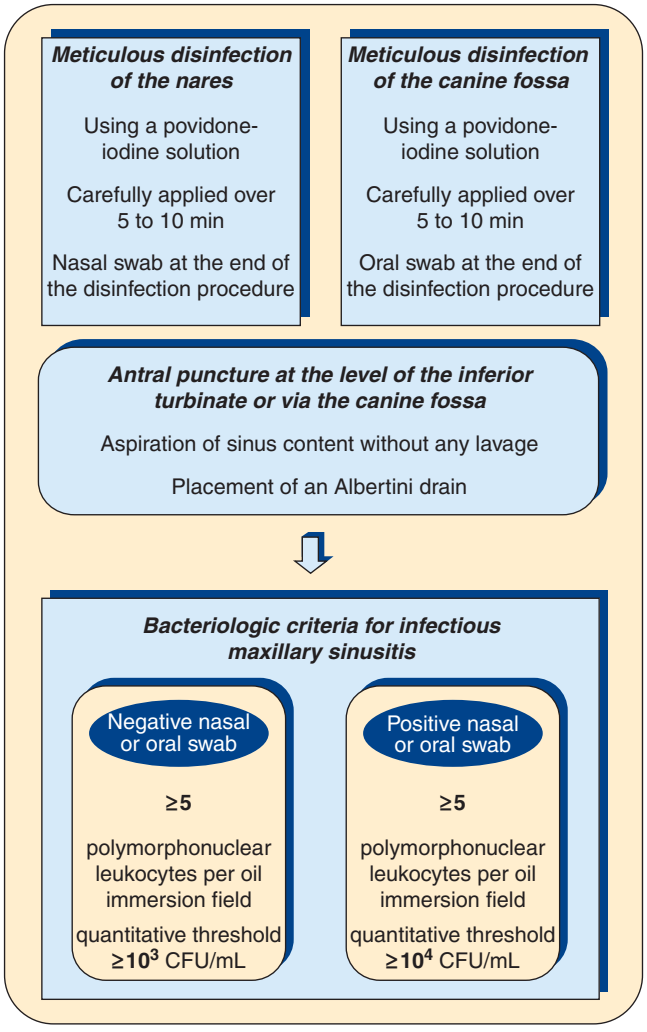


FIGURE 47-9 Chart summarizing a logical diagnostic approach and proposing criteria for infectious maxillary sinusitis. (Reproduced, with permission, from Lichtenstein D, Biderman P, Meziere G, et al. The "sinuso-gram", a real-time ultrasound sign of maxillary sinusitis. *Intensive Care Med.* 1998;24:1057–1061. With kind permission from Springer Science and Business Media.)

corticosteroids reduced the incidence of radiologic maxillary sinusitis by 29%.[99] The topical application of a nasal decongestant, together with locally applied corticosteroids to avoid rhinitis medicamentosa, may reduce ostial obstruction and edema of the ostiomeatal complex that initiates sinus inflammation and mucus accumulation. Further studies are required to confirm the efficacy of this mode of prevention. Third, the patient should be kept preferentially in the semirecumbent position to ensure patency of the different ostia. The observance of these preventive measures does not, however, fully protect against ventilator-associated sinusitis. General sepsis, restrictions in regional blood flow resulting from circulatory shock, as well as allergy and systemic inflammation, all factors encountered in the critical care environment, certainly contribute to antral disease and secondary infection of sinus cavities.

Treatment of Infectious Maxillary Sinusitis

Classically, sinus infection diagnosed in ventilated patients requires the administration of intravenous antibiotics.[11,62,78] Removal of nasal foreign bodies, semirecumbent positioning, sinus drainage, topical decongestants, and serum lavage of the antral cavity through the drains are useful adjunctive therapies.

PENETRATION OF ANTIBIOTICS INTO ANTRAL MUCOSA

Two studies have shown adequate sinus deposition of intravenous antibiotics in patients with ventilator-associated maxillary sinusitis.[100,101] In a series of six ventilated patients, a single intravenous dose of piperacillin 4 g achieved bactericidal concentrations for up to 8 hours in the sinus fluid obtained by maxillary drainage.[100] In a series of twenty ventilated patients with ventilator-associated sinusitis, a single intravenous dose of amikacin 15 mg/kg achieved high peak concentrations in the sinus fluid obtained by maxillary drainage.[101] These encouraging results, however, were challenged by a subsequent study performed in seven critically ill patients with inflammatory and bacterial maxillary sinusitis.[102] In all patients, extracellular tissue concentrations of cefuroxime, ampicillin, and vancomycin measured on biopsy samples obtained by sinuscopy were lower than the corresponding plasma concentrations. In patients with noninfectious maxillary sinusitis, the ratio between tissue and plasma concentrations varied from 10% to 73%. In one patient treated with intravenous cefuroxime for a nasogastric tube-induced purulent maxillary sinusitis, very low plasma concentrations with no measurable mucosal concentrations were found. In one patient treated with intravenous ampicillin for a nasotracheal tube-induced purulent maxillary sinusitis, high tissue concentrations were found, reaching 95% of the plasma concentration in the left antral mucosa and 53% in the right antral mucosa. In one tracheostomized patient treated with vancomycin for a left purulent maxillary sinusitis, high mucosal concentrations of vancomycin were found. Surprisingly, in the three patients with purulent maxillary sinusitis, bacterial cultures of the sinus biopsies were positive, irrespective of the antibiotic tissue concentrations.

SINUS DRAINAGE AND ANTIBIOTIC THERAPY

In critically ill patients, infectious maxillary sinusitis frequently emerges despite prior antibiotic administration to which the causative microorganisms are sensitive,[95,102] suggesting that antibiotics may not be a sufficient therapy for ventilator-associated maxillary sinusitis. Several hypotheses have been proposed for explaining the persistence of bacteria within the antral cavity despite the intravenous administration of appropriate antibiotics. As demonstrated in a small number of patients, antral penetration of systemic antibiotics is very variable and mucosal concentrations may remain below minimal inhibitory concentrations.[102] In patients on

long-term mechanical ventilation, the presence of a chronic anaerobic infection might be associated with biofilm formation protecting the bacteria against the bactericidal effects of antibiotics.[102] Measurements of antral antibiotic concentrations require sinuscopy and/or the insertion of drains into the sinus cavity.[100–102] Such invasive procedures may create a regional inflammatory reaction responsible for increased antral antibiotic concentrations that may no longer be representative of true tissue concentrations obtained in the intact sinus cavity.

The logical implication of these clinical findings and hypotheses is that sinus drainage should be adopted as a first-line therapy for ventilator-associated maxillary sinusitis, together with daily sinus lavage and topical antibiotic administration.[8,95] To avoid recurrence of infectious maxillary sinusitis, sinus drains should be left in place until endotracheal extubation and definitive weaning from mechanical ventilation.[8] Removing foreign bodies from the nostrils and positioning the patient in the semirecumbent position may help recovery from antral disease.

IMPORTANT UNKNOWNS

Clinical Relevance of Frontal, Ethmoid, and Sphenoid Sinusitis

Radiographic abnormalities of the ethmoid and sphenoid sinuses are found in more than 80% of ventilated patients.[8] In ventilated patients with computed tomography-delineated abnormalities of maxillary sinuses, more than 95% have radiographic ethmoid and sphenoid sinusitis. Half of ventilated patients with normal maxillary sinuses have computed tomography-delineated abnormalities (mucosal thickening or complete opacification of the sinus cavities) of the ethmoid and sphenoid sinuses.[8] The meaning and clinical impact of these abnormalities remain unknown. Despite sinus drainage associated with topical administration of appropriate antibiotics and the absence of other sites of infection, more than 10% of ventilated patients with documented infectious maxillary sinusitis remain febrile with persistent signs of sepsis, raising the possibility of a residual infection within the ethmoid and sphenoid cavities.[8] Although community-acquired infectious sphenoid sinusitis remains a rare entity,[103,104] further studies are required for assessing the exact incidence of infectious ethmoid and sphenoid sinusitis as a cause of occult fever in ventilated patients.

Role of Antibiotics in the Therapy of Ventilator-Associated Maxillary Sinusitis

There is an ongoing controversy as to whether intravenous or topical antibiotics should be administered to ventilated patients with documented infectious maxillary sinusitis. Available data on the penetration of systemic antibiotics into the diseased antral mucosa of ventilated patients are scarce and are based on very few critically ill patients.[100–102] In addition, the role of viruses in the infection of sinus cavities remains unknown. As with community-acquired acute maxillary sinusitis, the clinical course of which is not influenced by antibiotic treatment,[105] ventilator-associated infectious maxillary sinusitis might be caused by viruses and require specific antiviral therapy rather than intravenous antibiotics. Clinical data support the concept that radiographic maxillary sinusitis is the first step along the path to an established sinus infection[8] and raise the issue of whether removal of nasal foreign bodies and placement of sinus drainage catheters should not be undertaken before frank infection and sepsis occur.[10] Further studies are required to assess factors influencing the penetration of antibacterial agents into the sinus cavities and to clarify many uncertainties concerning treatment optimization of ventilator-associated sinusitis.

CONCLUSIONS AND FUTURE PROSPECTS

Infection of paranasal sinuses is an important cause of occult sepsis in critically ill patients receiving mechanical ventilation. It is a typical nosocomial infection resulting mainly from the presence of nasal foreign bodies. Mechanical and edematous obstruction of the sinus ostia, suppression of the normal sinus ventilation, inhibition of the maxillary production of nitric oxide, and cessation of the normal sinus mucociliary clearance are different factors causing an inflammatory antral disease that becomes rapidly superinfected by pathogens proliferating around nasotracheal and nasogastric tubes. Like any nosocomial infection that may weigh heavily against patients' chances of survival, an active policy of detection and prevention should be undertaken and not lead to antibiotic overuse. Faced with an unknown cause of sepsis, the clinician should systematically perform maxillary sinus ultrasonography at the bedside, searching for radiographic maxillary sinusitis. When present, maxillary sinus puncture should be performed with careful attention to avoid nasal contamination of sinus contents. Once confirmed by quantitative bacteriology and cell analysis, infectious maxillary sinusitis should be treated by prolonged sinus drainage, removal of nasal foreign bodies, positioning in the semirecumbent position, and administration of intravenous or topical antibiotics. If applied early after initiation of mechanical ventilation, orotracheal intubation, oral placement of gastric tubes, and semirecumbent positioning may decrease the incidence of ventilator-associated maxillary sinusitis. A large multicenter randomized study should be undertaken to assess whether these preventive measures are associated with a decrease in the incidence of ventilator-associated pneumonia and mortality.

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XII

EVALUATION AND MONITORING OF VENTILATOR-SUPPORTED PATIENTS

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48

MONITORING DURING MECHANICAL VENTILATION

Amal Jubran
Martin J. Tobin

Patients are admitted to an intensive care unit (ICU) for two main reasons. One is for delivery of mechanical ventilation, the varied aspects of which are the subject of this book. The second is to observe a patient more closely than is possible on a hospital ward; that is, to avail of specialized devices used for the monitoring of vital functions (and of staff who have expertise in their operation).

The literature published on these two subjects constitutes the unique corpus of knowledge required for the expert practice of intensive care medicine. Management of some critically ill patients is based on knowledge outside these two areas, such as patients with acute gastrointestinal bleeding or acute renal failure. The principles for managing such conditions have been developed by physician-investigators within the relevant subspecialties rather than by intensive care physicians. Beyond the areas of mechanical ventilation and monitoring, an intensivist seeking the most authoritative writing on a subject must turn to articles and texts published by nonintensivists.

Patients receiving mechanical ventilation are exposed to the full range of monitoring devices. An in-depth discussion of each device would require as much space as the rest of this book. For such discussions the reader is referred to the companion text, *Principles and Practice of Intensive Care Monitoring*.[1] Rather than attempting a synopsis of each individual monitoring technique, this chapter provides a bird's-eye view of the subject. We map out the territory of monitoring through discussion of its goals, the principles of measurement, usefulness of monitoring in various settings, the forms of clinical reasoning used in interpreting generated data, evaluation of the benefit of monitors, and the problems in designing studies that attempt such evaluations. To give a sense of the detailed contours of the terrain being traversed, we offer specific examples of how the general topics relate to the everyday use of monitors.

WHAT IS MONITORING?

An unsatisfactory—and embarrassing—aspect of writing about monitoring is the absence of a generally accepted definition. A definition tries to set criteria that demarcate the boundaries between concepts (or things) so as to prevent overlapping or confusion, and has the goal of providing order or a clear understanding.

The word *monitor* comes from the Latin *monere,* which means "to warn." This meaning connotes one goal of monitoring, to provide an alert, an alarm. But monitors serve

other functions. Monitors replicate many of the characteristics of diagnostic testing, and interpretation of the generated data must comply with the scientific principles developed for use of diagnostic tests. Thus, it might seem reasonable to define monitoring as the serial performance of diagnostic tests at frequent intervals. But how should we demarcate the frequency at which measurements are repeated? Certain signals have such a high-frequency content that obtaining fifty measurements in a second is insufficient to capture a critical data point.

Having struggled long and hard in trying to formulate a meaningful but precise definition of monitoring, we admit defeat. We can do no better than offer a naturalist's definition: Monitoring refers to what physicians and allied health personnel do with monitors.

GOALS OF MONITORING

The major goals of monitoring are to continuously measure key variables that enhance understanding of a patient's underlying disease state, to aid with diagnosis, and to guide management.[1] To accomplish these goals, the monitor should measure a variable that is pertinent to the disease process, be technically accurate, provide interpretable data, be practical for use, and not cause harm.[1,2] The ability of today's monitors to meet these goals depends largely on two factors: whether a monitor is capable of accurately measuring the function or disease manifestation in question, and whether the recorded information will help improve patient outcome. Inextricably linked to these two factors is the caregiver's ability to interpret data, integrate data from multiple sources, discard data that are not important, and then make a wise judgment about diagnosis and therapy.

ACCURACY OF MEASUREMENTS

Advances in electronic and computer technology over the last 30 years have generated several monitoring systems that are accurate and easy to use. To know how to operate a machine and interpret the provided data, a physician needs much more than a manufacturer's manual. The physician needs to know the principles of the monitoring device, how to operate it, the reliability of the measurements, indications and contraindications, complications with use of the device, and how to troubleshoot problems as they arise.

To determine whether the data generated by a monitor are valid, a physician needs to have a basic understanding of measurement theory and its applications. For an extensive review of the science of measurement, the reader is referred to the chapter by Chatburn[3] in the companion book, *Principles and Practice of Intensive Care Monitoring*.[4]

Fundamentals of Measurement Theory

Every measurement has errors. Accordingly, the observed measurement is a mixture of the true value and the error. Errors can be systematic or random. *Systematic error* (also termed *bias*) is the difference between the mean value of repeated measurements and the true value. Systematic errors occur in a predictable manner; they cause measurements to *either* consistently underestimate or consistently overestimate the true value (Fig. 48-1A). These type of errors are not affected by repeated measurements but can be reduced by proper calibration.

Random error (a measure of the imprecision of a measurement) is the difference between the mean of the sample and the measurement of individual values. Random errors occur in an unpredictable manner because of uncontrollable factors; they cause measurements to *both* underestimate and overestimate the true value (see Fig. 48-1B). Increasing the number of measurements can reduce random errors.[3] Figure 48-2 illustrates the effects of bias and imprecision (systematic and random errors) on measurements.

ACCURACY

Accuracy is the ability of a measuring device (or monitoring technique) to capture the true value of a quantity. When assessing accuracy, researchers commonly compare a new method with an established method to determine whether the new method can replicate the established method (Fig. 48-3).

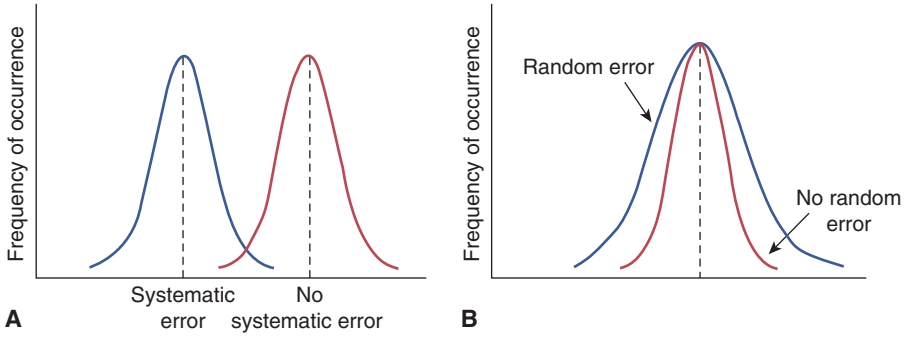


FIGURE 48-1 Distribution of measured values in the presence and absence of systematic (**A**) and random (**B**) errors. A systemic error increases or decreases the average value. A random error increases the variability around the average value.

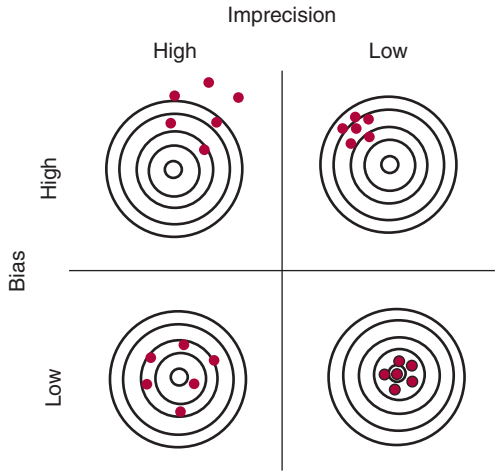


FIGURE 48-2 The effects of bias and imprecision (systematic and random errors) on measurements using the analogy of target practice at a rifle range. When bias is low, measurements (*red circles*) group around the true value (bull's-eye). When imprecision is low, the cluster of measurements is tight and the random error of repeated measurements (rifle shots) is small. Ideally both bias and imprecision are low, resulting in a small total error for repeated measurements. (Used, with permission, from Chatburn.[3])

Accuracy is usually expressed as a percentage of the full scale. In today's ventilators, pressure-measuring systems have an accuracy of ±2 cm H_2O plus 4% of the signal. In other words, if the true pressure is 25 cm H_2O, the displayed pressure could be anything between 22 and 28 cm H_2O.[5] In contrast, the accuracy of flow sensors within ventilators varies much more—from ±1% to ±20% of the setting, depending on the ventilator.[6] Despite their common use, remarkably little information on the accuracy of flow-measuring and pressure-measuring devices has been published in peer-reviewed journals; in general, users must resort to data on accuracy provided by the manufacturers.

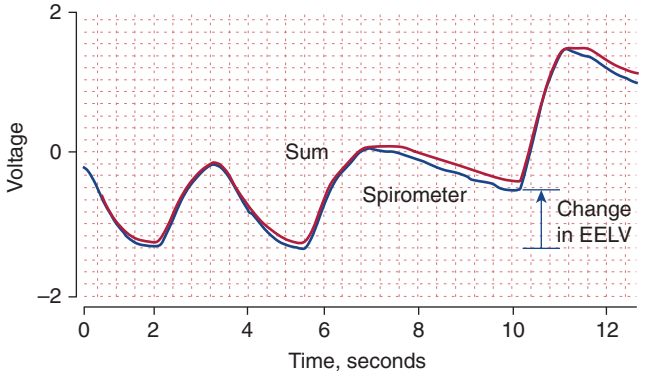


FIGURE 48-3 Changes in end-expiratory lung volume measured simultaneously with a calibrated respiratory inductive plethysmograph (*red*) and a spirometer (*blue*), the reference instrument. The two signals are almost superimposed upon one another indicating good agreement between the two techniques. *EELV*, end-expiratory lung volume.

The monitoring device that has been studied the most in critically ill patients is the pulse oximeter. Compared with the measurement standard (a multiwavelength Co-oximeter), pulse oximeters have a mean difference (bias) of less than 1% and a standard deviation (precision) of less than 2% when arterial oxygen saturation (Sa_{O_2}) is 90% or above (Fig. 48-4).[6–8]

PRECISION

Precision is the ability of a monitor to display the same value repeatedly assuming that the actual quantity has not changed; that is, the degree of consistency between repeated results. Precision is usually expressed in terms of variance, standard deviation, or confidence intervals. In ventilated patients, the precision (quantified as standard deviation) of pulse oximetry in measuring oxygen saturation, Sp_{O_2}) is less than 1.2% when Sa_{O_2} is greater than 90%, and it increases to 2.7% when Sa_{O_2} drops to 90% or less.[6–8]

Reproducibility is the ability of the monitoring technique (or device) to maintain its precision during long-term use. Knowing the reproducibility of a measurement is important for judging whether a change is truly of clinical significance. The reproducibility of the thermodilution technique in measuring cardiac output, quantified as the ratio of standard error to average cardiac output, varied between 2% and 5% when measurements were repeated (an average of three times), and varied between 2.5% and 8.7% for single measurements.[9] Thus, before concluding that a change in cardiac output is clinically significant, a clinician would need to observe a 12% to 15% difference between repeated determinations (three measurements per determination).

A technique may yield reproducible measurements at one sitting, but be unreliable when employed by a different investigator or on a different day. In ventilated patients, a single investigator obtained highly reproducible measurement of maximal inspiratory pressure at a single sitting: The coefficient of variation for triplicate efforts was 11%.[10] When different investigators undertook the measurements, however, the coefficient of variation was 32% ± 4%, despite the measurements being obtained in the same patient and on the same day.

LINEARITY

A device is considered linear when a plot of output data from the device (the measured values) versus the input data (the known values) can be fitted with a straight line. Occasionally, a system measures pressure accurately only over part rather than the entire range of pressures; that is, the system is alinear (Fig. 48-5). Alinearity may occur because the given transducer is not designed for use over the entire range or because it is not functioning properly.

CALIBRATION

Calibration is the process of adjusting the output of a device to match a known input value. Thus, systematic error is minimized. Calibration is considered static when pressure is

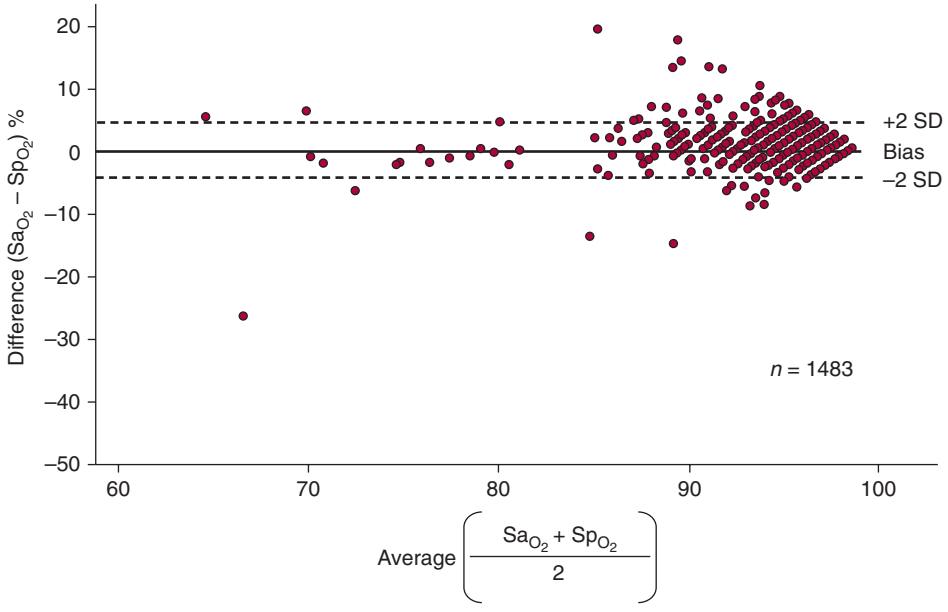


FIGURE 48-4 Differences between arterial oxygen saturation (Sa_{O_2}) measured by a blood-gas analyzer and oxygen saturation measured by pulse oximetry (Sp_{O_2}) plotted against the average O_2 saturation in 102 critically ill patients. The *solid line* is the bias and the *dashed lines* are 95% confidence intervals. Mean difference (bias) between two measurements is small. *SD*, standard deviation. (Reproduced, with permission, from Van de Louw A, Cracco C, Cerf C, Harf A, Duvaldestin P, Lemaire F, et al. Accuracy of pulse oximetry in the intensive care unit. *Intens Care Med.* 2001;27:1606–1613. With kind permission from Springer Science and Business Media.)

changed in steps and each step is maintained long enough to achieve a stable signal output. For a linear measurement system, calibration is a simple two-step procedure (Fig. 48-6). First, the readout is set at zero while no input signal is applied to the instrument. If an offset error occurs, it is adjusted. For a flow-sensing device, the flow sensor is occluded and a reading of no flow should result. If some flow is registered, the readout is adjusted to zero to correct for the offset error. Next, sensitivity (gain or slope) is set by applying an input signal of known value (say 12 L/s from a rotameter), preferably at the upper end of the output range; the readout on the flow sensor is then adjusted to read 12. If the system is linear, the readouts for all input values between these two calibration points will be accurate.

The dynamic response of a measurement system, such as a pressure transducer, is typically tested using a square wave (or sinusoidal) pressure generator. A step change in pressure is followed by a brief delay before the measured pressure begins to change.[11–14] The amplitude of the test should be within ±5% of the amplitude of the reference system at the highest frequency tested. The phase lag is the temporal difference between the two systems.

Sources of Measurement Error during Monitoring

A major challenge in interpreting data from monitors is to determine which data constitute truth and which constitute artifact. Although both systematic and random errors can cause artifact, the major source of error in biologic research is systematic errors.[15]

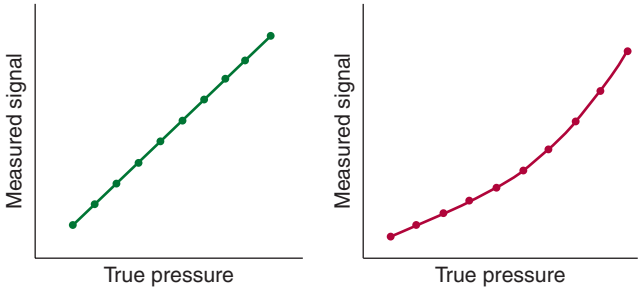


FIGURE 48-5 A measured pressure signal plotted against a reference measurement of pressure ("true pressure") in a linear (*left panel)* and nonlinear (*right panel*) pressure-measuring system. (Used, with permission, from Gallagher.[5])

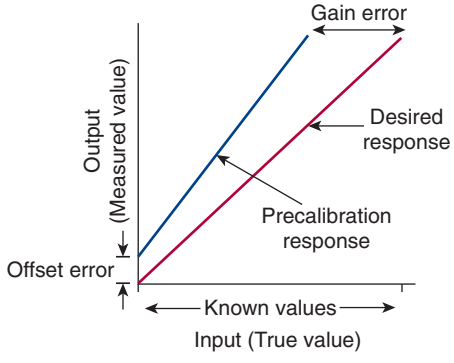


FIGURE 48-6 The two-point calibration procedure. First, the readout on the instrument is adjusted to read zero to overcome offset error. Then, the gain is adjusted to read the desired response. See text for details. (Used, with permission, from Chatburn.[3])

SYSTEMATIC ERROR

Zero offset error occurs when the zero point is not correctly set during calibration but the gain is correct. Consequently, the instrument will read consistently either an inaccurately low or an inaccurately high value over the entire scale. Drift error is a form of time-dependent offset error in which the changes occur over time. The zero point can also change secondary to patient movement without staff being aware.

Range errors occur when the true value of the input system is beyond the operating range of the device. Signals that are either below or above the calibrated scale value may be clipped (the displayed value is different from the true value) (Fig. 48-7).

Response time is the time that a monitoring device takes to respond to a step change in a recorded physiologic variable. The 90% response time is the time from the step change in pressure until the measured signal settles within 10% of its final value. The response time for a pulse oximeter probe varies with its location. Probes placed on the ear respond more rapidly than probes on the finger.[16–18] During calibration of a monitoring device, a slow response time causes error if the user does not allow sufficient time for the instrument to stabilize at the known value.

Frequency response is an instrument's ability to accurately measure an oscillating signal. When the frequency of a signal increases, a measurement system will generate either an underestimate (attenuation) or overestimate (amplification) of the true amplitude of the signal. An optimally damped system will measure all signal frequencies within the working range with equal amplitude (Fig. 48-8).

A system is considered damped when some of the signal-component frequencies are attenuated. Overdamping causes systolic pressure to decrease and diastolic pressure to increase. In a system for measuring vascular pressure, sources of overdamping include air bubbles in the transducer or pressure tubing, clot or fibrin at the catheter tip, and a kinked or partially occluded catheter. Underdamping amplifies the higher harmonics, producing oscillations, which obscure systolic and diastolic values. As such, underdamping causes systolic pressure to increase and diastolic pressure to decrease. Common sources of underdamping include an increase in heart rate interfering with the natural frequency of the pressure-transducer system; a "catheter whip," commonly observed with a pulmonary artery (PA) catheter, can produce an underdamped signal (see Fig. 48-8).

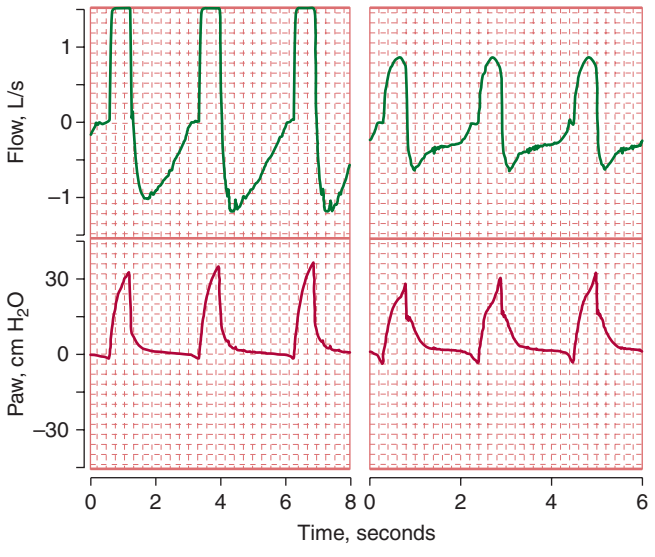


FIGURE 48-7 Flow and airway pressure in two patients receiving assist-control ventilation at a flow rate of 60 L/min. For the patient in the *left panel*, the flow signal is "pinned" or "clipped." The clipping of the flow signal in the left panel was caused by clogging of the pneumotachograph with secretions.

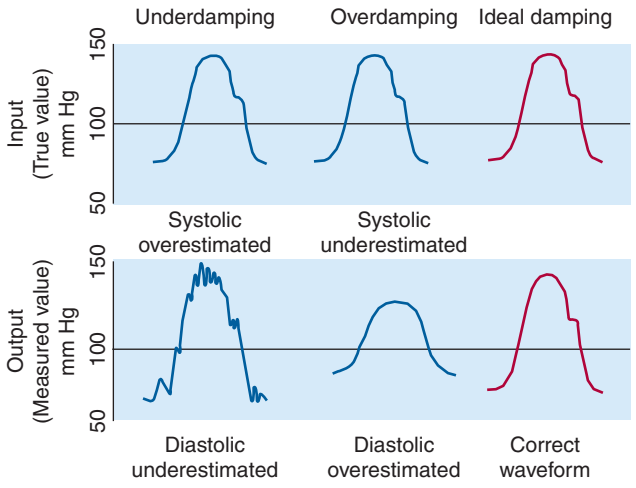


FIGURE 48-8 Effect of three different blood pressure transducers, which exhibited different damping characteristics, on the measurement of blood pressure. (Used, with permission, from Chatburn.[3])

PA waveforms generally contain more high-frequency information than do systemic arterial waveforms, and small errors in pressure assume more clinical significance. Poor dynamic frequency response and overdamped pressure tracings accounted for over half the technical problems encountered in measuring PA wedge pressure.[19] A simple test for assessing the dynamic response of a vascular pressure catheter system is the rapid-flush test.[20]

Alignment of Signals. When employing two different signals to quantify lung mechanics (flow and pressure), it is important to ensure the absence of a phase lag between the two signals. A lag can induce large errors in measurement of resistance and compliance.[5] Phase lags also cause major errors when dynamic intrinsic positive end-expiratory pressure (PEEPi) is measured using an esophageal balloon-catheter system. If a phase lag causes the esophageal signal to occur before flow, PEEPi will be overestimated or considered present when it is truly absent. If a phase lag causes the esophageal signal to occur after flow, PEEPi may be underestimated (Fig. 48-9).

Variable Conditions between Calibration and Data Collection. If a measurement system is used under conditions that differ from the conditions of calibration, and no correction is

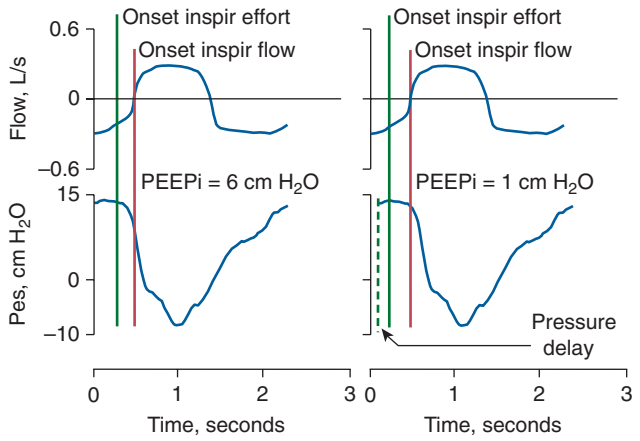


FIGURE 48-9 *Left panel.* Flow and esophageal pressure (*Pes*) signals are properly aligned. Intrinsic PEEP (*PEEPi*), measured as the difference between the onset of inspiratory (*Inspir*) effort and onset of inspiratory flow, is 6 cm H_2O. *Right panel.* Flow and Pes signals are not properly aligned in terms of phase: flow precedes Pes, causing underestimation of PEEPi.

made, systematic errors may result. Flow or volume readings on a ventilator are inaccurate if the temperature or humidity during the recording differs from those present during calibration.[21,22] During calibration, volume may be measured under conditions of ambient temperature, with gas fully saturated with water vapor. If appropriate corrections are not made, subsequent readings of volume, under conditions of normal body temperature and with pressure saturated with water vapor, will underestimate the true volume of gas moving through the lungs. A mass of gas that is 1000 mL at 21°C (69.8°F) can become 1095 mL at 37°C (98.6°F).

Pneumotachographic measurements during mechanical ventilation will become inaccurate if the dimensions of the ventilator tubing during data recording differ from the dimensions used during calibration. The differences in air turbulence and the distribution of flow through the resistive element under the two conditions can lead to measurement errors. When a pneumotachograph was initially calibrated under ideal conditions (with tubing that provided optimized flow characteristics) and then subsequently attached to commonly used ventilator tubing, flow was underestimated by as much as 10% and volume by as much as 15%.[23]

RANDOM ERROR

Noise. All measurements are subject to some degree of rapidly changing interference, termed *noise* or *artifact* (Fig. 48-10).[24] The source of noise can be difficult to trace. Noise distortions occur randomly, so their effects are lessened if measurements are repeated sufficiently. The distortions are not reduced by calibration. The efficiency with which the signal can be distinguished from background noise is defined as the signal-to-noise ratio. Unless the ratio exceeds 1, the signal will be undetectable.

Noise is particularly troublesome when weak signals are highly amplified. Noise is then amplified along with the signal, which eventually limits the sensitivity of the measurement. Cardiac contractions can distort an esophageal pressure signal such that pressure swings appear greater than they truly are. Likewise, the electromyogram signal can be contaminated by the electrical activity from other muscles (Fig. 48-11). As a signal is being transmitted to an amplifier, it is subjected to electrostatic and electromagnetic noise from nearby power lines (Fig. 48-12).[25] Radiofrequency noise may also be added from cellular phones. Finally, physical movement of the catheter cable changes its capacitance and may add low-frequency noise.

Physiologic factors, such as a patient coughing, can lead to error or noise (Fig. 48-13). Physical factors such as slippage of transducers or improper placement of electrodes are also sources of noise. A pulse oximeter probe slipping off the patient's skin accounted for 35% of false alarms recorded in

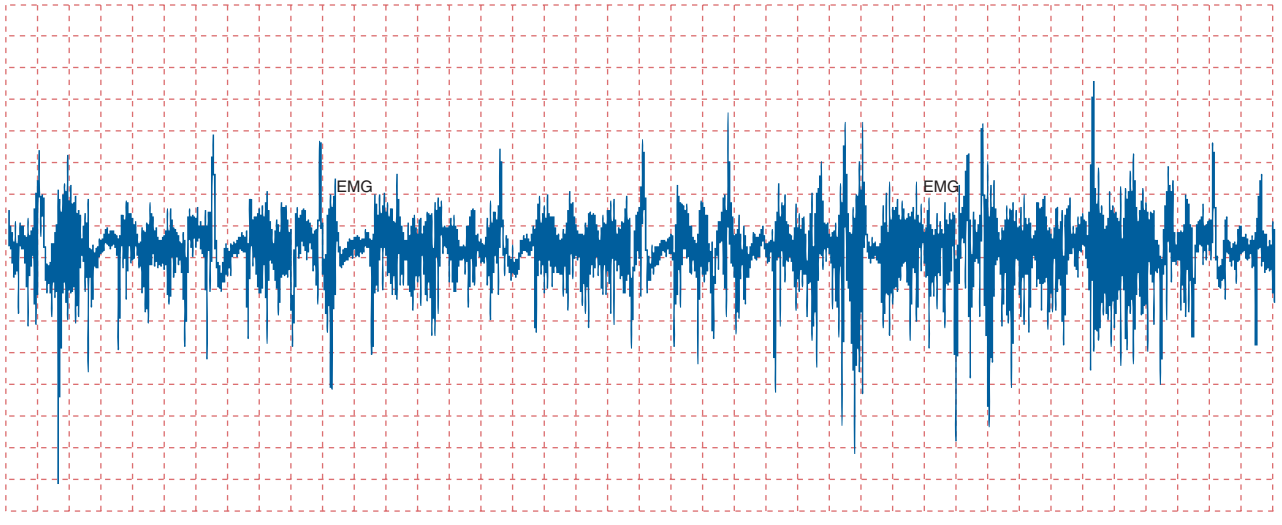


FIGURE 48-10 Electromyelogram tracing of the frontalis muscle reveals considerable noise.

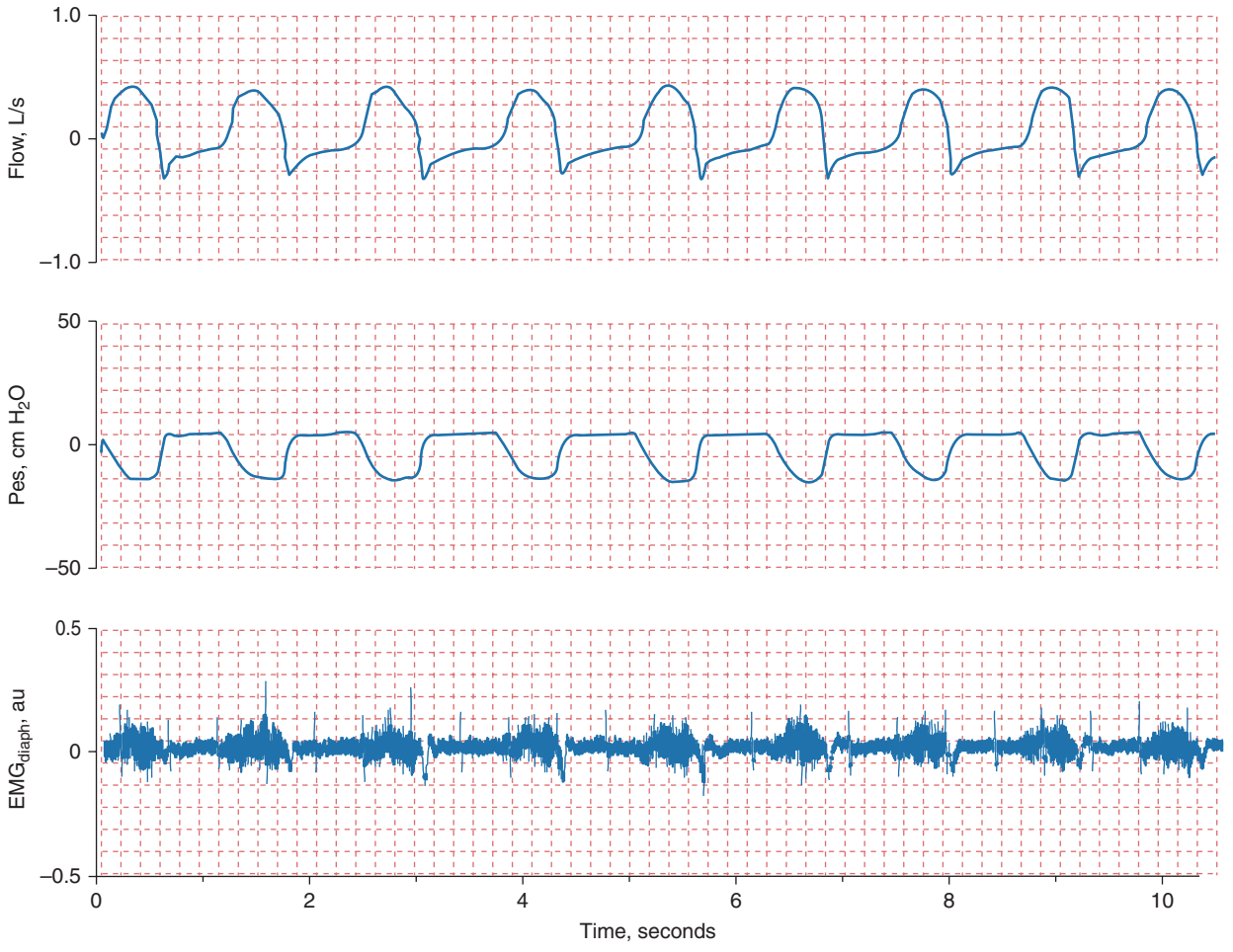


FIGURE 48-11 Flow, esophageal pressure (*Pes*) and electromyogram of the diaphragm (EMG_{diaph}). The diaphragmatic EMG signal is contaminated by spikes from the electrocardiogram signal.

an ICU.[26] Patient movement disturbs the electrode-skin interface and causes electrocardiogram (ECG) noise.[27] "Ringing" after flushing an arterial catheter can interfere with the blood pressure signal and cause faulty readings.[28]

A particularly annoying consequence of signal noise is false alarms.[29–31] Investigators prospectively waited at the bedside for 298 hours in an adult ICU. Of 2942 alarms, 2525 (86%) were false.[26] In a pediatric ICU, 68% of alarms were false.[30] A high rate of false alarms causes noise pollution, wastes nursing time, and contributes to staff burnout.[32]

Nonlinearity. Nonlinearity introduces unpredictable error that varies over the operating range. With measurements of O_2 consumption, nonlinearity of the O_2-sensing system causes a progressive increase in error as fractional inspired oxygen concentration (FI_{O_2}) is increased from 0.21 to 1.0.[33,34]

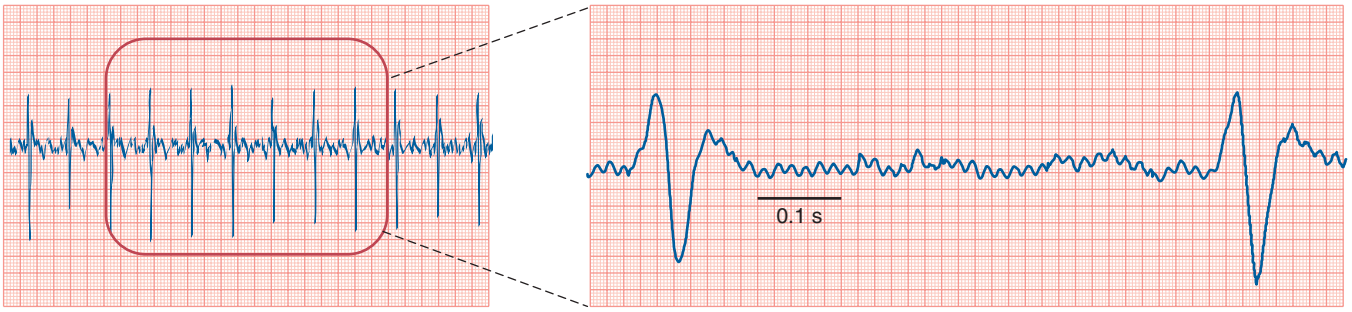


FIGURE 48-12 Electrocardiogram tracing (*left panel*) exhibits background noise. On magnification, the noise in the signal is occurring at a rate of 60 cycles per second (a frequency of 60 Hertz), which is the frequency of electrostatic and electromagnetic signals of power lines.

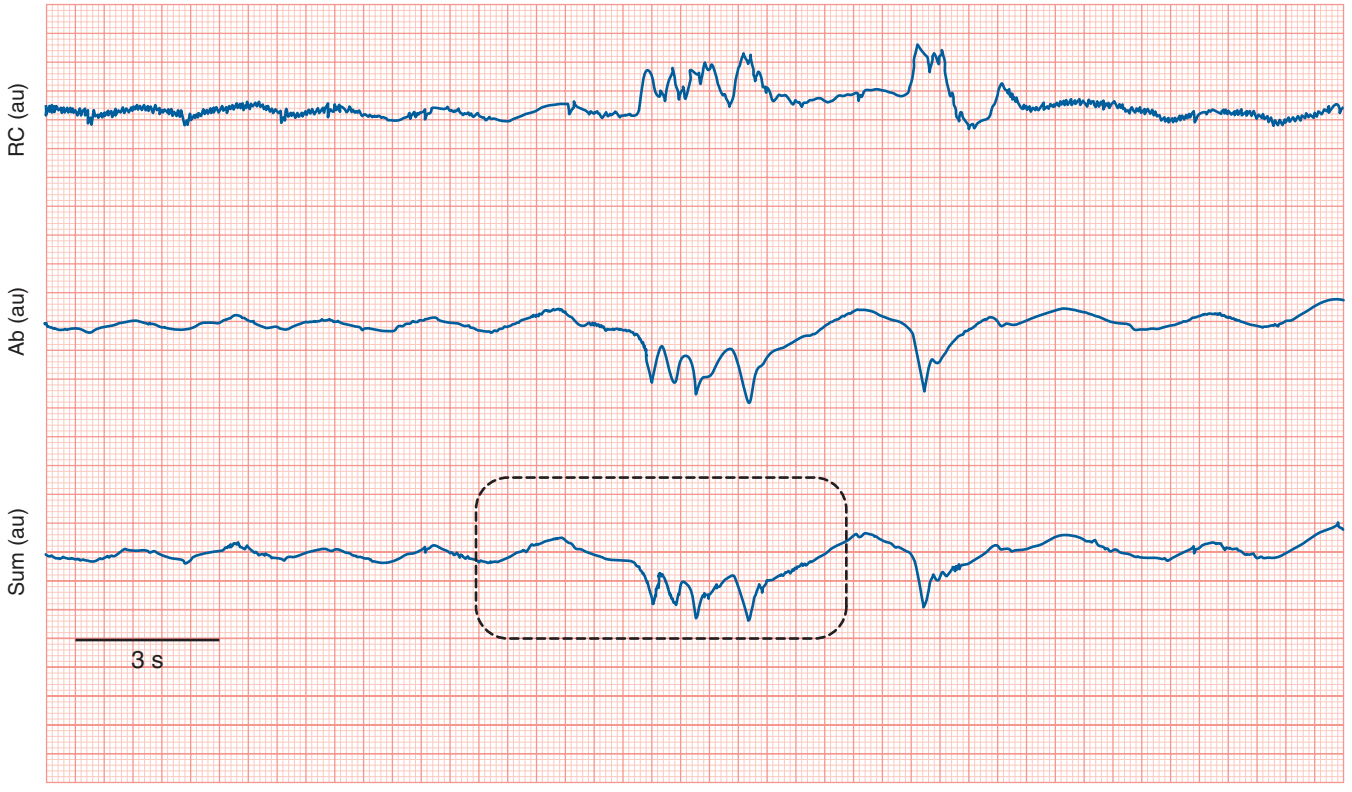


FIGURE 48-13 Recordings of motion of the rib cage (*RC*) and abdomen (*Ab*) obtained with a respiratory inductive plethysmograph in a patient being weaned from mechanical ventilation. The noise in the signal (*dotted rectangular area*) was caused by the patient starting to cough.

Thus, error in measurements of O_2 consumption increases from 2.6% at room air to 17% at an $F_{I_{O_2}}$ of 0.80.[33]

Human Error. Human mistakes in acquiring data are another source of error. Depending on the angle at which the needle on an analog scale is read, different people can perceive different values for the same actual plateau pressure. Measurements that require patient cooperation introduce another source of error. Use of the end-expiratory airway occlusion method to measure PEEPi requires a cooperative patient who does not resist the occlusion.[35] Of 283 attempts in ventilated patients, PEEPi could be quantified in only eighty-six (30%); most of time PEEPi could not be quantified because the patient made an expiratory effort during the occlusion maneuvers (Fig. 48-14).[36]

Patient cooperation is also needed for reliable measurement of maximal inspiratory pressure, a measure of respiratory muscle strength.[37] In patients with low respiratory drive, coaching patients to make vigorous inspiratory efforts led to a 28% increase in pressure.[38]

FIDELITY OF RECORDINGS

Figure 48-15 shows the typical configuration of a data collection system used for bedside monitors in the ICU.[39] The physiologic quantities being measured are referred to as *signals*. A signal (blood pressure, respiratory rate) is converted from a mechanical format to an electrical format using a transducer. The signal is then amplified and conditioned. Next, it is converted from an analog signal to a digital signal with an analog-to-digital converter. Once digitized, the signal is transmitted through a microprocessor. The signal then appears on the monitor screen as a waveform or digital display.[39]

Numbers appearing on the screen of a monitor do not provide all of the information needed to care for a critically ill patient. Studies have revealed that data from bedside monitors account for only 13% to 22% of the data needed to make medical decisions in the care of a critically ill patient.[40]

Of the other data used in clinical decision making, 21% to 22% is derived from observations of a patient by physicians, nurses, and other staff, 38% to 41% from laboratory data, and 13% to 23% from information on medication usage. Caring for a critically ill patient requires the incorporation of all of these data into clinical judgments. Ignoring data that are not important or simply noise is one of the major tasks for a caregiver in the ICU.

Acquiring high-fidelity (minimal amount of noise) data involves the following three factors. First, the transducer and data collection equipment needs to be well designed. For example, to detect the development of dynamic hyperinflation by means of monitoring of changes in end-expiratory

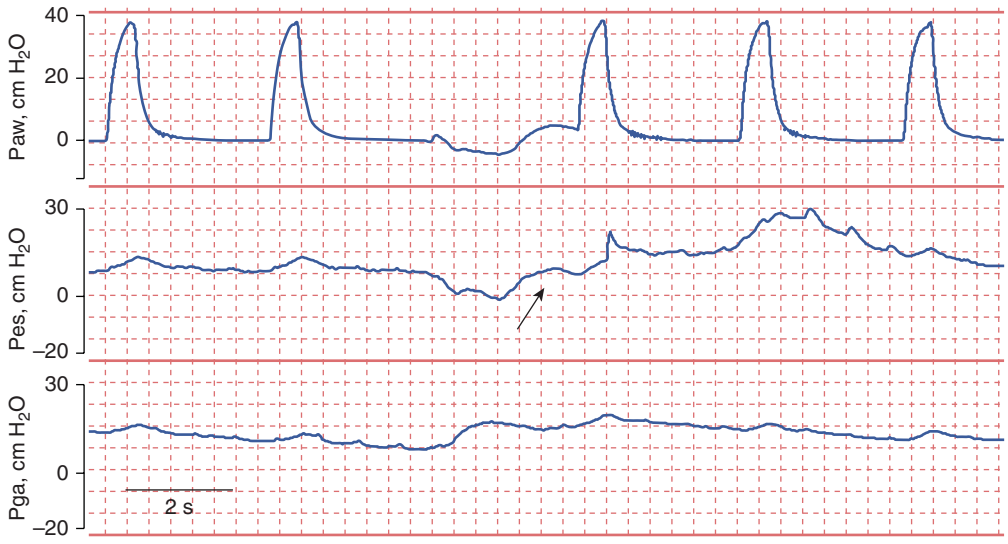


FIGURE 48-14 Airway pressure (*Paw*), esophageal pressure (*Pes*), and gastric pressure (*Pga*) in a patient with chronic obstructive pulmonary disease being ventilated with assist-control ventilation. The airway was occluded during expiration in order to quantify intrinsic PEEP (PEEPi). The patient made an expiratory effort during the occlusion (*arrow*), and thus the recorded pressure overestimated the true PEEPi.

lung volume, one cannot employ a pneumotachograph that exhibits baseline drift (Fig. 48-16). To help in the design of reliable equipment, several standards have been established by organizations such as the Association for the Advancement of Medical Instrumentation (AAMI) and the American National Standards Institute (ANSI).

Second, the clinical staff must properly carry out certain procedures. A perfect catheter, transducer, and flush system can be set up to measure PA wedge pressure. If the catheter, however, is not positioned in the proper location in the PA, overwedging or incomplete wedging can occur, leading to erroneous readings (Fig. 48-17).

Third, rigorous and appropriate processing of the signals generated by a well-designed transducer can eliminate noise in physiologic signals. When signal extraction technology was employed in a pulse oximeter, a 22-fold reduction in noise secondary to gross motion and tremors was observed.[41]

OTHER BARRIERS TO ACCURATE DATA GATHERING

Factors other than accuracy of the measurement can lead to faulty interpretation by the clinician.

Physiologic Variation

Even when a patient is in a steady state, variables monitored in the ICU may not be consistent. To know if a new recorded value of a variable is truly different from an earlier recorded value, it is necessary to know the normal physiologic variation of the variable (Fig. 48-18).[19] Breathing pattern varies considerably. Breath-to-breath variability in tidal volume, as reflected by coefficient of variation, was 33.0 ± 14.9% (SD) in forty-seven young healthy subjects

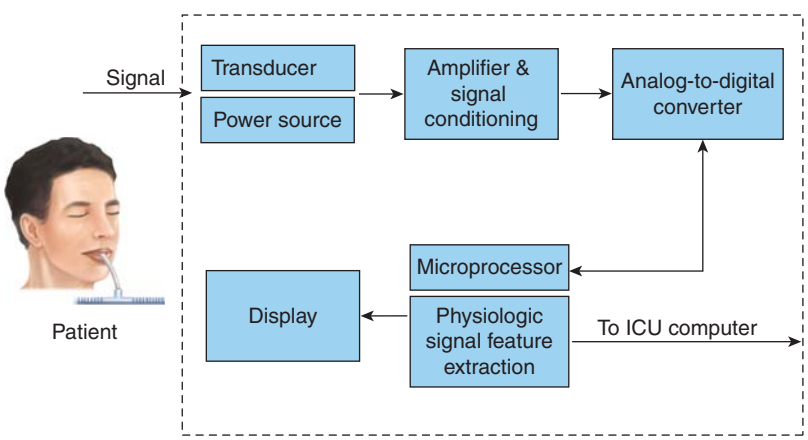


FIGURE 48-15 Schematic of a bedside monitor data-acquisition system. (Modified, with permission, from Gardner.[39])

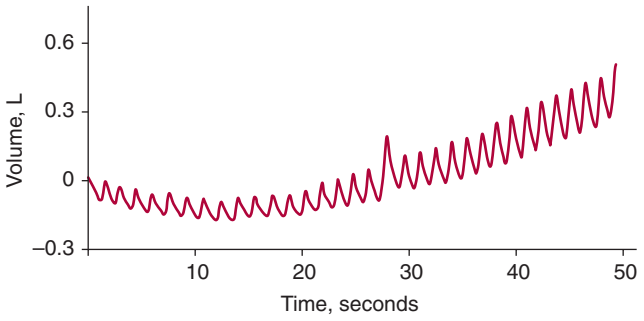


FIGURE 48-16 Breath-by-breath measurements of volume obtained with a pneumotachograph in a spontaneously breathing patient. The drift in the baseline of the signal means that the pneumotachograph does not provide a reliable measure of breath-by-breath change in end-expiratory lung volume, which is desired for detecting the development of dynamic hyperinflation.

(ages 21 to 50 years) and significantly higher in eighteen healthy older subjects (ages 60 to 81 years), 44.0 ± 14.7%.[42] The substantial variability in breathing pattern between subjects, which is further magnified by the considerable breath-to-breath variability within subjects, poses a problem in selecting settings during mechanical ventilation. In a patient being ventilated with the volume-cycled form of assist-control ventilation, if tidal volume is set at the average value during unassisted breathing (approximately 5 to 7 mL/kg), the wide breath-to-breath variation in ventilatory demand means that around half of the delivered tidal volumes will be lower than the patient's demand and may lead to dyspnea.[43]

Arterial pressure varies throughout the respiratory cycle. Minute-to-minute variation in systolic pressure (quantified as standard deviation) is approximately 4 mm Hg, and diastolic pressure varies 2 to 3 mm Hg. In healthy subjects, arterial pressure differs by as much as 20 mm Hg between the two arms.[44] Consequently, a difference of 20 mm Hg between the two arms does not necessarily indicate an underlying disorder such as aortic dissection.

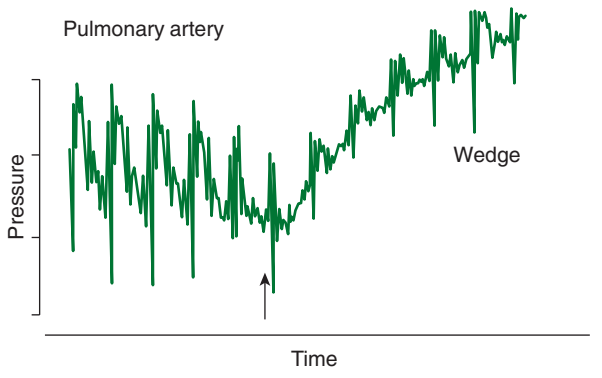


FIGURE 48-17 Pulmonary artery pressure tracing demonstrating overwedging. The *arrow* indicates the point of balloon inflation.

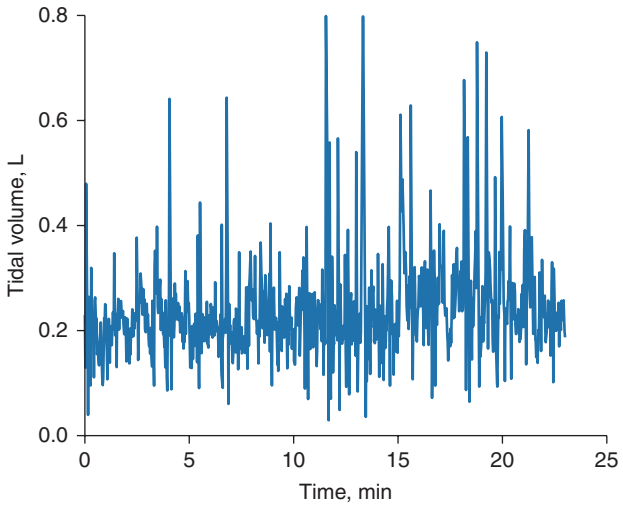


FIGURE 48-18 Breath-by-breath measurements of tidal volume in a patient during a weaning trial. Average tidal volume was 0.23 L. Note the considerable breath-by-breath variability (coefficient of variation was 43%).

Inherent Limitations of Monitors

No machine, including a monitor, is 100% reliable. Despite its undisputed popularity, pulse oximetry fails to provide valid measurements of Sa_{O_2} in a variety of settings.[45] The incidence of overall failure (defined as at least one continuous gap in data that exceeded 10 minutes) in anesthetized patients in an operating room was 9%.[46]

Complexity of Measurements

Many users of monitors have a limited understanding of how a machine functions and the implications of its measurements. Iberti et al[47] found that 47% of physicians (77% of whom were in training) were unable to interpret a straightforward recording of a PA wedge pressure. On average, physicians incorrectly answered ten of thirty-one questions dealing with insertion and complications, cardiac physiology, and interpretation and application of data. More respondents had difficulty with questions regarding data interpretation and patient treatment than with questions related to catheter insertion or cardiac physiology.

Modern ventilators provide a continuous online display of physiologic signals (such as flow, volume, and airway pressure) and numeric computations (resistance, compliance, and work of breathing). The complexity of the physiologic principles that underpin respiratory mechanics, however, has impeded the use of the measurements in clinical practice. The poor understanding of lung mechanics by medicine residents was highlighted in the recent survey.[48] Some 35% of residents were unable to select a ventilator setting that would decrease PEEPi in a patient with chronic obstructive pulmonary disease (COPD) who had become hypotensive immediately after intubation (Table 48-1).

TABLE 48-1: MEDICAL RESIDENT'S KNOWLEDGE OF MECHANICAL VENTILATION

Test items	% Incorrect
Appropriate use of PEEP in hypoxemia	44
Identifying patient's readiness for a weaning trial	38
Managing auto-PEEP correctly	35
Identifying candidate for noninvasive mechanical ventilation	27
Diagnosing tension pneumothorax	14

Abbreviation: PEEP, positive end-expiratory pressure.

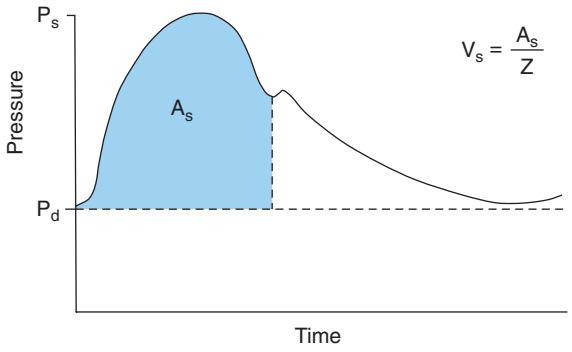


FIGURE 48-19 Schematic of the arterial pressure waveform versus time. P_s represents the systolic pressure, P_d the diastolic pressure, and A_s area under the systolic portion of the pressure-time curve. The heart's stroke volume V_s is related to A_s and the vascular impedance (Z). (Used, with permission, from Mahutte.[57])

The mountains of data generated by monitors make it extremely difficult to differentiate relevant from irrelevant information. More than 230 new data points may be available for review in a single patient on morning ICU rounds.[49] Psychologists have shown that the human mind is capable of assimilating no more than seven variables simultaneously.[50] When the same variable is measured by more than one machine (heart rate recorded by an ECG monitor and a pulse oximeter), the problem is compounded.

Monitoring the Right Physiologic Phenomenon

A major purpose of monitoring is to measure key variables that enhance understanding of underlying pathophysiology. Because of technical limitations, however, we tend to monitor that which we can rather than seeking the information we need.[2,51]

The primary goal of mechanical ventilation is to rest the respiratory muscles. Thus, activity of the respiratory muscles is the single variable most needed when monitoring a ventilated patient. Ventilator settings, however, are usually adjusted on the basis of arterial blood gases. Yet, arterial blood gases provide zero information about whether the respiratory muscles are being adequately rested. Consider synchronized intermittent mandatory ventilation, which has always been adjusted according to arterial blood gases. The failure of arterial blood gases to provide insight into work of breathing probably accounts for the gap of 20 years between the introduction of this mode and recognition of its harmful effects.[52–54]

Investigators recently have argued that calculations derived from the arterial pressure waveform provide a reliable continuous estimate of cardiac output (Fig. 48-19).[55–57] In patients with sepsis, Monnet et al[58] compared the accuracy of calculations based on the arterial pulse contour against a new transpulmonary thermodilution technique (the reference measurement) in detecting short-term changes in cardiac index (<1 hour). The contour technique was reliable in detecting a 15% increase in cardiac index induced by volume expansion (area under the receiver operating characteristic [ROC] curve, 0.87) or by norepinephrine (area under ROC curve, 0.92). Although promising, the ability of the arterial pressure contour to reliably estimate cardiac output needs further investigation in a more heterogenous group of ICU patients (not just sepsis) and over a longer period of observation (>1 hour).

Thinking in terms of ventricular preload, knowledge of end-diastolic volume is pivotal for logical assessment of hemodynamic performance in a critically ill patient.[59] No simple method is available, however, to measure end-diastolic volume. Many clinicians use central venous pressure to assess preload despite numerous studies showing that central venous pressure is extremely unreliable in estimating end-diastolic volume in critically ill patients.[60–65]

Different Techniques for Measuring the Same Physiologic Process

In the ICU, different techniques can be used to measure the same physiologic function. The resulting differing numbers, however, may suggest different clinical states. Arterial oxygenation can be assessed by measuring O_2 saturation with a pulse oximeter or partial pressure of oxygen (P_{O_2}) by blood-gas analysis. In a study of patients with acute respiratory distress syndrome (ARDS), change in Sp_{O_2} moved in an opposite direction to the change in Pa_{O_2} in 25% of the measurements. In some patients, a decrease in partial pressure of arterial oxygen (Pa_{O_2}) of 20 mm Hg was accompanied by a simultaneous increase in Sp_{O_2} of 20%.[66] Therapeutic decisions based on Sp_{O_2} alone differed from decisions based on Pa_{O_2} on 16% of occasions.

CLINICAL APPLICATIONS

The range of options for monitoring a ventilated patient is enormous and beyond the scope of this chapter. A few examples are provided. For a comprehensive review of the clinical

applications of ICU monitoring, the reader is referred to the companion book, *Principles and Practice of Intensive Care Monitoring*.[4]

Enhance Understanding of Pathophysiology

To properly interpret information—medical or nonmedical—a person must take into account the relevant context. To properly understand the results of a diagnostic test, a clinician requires a good understanding of pertinent pathophysiology.

Measuring pressure, flow, and volume during mechanical ventilation assists in the differential diagnosis of respiratory failure. The airway occlusion technique makes it possible to carefully characterize the mechanics of the lung, the chest wall, and the total respiratory system.[67–70] During a weaning trial, esophageal pressure and flow measurements can be used to partition patient effort into its resistive, elastic, and PEEPi components.[71,72] All three components are increased in weaning-failure patients, with PEEPi increasing the most. Therapy to decrease these abnormalities (such as bronchodilators or diuretics) may help expedite weaning outcome (Fig. 48-20).[73,74]

Recording expiratory muscle activity during spontaneous breathing helps differentiate PEEPi caused by dynamic hyperinflation from that caused by expiratory muscle activity (Fig. 48-21).[75–78] If PEEPi is mostly caused by dynamic hyperinflation, addition of external PEEP is likely to decrease work of inspiration.[71,79] If, however, an increase in PEEPi is caused by increased activity of the expiratory muscles,[80] addition of external PEEP will impose an additional elastic load. More importantly, it will also increase the operating lung volume.

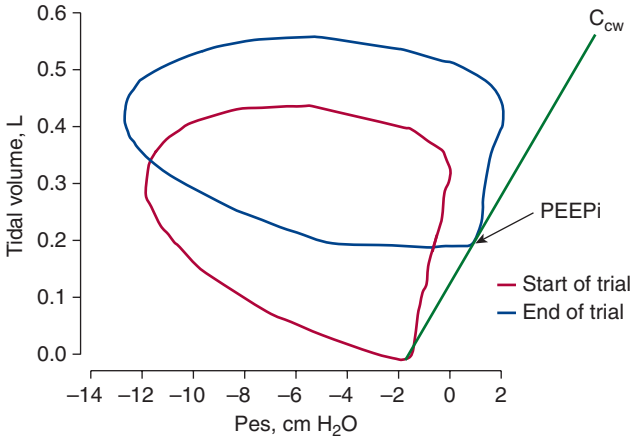


FIGURE 48-20 Esophageal pressure (*Pes*) versus tidal volume curves (Campbell diagrams of work of breathing) in a patient at the start (*red*) and end (*blue*) of a trial of spontaneous breathing. The *green line* represents the static compliance of the chest wall (C_{cw}) measured during controlled mechanical ventilation. At the end of the trial, the Pes-volume curve is displaced upward, indicating an increase in end-expiratory lung volume as reflected by the presence of intrinsic positive end-expiratory pressure (*PEEPi*).

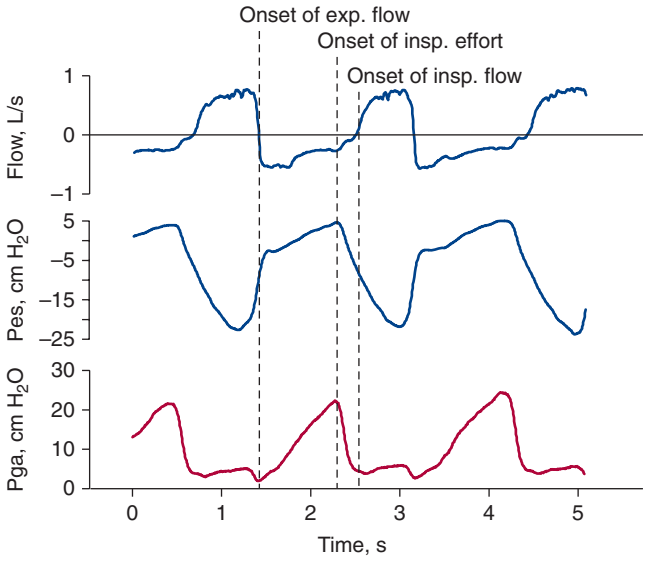


FIGURE 48-21 Flow, esophageal pressure (*Pes*), and gastric (*Pga*) pressure in a patient during a trial of spontaneous breathing. Dynamic intrinsic positive end-expiratory pressure (*PEEPi*) is estimated as the decrease in Pes between the onset of inspiratory (*insp.*) effort (*second vertical line*) and the onset of inspiratory flow (*third vertical line*). Estimation of the expiratory muscle contribution to swings in Pes and dynamic PEEPi is obtained by measuring the increase in Pga between the onset of expiratory flow (*exp.*; *first vertical line*) and the onset of inspiratory effort (*second vertical line*). (Used, with permission, from Parthasarathy et al.[78])

Aid with Diagnosis

Capnometry helps in detecting esophageal intubation.[81–83] The use of end-tidal CO_2 monitoring is based on the premise that CO_2 recorded at the end of a tidal breath reflects arterial partial pressure of carbon dioxide (P_{CO_2}). When the trachea of a patient with an intact pulmonary circulation is intubated, end-tidal CO_2 is recorded. When, however, the endotracheal tube is erroneously placed in the esophagus, end-tidal CO_2 is zero. Monitoring of end-tidal CO_2 has been compared with three other methods (auscultation, a negative pressure test using a self-inflating bulb, and transillumination) for verifying tracheal tube placement.[84] (The second approach, the negative-pressure test, uses a self-inflating bulb: If the endotracheal tube is in the esophagus, suction on the bulb causes the pliable esophageal wall to collapse and no air can be aspirated; if the tube is in the trachea, the semirigid walls prevent tube occlusion when suction is applied and air can be aspirated.) Monitoring of end-tidal CO_2 was found to be the most reliable (Fig. 48-22).

Persistence of expiratory flow throughout expiration, without return to zero, suggests PEEPi (Fig. 48-23); this suspicion can be verified by occluding the expiratory port of the ventilator immediately before the onset of the next breath.[85] Occlusion causes pressure in the lungs and ventilator circuit to equilibrate. The pressure displayed on the ventilator manometer is PEEPi.[86] The presence of PEEPi can help

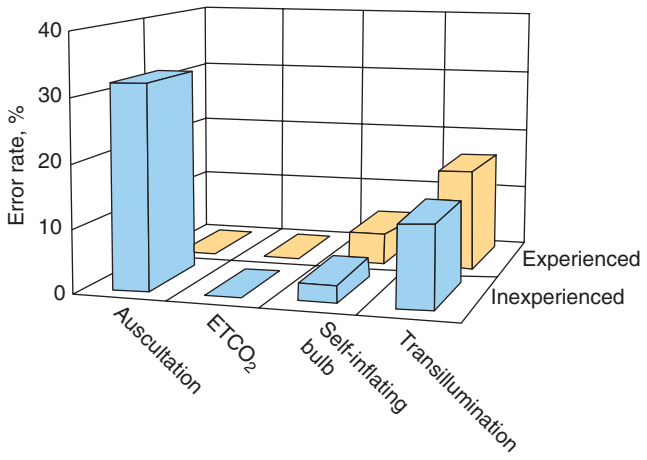


FIGURE 48-22 Error rates of experienced and inexperienced examiners in verifying the placement of a tracheal tube using four methods: *auscultation*, capnographic determination of end-tidal CO_2 ($ETCO_2$), negative-pressure test using a *self-inflating bulb*, and *transillumination* using a lighted stylet. Capnography was the most reliable method regardless of the examiner's experience. (Used, with permission, from Knapp et al.[84])

explain an unexpected drop in cardiac output or electromechanical dissociation (during cardiopulmonary resuscitation).[87] Steps to overcome PEEPi can decrease patient work of breathing and improve triggering of the ventilator.[86,88,89]

Guide Management

ASSESS THE RESPONSE OF DRUGS

Monitoring is essential with administration of therapeutic agents that can produce rapid and dramatic changes in a patient's condition. A physician would not dream of administering a potent, rapid-acting intravenous vasoactive agent (vasodilator, vasopressor, or inotropic agent) without monitoring arterial pressure. It would be unconscionable to perform cardiac resuscitation without ECG monitoring.

Measurement of airway resistance helps in assessing the response to bronchodilator therapy. In ventilator-dependent patients with COPD, delivery of albuterol from a metered-dose inhaler produces a decrease in airway resistance within 5 minutes; the effect is sustained for at least 60 minutes.[90,91]

During mechanical ventilation, pulse pressure (the gradient between systolic pressure and diastolic pressure) is maximal (PPmax) at end-inspiration and minimal (PPmin) during expiration. These respiratory variations in pulse pressure have been shown to reflect changes in left-ventricular stroke volume.[92] Accordingly, it has been reasoned that fluid responsiveness may be assessed by estimating the respiratory changes in pulse pressure (referred to as ΔPP) in terms of the following formula:

$$\Delta PP = \left[\frac{PPmax - PPmin}{(PPmax + PPmin)/2}\right] * 100$$

ΔPP was found to be reliable in identifying fluid responsiveness in sedated patients receiving mechanical ventilation; this variable, however, was inaccurate in spontaneously breathing patients and in patients ventilated with low tidal volume (<8 mL/kg).[93,94]

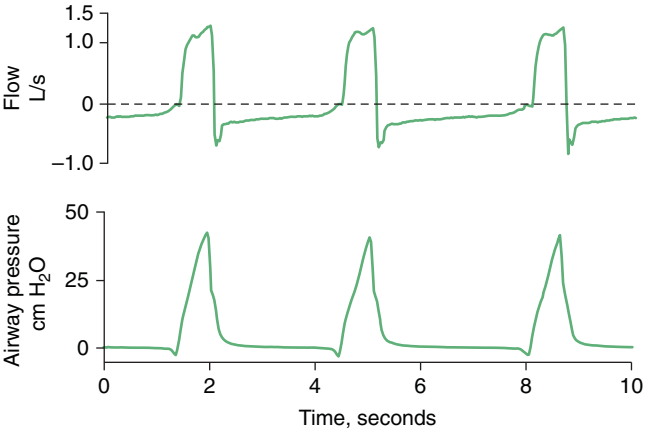


FIGURE 48-23 Flow and airway pressure in a patient being ventilated using assist-control ventilation. The failure of expiratory flow to return to zero at the onset of the successive mechanical breaths indicates the presence of intrinsic positive end-expiratory pressure (PEEPi).

OPTIMIZE VENTILATOR SETTING

Titrating FI_{O_2}. Pulse oximetry is commonly used when titrating FI_{O_2} in ventilated patients (Fig. 48-24). A Sp_{O_2} of 92% is a reliable target in white patients. In black patients, however, an Sp_{O_2} of 92% is associated with significant hypoxemia, and a higher target, 95%, is required.[95]

Adjusting Pressure Support. Tidal volume and respiratory rate are commonly used to set pressure-support ventilation.[96–100] A reasonable level of inspiratory effort is an inspiratory pressure-time product less than 125 cm H_2O·sec/min. Using this target, a respiratory rate of 30 breaths/min and tidal volume of 600 mL resulted in the fewest false classifications.[100]

Setting Positive End-Expiratory Pressure. In a patient with acute lung injury, the right level of PEEP is that which optimizes arterial oxygenation without causing O_2 toxicity or ventilator-induced lung injury.[101–104] Balancing the benefit of keeping the lung open (during tidal ventilation) against the risks of lung overinflation may require monitoring of the pressure-volume curve, lung morphology, and gas exchange.[105–110]

When loss of aeration has a focal distribution (atelectatic lower lobes coexisting with aerated upper lobes), a high level of PEEP can cause overinflation of already aerated areas and only partial recruitment of atelectatic areas.[111] In such patients, some experts recommend limiting PEEP to low levels (approximately 10 cm H_2O).[101] In patients who have

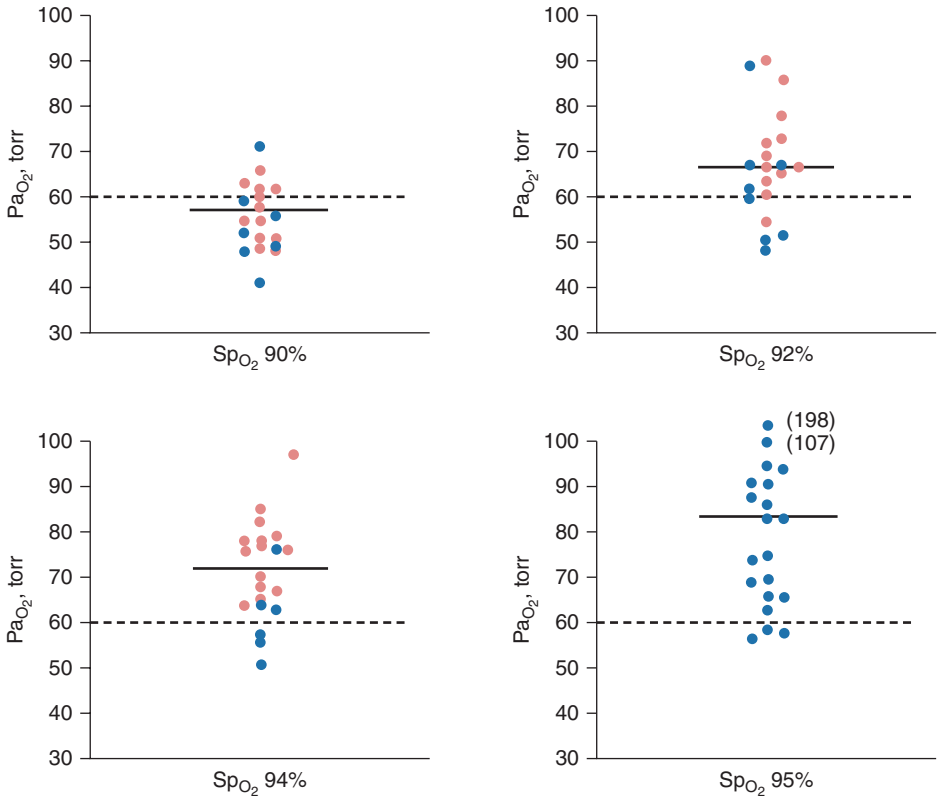


FIGURE 48-24 Values of arterial oxygen tension (Pa_{O_2}) at pulse oximetry oxygen saturation (Sp_{O_2}) readings of 90%, 92%, 94%, and 95%. Inspired oxygen concentration (FI_{O_2}) was adjusted to achieve a particular steady-state Sp_{O_2} value in a group of fifty-four critically ill patients. The *solid horizontal line* represents the mean Pa_{O_2} value obtained at each Sp_{O_2} target. The *orange* and *blue circles* represent values obtained in white and black patients, respectively. In white patients, a Sp_{O_2} target of 92% resulted in a satisfactory level of oxygenation, whereas a higher Sp_{O_2} target, 95%, was required in black patients. (Modified, with permission, from Jubran and Tobin.[95])

diffuse loss of aeration, the risk of overinflation with PEEP is low.[112] Thus, a higher PEEP can be used provided it does not cause the plateau pressure to rise above the upper inflection point of the pressure-volume curve.[101,113]

Assessing Patient Work of Breathing. Inspection of the airway pressure contour during assisted ventilation can help assess patient work of breathing. Excessive scalloping of the airway pressure tracing indicates increased work, such as that caused by insufficient inspiratory flow (Fig. 48-25). During assist-control ventilation, an increase in flow can decrease work of breathing by as much as 60% in patients with acute respiratory failure. Higher flow rates can also decrease inspiratory effort in stable patients with COPD.[114,115]

Continuous displays of pressure and flow have led to increased awareness that patient effort is frequently insufficient to trigger the ventilator.[75,88] During pressure support or assist-control ventilation, up to a third of patient efforts may fail to trigger the machine (Fig. 48-26). Such nontriggering has been shown to result from premature inspiratory efforts that are insufficient to overcome the elastic recoil associated with dynamic hyperinflation.[88] To trigger the ventilator, patient effort has to first generate a negative intrathoracic pressure to counterbalance the elastic recoil and then overcome the set sensitivity. The full consequences of wasted inspiratory efforts are not known. They certainly place an unnecessary burden on patients whose inspiratory muscles are already under stress. Such added stress can interfere with subsequent weaning.[116–118]

Avoid Complications

The heterogeneous lung involvement in ARDS puts some regions at risk of developing alveolar overdistension when a ventilator breath is delivered.[119–121] Plateau pressure is monitored as a surrogate for end-inspiratory alveolar pressure, and its monitoring may help to minimize lung injury.[122] Studies show that patients with ARDS who have plateau pressures greater than 32 cm H_2O have higher mortality.[113,123,124]

Daily radiographs in ventilated patients can reveal unsuspected or significant abnormalities.[125,126] Malpositioning of devices (endotracheal tubes, nasogastric tubes, and central venous pressure lines) and pneumothorax or pleural effusions are detected in 20% of patients.[127] Physicians had not anticipated these findings. The importance of early detection of abnormalities was underscored in a study by Steier et al.[128] Mortality was 7% when pneumothorax was diagnosed

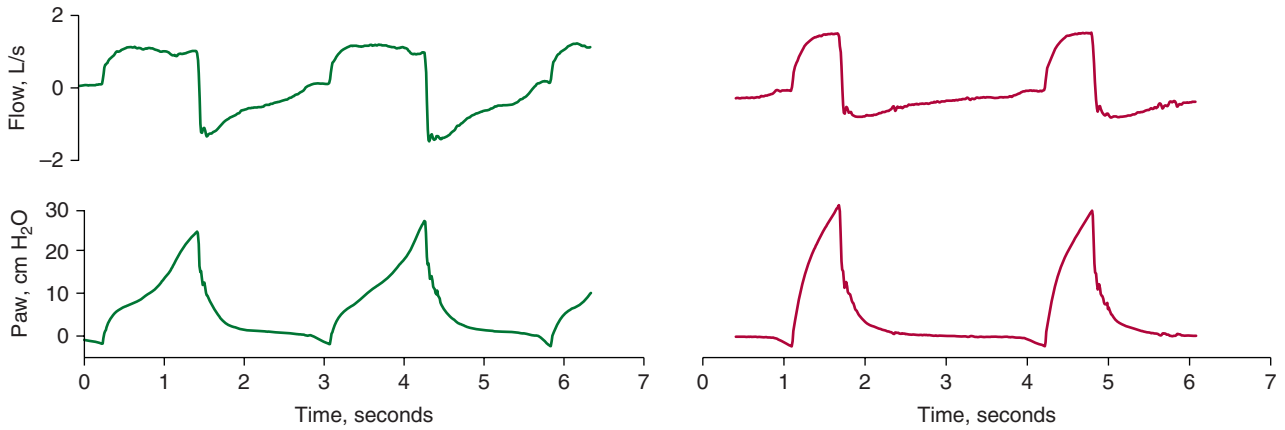


FIGURE 48-25 Flow and airway pressure (*Paw*) during assist-control ventilation at a flow of 30 L/min (*left panel*) and a flow of 60 L/min (*right panel*). On the *left panel*, the pronounced negative phase together with excessive scalloping of the Paw waveform indicates that the patient is making a strenuous effort to breathe as a result of the inadequate flow setting. On the *right panel*, the small negative phase and smooth rise and convex appearance of the Paw waveform indicate that the patient is making a slight inspiratory effort to breathe.

immediately. Mortality quadrupled when diagnosis (and treatment) was delayed.

Provide Alarms

Pulse oximetry can provide an early warning of hypoxemia. In 20,802 surgical patients, use of pulse oximetry resulted in 19-fold greater detection of hypoxemia (defined as an Sp_{O_2} <90%) as compared with patients in whom an oximeter was not used.[129] Myocardial ischemia was less common in the oximetry group than in the control group, twelve and twenty-six patients, respectively. The anesthesiologists reported that oximetry led to a change in therapy on one or more occasions in 10.5% of patients in the operating room and in 17% in the postanesthesia care unit.

An alarm on a ventilator may sound (or flash) because of a change in ventilator performance or patient clinical status. An abrupt increase in peak airway pressure can arise with endotracheal obstruction or ventilator malfunction. A decrease in peak pressure can arise with a leak in the circuit. An increase in the baseline airway pressure can signal malfunction of the exhalation valve (or inadvertent PEEP).[130,131]

The role of monitoring as a warning sign was highlighted in a study of anesthesia-related malpractice claims.[132] Of 1097 cases reviewed, negative outcomes were prevented in 32% by the use of additional monitors. The authors estimated that use of a pulse oximeter and capnometer would have prevented 93% of the mishaps.[132]

Assessment of Trends

Monitoring of physiologic variables over time helps in assessing a therapeutic response.[133] When vasopressor therapy is being titrated, continuous monitoring of arterial pressure is

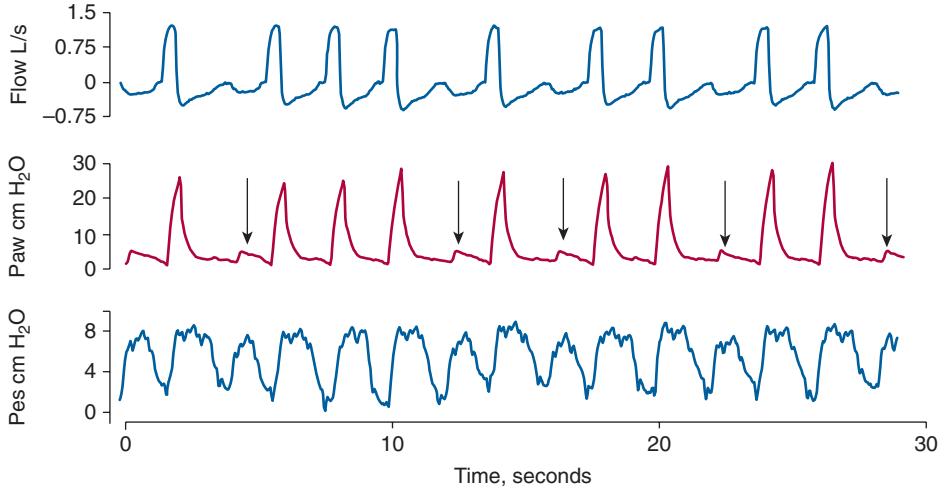
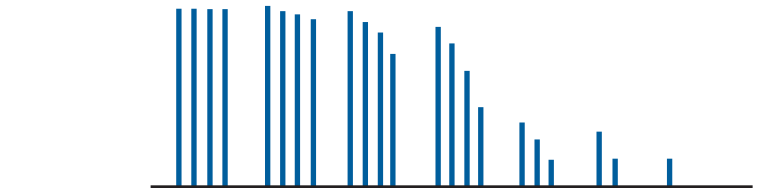


FIGURE 48-26 Flow, airway pressure (*Paw*), and esophageal pressure (*Pes*) in a patient receiving assist-control ventilation. The *arrows* indicate inspiratory attempts that failed to trigger the opening of the ventilator valve.



Receptor blockade (%)	60	70	75	77.5	80	85	90	95
T1 (%)	100	100	100	80	25	20	10	0
T4/T1 Ratio	100	0.9	0.75	0.6	0	0	0	0

FIGURE 48-27 Train-of-four stimulation consists of a series (train) of four electrical impulses delivered at a frequency of two stimuli per second. When neuromuscular blocking agents are not being used, the response to train-of-four stimulation is four strong twitches. As the receptors begin to load up with the neuromuscular blocking agent, four twitches are still present, although the response is weaker and a decrease is evident between the first and the fourth twitch. Comparison of muscular movement on the first (*T1*) and fourth twitch (*T4*) enables the calculation of a *T4/T1* ratio; this ratio can detect an earlier stage of receptor blockade than twitch loss. (Used, with permission, from Strange.[136])

essential. Monitoring the motor response to peripheral nerve stimulation helps avoid the accumulation of neuromuscular blocking agents (with risk of prolonged paralysis).[134,135] Train-of-four stimulation uses a series of four supramaximal stimuli delivered at a frequency of two stimuli per second (Fig. 48-27). The dose of a neuromuscular blocking agent is usually titrated to obtain no more than two visible muscle twitches in response to each train-of-four. If the patient fails to demonstrate any response with the train-of-four stimulation, the blocking agent should be discontinued temporarily or the dosage reduced.[135–137]

Changes in esophageal pressure over the first 9 minutes of a trial, quantified as a trend index, revealed sensitivity 0.91, specificity 0.89, positive predictive value 0.83, and negative predictive value 0.94 (Fig. 48-28).[74] The area under a ROC curve for the trend index (0.94) was greater than for first-minute measurement of esophageal pressure (0.44, $p < 0.05$) and tended to be greater than that for frequency-to-tidal volume ratio (f/V_T).

EFFECT OF MONITORING ON PATIENT OUTCOME

Because of expectation of improvement in patient outcome, monitoring is subjected to closer scrutiny than most diagnostic tests.[51] Although complications derived from use of a monitor are relatively easy to evaluate, few monitoring devices have been subjected to studies of their effect on mortality or other clinical outcomes. Those few studies have not revealed clearcut benefits. Three recently conducted randomized trials of the PA catheter (in 2714 patients and 120 ICUs) did not reveal improved outcome.[138–140] The negative results of these studies have led to a substantial decline in the use of the PA catheter (Fig. 48-29).[141]

In 20,802 surgical patients, Moller et al[129] found that pulse oximetry had no demonstrable benefit on the rate of postoperative complications. Accordingly, it is reasonable to ask whether monitoring has any role in the management of a critically ill patient. At first glance, the studies say no. Before reaching that conclusion, however, we need to scrutinize the data.

A randomized controlled trial is generally adopted as the most definitive method for evaluating the benefit of some intervention. In a typical trial, the effect of an intervention on some outcome is assessed in a well-defined patient population. Such trial designs are mostly used to assess the risks and benefits of a therapeutic agent. Using a randomized trial to assess the benefits of a monitoring device can be problematic because of poorly defined patient populations, complexity of the therapeutic intervention (because monitoring is also linked to treatment), and choice of the primary outcome.

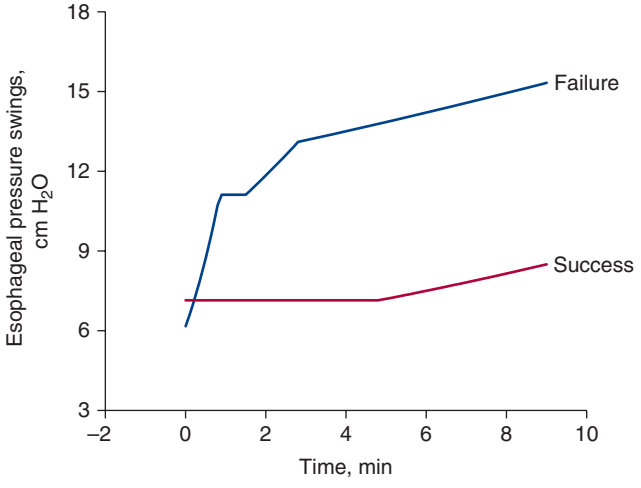


FIGURE 48-28 Change in esophageal pressure (Pes) swings, quantified using a nonlinear model, namely the multivariate adaptive regression spline (MARS) analysis, during the first nine minutes of weaning trials in weaning-failure patients (*blue line*) and weaning-success patients (*red line*). The mathematical technique was used to capture all of the data points in the two groups over the time span. The greatest rate of increase in Pes swings in the failure patients occurred during the first minute. The greatest difference in Pes swings between the failure (14.5 cm H_2O, 95% confidence intervals 18.9 to 11.2) and success groups (7.9 cm H_2O, 95% confidence intervals 11.8 to 0.8) was at the transition between the ninth and tenth minute. (Used, with permission, from Jubran et al.[74])

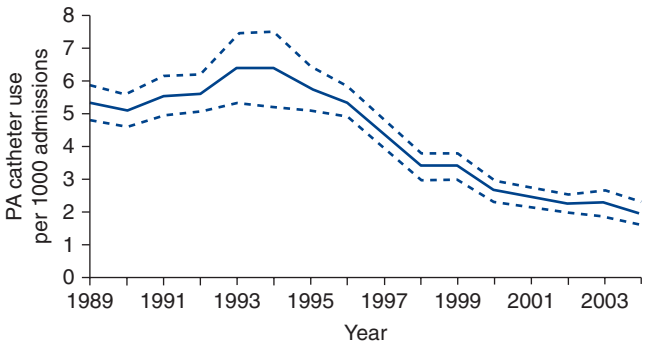


FIGURE 48-29 Pulmonary artery (*PA*) catheters placed per 1000 patients (*solid line*) and 95% confidence intervals around the annual rate of catheter utilization (*dashed lines*) in nine American states as part of a nationwide inpatient sample. Between 1993 and 2004, use of pulmonary artery catheterization decreased by 65%, from 5.66 to 1.99 per 1000 medical admissions. (Modified, with permission, from Wiener et al.[141])

Failure to Precisely Define Disease State

The first step in evaluating the effect of an intervention is to ensure a well-defined study population. Definition and categorization of disease states—the discipline of nosology—is especially difficult in critically ill patients.[142] (The reader is referred to a detailed discussion of nosology in Chapter 4.) The most precise way to define a disease is in etiologic terms (e.g., Legionnaire disease). Most randomized trials of monitoring techniques have been conducted in groups of patients identified in terms of a syndrome—that is, a condition defined on the basis of a constellation of symptoms and signs. A typical definition of sepsis is the following: temperature greater than 38°C (100.4°F) or less than 36°C (96.8°F), respiratory rate greater than 20 breaths/min or P_{CO_2} less than 32 mm Hg, and signs of hypoperfusion, among others.[139] (Note that the respiratory rate commonly listed as a criterion for sepsis falls in the middle of the normal range.) When a disease is defined in an imprecise manner, very different types of patients may be assigned to the two arms of a trial. This factor could be a major contributor to negative outcome of a study of a monitoring technique.

Complexity of Evaluating the Intervention

Evaluating the benefit and risk of any intervention in the ICU is challenging. The huge number of procedures and treatments typically used in any single ICU constitute confounding variables. These covariates contribute to considerable experimental noise in a trial, masking benefits that are truly present.

To illustrate these considerations, we discuss a hypothetical study designed to determine whether PA catheter monitoring improves survival in septic shock. In designing such a trial, the covariables shown in Figure 48-30 must be controlled for or taken into account.

PATIENT SELECTION: DISTINCTION BETWEEN TRUE INDICATIONS VERSUS STUDY INCLUSION CRITERIA

The choice of the most appropriate monitoring device is dictated by a patient's condition. To decide whether a monitor is indicated in a particular patient, the physician must balance potential benefits and risks. When wondering whether to insert a PA catheter in a patient with septic shock who is unresponsive to fluid and vasopressor therapy, a physician should consider three factors. One, will end-organ dysfunction proceed and become irreversible if therapy is not changed? Two, will large volumes of fluids, administered empirically but on an incorrect assumption that intravascular volume is depleted, predispose to hypoxemia should acute lung injury be present? Three, if a PA catheter is inserted, will the physician withhold fluids if the wedge pressure is normal?

The uncertain probability of organ dysfunction and its time course, the risks of monitoring, and the variable efficacy of therapy highlights the complexity of clinical decision making, even when the clinician is highly skilled and experienced. The above three questions, and other factors that impinge on the decision of whether a PA catheter is indicated in a particular patient, are omitted from the design of a randomized clinical trial. Instead, patients are selected on the basis of carefully defined eligibility criteria. The study is thus focused on a narrowly defined spectrum of patients who poorly reflect the more heterogeneous range of disease seen in everyday practice. As a result, the patients receiving a PA catheter in a randomized trial may bear little relationship to what an experienced and cautious physician does in everyday practice. A skilled physician is unlikely to insert a PA catheter in many of the patients assigned to the intervention arm of a trial, believing that the resulting information would have little likelihood of influencing patient management. If patients are entered into a trial and are randomized to the PA catheter arm, although a judicious physician would not insert a catheter in the same patients, the consequence will be to dilute any likely benefit from the catheter but at the same time increase the risk of complications.

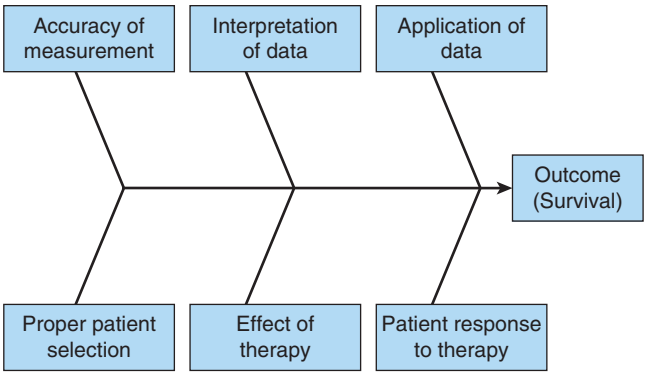


FIGURE 48-30 Factors that can influence the effect of a monitoring device on patient outcome, such as survival. See text for details.

In a study of a mixed group of medical and surgical patients, Connors et al[143] found that a PA catheter was more likely to be used in patients who were sicker and more likely to die. Richard et al[139] studied the benefit of a PA catheter in patients with shock and ARDS. Patients were eligible for monitoring with a PA catheter if their systolic blood pressure was equal to or greater than 95 mm Hg (on 3 mcg/kg per minute of dopamine), heart rate equal to or greater than 92 beats/min, Pa_{CO_2} equal to or less than 32 mm Hg while breathing spontaneously, and an elevated lactate level. We suspect most physicians would not insert a PA catheter in all (or even most) patients who meet these four criteria. In the study of Sandham et al[138] in high-risk surgical patients, 87% of patients who had a PA catheter inserted were not at high risk for death (as identified by New York Heart Association or American Society of Anesthesiologists classifications). In the study by Harvey et al[140] of 1041 medical and surgical ICU patients, patients were randomized to the PA catheter arm if the primary physician considered the patient as someone who "should" be managed with a PA catheter; precise criteria of what constitutes "should" were not given. Again, this study did not demonstrate a benefit from a PA catheter. But if a PA catheter is inserted in a patient in whom there is no clear indication for its use, would you expect the catheter to improve outcome? We expect all readers to answer no. Thus, the outcomes in the randomized trials by Richard et al,[139] Sandham et al,[138] and Harvey et al[140] were all preordained as negative before the first patient was enrolled.

ACCURACY OF THE MONITORS

Studies evaluating the impact of monitoring devices on outcome are predicated on the assumption that the clinical staff are employing the monitor in a knowledgeable manner and obtaining reliable readings. Reliability of PA catheter readings is highly dependent on catheter placement, calibration of the transducers, and interpretation of the data. Of 282 measurements of PA wedge pressure, Morris et al[144] found that 103 (36%) of the readings were inaccurate. Of 103 erroneous readings, eighty-nine were associated with technical problems, such as damped tracings, poor dynamic response, overinflation of the balloon, or incomplete wedging (Fig. 48-31). Technical problems with use of the PA catheter, or steps taken to correct them, were not taken into account in the randomized trials conducted by Richard et al[139] and Sandham et al.[138] Specifically, Harvey et al[140] state,"We did not assess the quality of use." Even with great care, these technical problems cannot be eliminated completely. For a simple device, such as a pulse oximeter, overall instrument failure was 7.2% among the sicker patients in the study of Moller et al.[129] Such operational problems are commonly not listed in reports of clinical trials.

INTERPRETATION OF THE DATA

Several studies reveal that many clinicians have limited skills in the accurate interpretation of data generated by a PA catheter.[47,145–147] In their survey, Iberti et al[47] found that almost half of physicians incorrectly interpreted a straightforward recording of wedge pressure. Another study revealed that physicians arrived at a wide range of wedge pressures for the same tracing.[148] If the wedge pressure is incorrectly and repeatedly read as low in a patient with ARDS, then continued administration of fluids is likely to result in an unfavorable outcome.

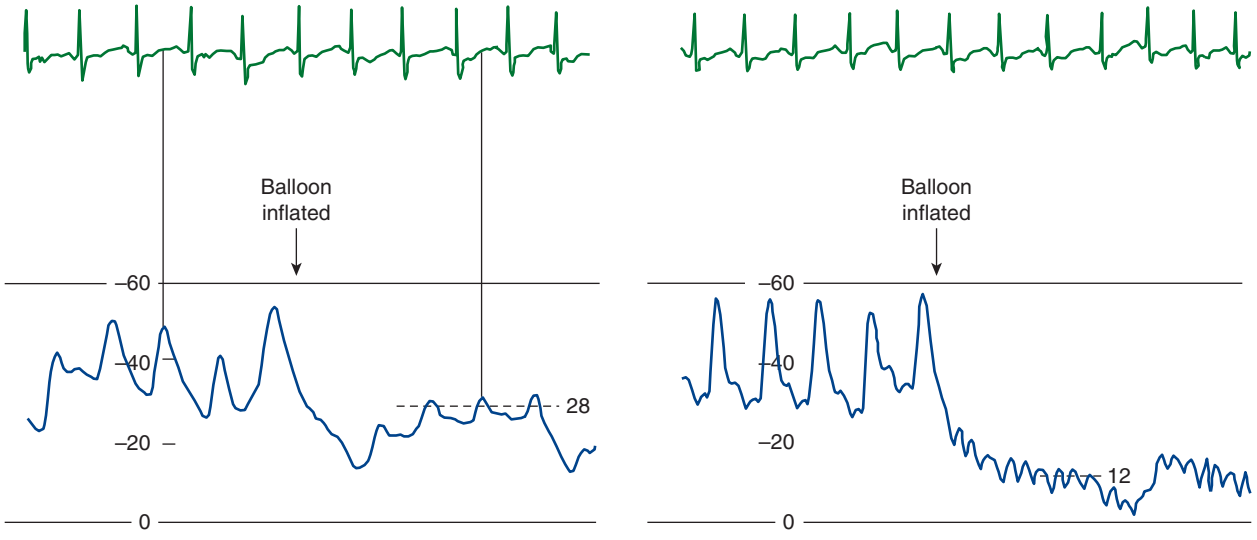


FIGURE 48-31 Simultaneous recordings of electrocardiogram (*ECG*) and pulmonary artery (*PA*) pressure to illustrate incomplete wedge pressure (*Ppw*). *Left panel.* With balloon inflation, wedge pressure falls to a value that approximates pulmonary artery diastolic pressure (*Ppad*). After balloon inflation, a single positive wave coincides with the T wave on the ECG—a pattern inconsistent with a left-atrial waveform. *Right panel.* Waveforms after the catheter has been retracted and the balloon reinflated. A large Ppad–Ppw gradient is evident and the tracing is consistent with a left-atrial waveform. Scale in mm Hg. (Used, with permission, from Leatherman and Marini.[20])

APPLICATION OF DATA IN CLINICAL DECISION MAKING

Even if data are accurate and properly interpreted, benefit will occur only if the physician applies the information logically in the management of patients. Some monitoring decisions can be made by simple rules of thumb (heuristics); these are easy to incorporate into an algorithm.[149,150] Simple rules take the *if-then* form. If serum glucose in a patient with insulin-dependent diabetes is high, then insulin should be administered. This strategy is straightforward because the probability of hyperglycemia is high, the consequences of untreated hyperglycemia are great, the risk of monitoring (drawing a blood sample) is low, the benefit of treatment is high, and the risks when insulin is properly administered are small.

The monitoring dilemmas that arise in most critically ill patients are complex and cannot be captured in an algorithm. Intensivists frequently have to make rapid decisions under conditions of considerable uncertainty, involving substantial risks and unpredictable benefit. To combine, integrate, and interpret diagnostic data in their decision-making process, intensivists employ a number of strategies of clinical reasoning.

Probabilistic Reasoning. Diagnostic uncertainty arises because data are insufficient or because the relationship between the data and the disease process is poorly understood.[150] To cope with uncertainty, physicians may use probabilities if available.[151] Probabilistic reasoning is based on the known sensitivity and specificity of a diagnostic (or monitoring) test. A physician forms an initial gestalt as to the likelihood of some condition, which is the *pretest probability*. Then, based on the known sensitivity and specificity of the test, the physician forms a new estimate of likelihood, the *posttest probability*. Take a physician who has no inkling as to whether a patient can (or cannot) tolerate a weaning trial. The pretest probability will be 50%. The physician then measures f/V_T and obtains a reading of 80. This reading has a likelihood ratio of 7.5 (that the patient will tolerate a weaning trial). Based on the nomogram of Fagan,[152] a likelihood ratio of 7.5 is associated with a posttest probability of 95% (if pretest probability is 50%). This means that when physicians are in complete doubt (50-50) as to whether a patient can be weaned, obtaining an f/V_T value of less than 80 will substantially decrease their doubt.

Unfortunately, the published data necessary for precise application of probabilistic reasoning are available for few diagnostic (or monitoring) techniques in the ICU. Because physicians cannot communicate in precise quantitative terms, they use expressions such as "most likely," "unlikely," and "rare." Consider a patient in septic shock who remains hypotensive despite fluid resuscitation and a moderate dose of a vasoactive agent (dopamine > 10 mcg/kg/min). A common cause of hypotension in such a patient is left-ventricular-dysfunction. To determine whether left-ventricular-dysfunction is present or absent, the physician measures the patient's cardiac index. Before measuring cardiac index, the physician forms a gestalt of the patient's likelihood of left-ventricular dysfunction (based on previous experience of patients with similar clinical characteristics). After inserting a PA catheter, measuring cardiac index, and based on the reported sensitivity and specificity of cardiac index, the clinician revises his or her assessment of the patient's likelihood of left-ventricular dysfunction. This scenario is idealistic, not realistic, because sensitivity and specificity of cardiac index for detecting left-ventricular-dysfunction in patients with septic shock have not been studied.[153,154]

Another problem arises with use of monitored data. Although data are generally recorded as continuous variables, clinicians typically view data in dichotomous terms. What is the breakpoint in cardiac index below which a patient is classified as having left-ventricular-dysfunction? Reports on cardiac index as a diagnostic criterion of left-ventricular-dysfunction usually present a range of possible values, such as 1.6 to 2.3 L/min/m^2, rather than a discrete value.[155] The threshold value of cardiac index that is best in distinguishing between the presence and absence of left-ventricular-dysfunction has never been determined. Is it an index of 2.2 L/min/m^2? Is it 2 L/min/m^2? Without a defined threshold value, one cannot attempt to measure the sensitivity and specificity of a diagnostic test.

A further layer of complexity arises with the choice of reference standard. All tests are inaccurate to varying degrees. Thus, the degree of accuracy of a diagnostic (or monitoring) test is measured against a reference test. Ideally, the reference standard should be measurable in concrete terms: histology or precise level of narrowing on angiography. For left-ventricular-dysfunction, however, the reference standard is based on clinical criteria. Studies suggest that a cardiac index of 2.2 L/min/m^2 is an important threshold in predicting the outcome of patients with acute myocardial infarction.[155] Will the physician use the same cardiac index threshold in deciding whether to start treatment with dobutamine in the above-described patient with sepsis who has failed dopamine therapy? Moreover, in making decisions in a particular patient, a clinician may decide to raise or lower the threshold value, taking into account aspects unique to a particular patient's condition. Because of dobutamine's chronotropic action on the heart, a physician may decide to withhold this drug in a patient with underlying coronary artery disease until the cardiac index falls to 1.8 L/min/m^2.

There is a deeper, more fundamental problem with probabilistic reasoning. This relates to its epistemologic grounding. (Epistemology is the branch of philosophy concerned with the study of the very foundation on which our knowledge rests.) On their own, data derived from randomized trials are unable to explain *why* a particular relationship exists. In contrast research in physiology, molecular biology, and many other fields has as its objective the elucidation of underlying mechanisms (explanations for why relationships occur). Tanenbaum[156] undertook an ethnographic study of the reasoning employed by physicians as

they made clinical decisions. She found that the clinicians were primarily realists (or determinists): They based decisions on a mental picture of a world of real relationships, real events. Data from mechanistic research enrich this mental picture, offering explanations (meaning) on which physicians can base clinical decisions. When physicians operate as realists, they conduct themselves as if they know what is really happening inside a sick person. Data from a randomized trial simply show that some relationship was observed, but provide no epistemologic basis for its occurrence, no understanding of cause and effect. In clinical decision making, realists image a disease process; probabilists play the odds.

Physiologic Reasoning. To attain greater confidence in diagnosis, clinicians employ physiologic (or causal) reasoning. As discussed under "Probabilistic Reasoning" above, the hope is to form a more coherent picture of cause-and-effect relationships in a given patient. This type of reasoning is particularly suited to the ICU, because monitoring is geared toward detecting changes in pathophysiology. Causal reasoning involves testing and validating (or refuting) apparent cause-and-effect connections.

Consider a patient with COPD and congestive heart failure who is being ventilated. A PA catheter is inserted and reveals a wedge pressure of 28 mm Hg. Based on probabilistic considerations, the likelihood of pulmonary edema is great. Using causal (physiologic) reasoning, wedge pressure is viewed as a reliable estimate of preload (left-ventricular end-diastolic volume). In this patient, the clinician judges the elevated wedge pressure to signify hypervolemia. The true advantage of causal reasoning becomes more clear when we learn that a 60-second interruption of positive-pressure ventilation caused this patient's wedge pressure to fall to 15 mm Hg. Probabilistic reasoning would steer us toward diagnoses such as hypervolemia or cardiac dysfunction. Physiologic (or causal) reasoning leads us to suspect that the high wedge pressure (28 mm Hg) is caused by PEEPi rather than hypervolemia or cardiac dysfunction.

Causal reasoning forms the bedrock for many diagnostic decisions made outside the ICU. Our understanding of the pathophysiology of critical illnesses, however, is too rudimentary to apply it when managing most ICU patients. The above example highlights the need for much more research into pathophysiologic mechanisms in critically ill patients. Data generated by randomized, controlled trials can never provide the information needed for causal reasoning—the type of reasoning that is dominant in the decisions made by physicians in their everyday practice.[156]

Deterministic Reasoning. Deterministic or categorical reasoning is used to reduce information overload. Deterministic reasoning applies a set of rules that take the form of *if-then* statements. For example, *if* a ventilated patient with COPD develops a sudden and equivalent increase in peak and plateau pressures, *then* a nonairway problem, such as a pneumothorax, should be considered. If a patient develops acute renal failure without proteinuria and the fractional excretion of sodium is less than 1%, then the renal failure is prerenal in origin.

Such *if-then* rules look simple and attractive. The difficult part is figuring out if the antecedent condition (the *if* part of the rule) has been met. When the developers of clinical protocols incorporate such rules into an algorithm, they deliberately eliminate contingencies that can influence the application of the rule. The elimination of such ambiguities means that the rule can be more precisely and concisely expressed on paper. But the elimination of context means that the rule is artificial and cannot be applied in a consistent manner during routine clinical practice.

An algorithm is available for treating hypokalemia in an ICU patient receiving diuretics. If serum potassium is 3.5 mEq/L and the patient is asymptomatic, the algorithm dictates not to give a potassium supplement. The context of everyday ICU practice, however, is more complex. If the patient has heart disease and is taking digitalis or undergoing cardiac surgery, most clinicians would administer potassium if serum potassium is 3.5 mEq/L to prevent life-threatening arrhythmias. Likewise, if a patient has cirrhosis, physicians would treat a potassium of 3.5 mEq/L to minimize the risk of hepatic coma. The problem of hypokalemia is further complicated if there is concurrent hypomagnesemia, which promotes potassium wasting. It would be difficult if not impossible to capture all such nuances in the few steps of an algorithm.

Research studies of monitoring devices have included algorithms in an attempt to control for variations in clinical practice. These attempts did not achieve their desired goals. Gattinoni et al[157] undertook a study to evaluate the benefit of directing fluid and pharmacotherapy to achieve a supranormal cardiac index (guided by a PA catheter). Survival was equivalent in the groups with supranormal and normal cardiac index. At first sight, the findings suggest that targeting therapy to a supranormal cardiac index does not improve outcome. Perhaps that is true. But such a conclusion cannot be rationally defended based on the presented data. The target of supranormal cardiac index was reached in only 46% of patients in that study arm. Canadian researchers strove for a similar goal.[138] They compared therapy based on predefined physiologic targets (guided by a PA catheter) versus therapy based on usual care (without a PA catheter). The O_2 delivery target in the experimental arm was reached in only 21% of patients at study entry and in 63% of patients after surgery. These two studies provide a vivid illustration of the problems that investigators face in achieving the physiologic objectives that are the true focus of their randomized trial. If the target is not being achieved, what exactly is being studied in these clinical experiments?

Casuistry. Physicians face many decisions that have never been the subject of a randomized, controlled trial. A physician with many years of experience will relate a current patient to previously similar cases that he or she has handled, paying close attention to how the present patient is similar to, or differs from, the previously managed cases. The physician

may also draw on knowledge gained from case reports and observational studies—the only type of literature that pertains to many problems in the ICU. Few randomized controlled trials have specifically addressed fluid management of patients with ARDS. A number of observational studies have been conducted,[158,159] and knowledge gained from such reports combined with previous experience guide decisions on fluid management in this setting.

Reasoning along these lines, primarily in terms of analogy, is referred to as *casuistry*. Casuistry literally means being concerned with concrete individual cases, as opposed to abstract generalities.[160,161] Casuistry involves reasoning based on precedent (previous example). It is the type of reasoning used in case law, and is the main foundation of the legal system. In deciding how best to manage a particular patient, a physician also needs to take into account a patient's personal preferences.

Tacit or Implicit Knowledge. Physicians make many decisions using tacit knowledge: the type of inexpressible knowledge in *knowing how* versus *knowing what*. Tacit knowledge is knowledge that cannot be articulated. It is implicit knowledge based in actions rather than in conscious thoughts.[162] For more than 80% of complex situations, cognitive psychologists have found that experts such as intensive care staff did not employ an analytical approach to decisions. Instead, they relied on tacit knowledge.[162]

The term *tacit knowledge* was introduced by Michael Polanyi, who pointed out that human beings know more than they can impart.[163] Tacit knowledge is acquired without the intervention of explicit reasoning. It suggests an activity that takes place below the level of conscious reasoning, whether by habit, by being deeply ingrained, or by instinct. By definition, its content is indefinable.

Examples of tacit knowledge include the surgeon's knowledge of the right amount of tension to place on a suture, knowing when to intubate a patient in respiratory distress, and knowing when to extubate a patient after completion of a weaning trial. The skill in performing bronchoscopy is another example. The physician knows how to position the bronchoscope spatially as if it were an extension of his or her fingertips, and how to serially weave the instrument to enter the posterior segment of right lower lobe bronchus. An added dimension is knowing how much pressure to exert, and sensing resistance, when performing a transbronchial biopsy. The physician cannot communicate this knowledge in explicit terms. Instead, the knowledge is something the physician feels and shows while performing the procedure.

The failure of the possessor of tacit knowledge to identify and communicate its content is often attributed to poor power of introspection. When a physician is asked to recount the mental steps involved in solving a complex problem, the reconstruction often sounds unconvincing, even naïve. An attending physician may decide not to extubate a patient who is breathing at a rate of 28 breaths/min and who has reasonable arterial blood-gas values. The fellow may appear puzzled by this decision. To explain his (or her) decision, the attending physician may use words such as "intuition" or "gut feeling." The word *intuition* is loaded with negative connotations. It is equated with random guessing, confused superstition, mystical thought, weird unfathomable emotion, and an excuse for prejudice. Yet, intuition, not explicit logical reasoning, lies at the heart of originality in science.

People are not born with some free-floating gift of intuition. Instead, the unconscious decisions and automatic actions that reflect tacit knowledge stem from years and years of experience and reflection in a particular field. Intuition is needed to know *when* is the right time to adapt (to judge when is a plan falling apart); to know *how* to adapt (hatching a scheme on the hoof); and in *evaluating* adaptive steps (spotting new steps that may cause problems subsequently). Tacit knowledge is exemplified by an experienced clinician who knows at what juncture it is prudent to insert a PA catheter in a patient who is septic, who remains hypotensive despite 20 mcg/kg per minute of dopamine, and who has started to exhibit a decrease in urine output. Improvisation in patient care requires considerable expertise; it is the antithesis of following a protocol.

Experts do not use guidelines or analytical reasoning when faced with familiar problems. Instead, they generate a single course of action—they do what normally works. An expert sees the world differently than does a novice. An expert spots things that other people miss: how things usually work, patterns, anomalies, fine details but at the same time the big picture, and soft underbellies for attack. The expert is not using tacit knowledge as a substitute for the explicit analytical method, but as an improvement over it.[162]

Consider the case of a patient who is admitted to the ICU with fever, respiratory distress, and hypotension. The resident examines the patient, but is unable to find an obvious source for the fever. Chest radiography and urinalysis are negative. The resident makes a presumptive diagnosis of septic shock. He begins therapy with vasopressors, fluids, and broad-spectrum antibiotics. The patient remains hypotensive. The next day, the attending physician hears a crunching sound over the apex, and suspects a Hamman crunch. At first, the physician is not convinced it is present, because the crunch is obscured by the noise of the ventilator. On closer listening, the crunch is synchronous with the heartbeat. The attending physician infers that the patient has an esophageal perforation, which is causing the sepsis. Surgical repair is successfully undertaken. The resident asks the attending physician, "How did you know what to look for?" "I don't know why," the physician replies, "I just sensed it." This is an example of tacit knowledge used by the attending physician. The attending answers, "I don't know why," because the physician is unable to recall the precise train of thought that inspired the physician to suspect mediastinal emphysema. In part, the attending physician's thinking is based on extensive experience, and the many similar cases the physician has seen in the past—an example of casuistry. The physician's inspired guess, diagnostic acumen, does not stem solely from tacit knowledge. It is also based on explicit knowledge. Hearing a crunching sound in the precordium is of no value

without the book learning that tells the physician what the sound signifies. The case exemplifies the intermingling of tacit and explicit knowledge.

The skills of an outstanding diagnostician are like those of the connoisseur, a refined ability to discern between nuances governed by a heightened sensibility (good taste). It is a mistake to imagine that the listing of a series of explicit steps in a protocol can substitute for the skills of a connoisseur.

CLINICAL JUDGMENT

To understand the contribution of the above five forms of reasoning, it is useful to consider each on its own. Expert clinicians, however, call on all these forms of reasoning, and blend them together without using each on an independent basis. The amalgam of these forms of reasoning constitutes *clinical judgment*—a term widely used but rarely explicated.

Clinical judgment refers to the totality of mental resources and cognitive processes that a physician uses in deciding what to do for a particular patient. A good judge is someone who examines different pieces of evidence; he or she compares critically and impartially the merits of each, and makes a decision as to where the truth lies. An experienced clinician blends tacit and explicit knowledge in the process of making clinical decisions. Such blending of knowledge cannot be reduced to, or captured in, a mathematical model that would apply universally in all critically ill patients. It is obviously impossible to control or standardize tacit knowledge and clinical judgment among the clinicians participating in a randomized controlled trial. The marked variation in degree of skill among participating physicians is an important unmeasurable factor that can confound the outcome of a trial. Recognition of this factor has led to calls for the inclusion of an extra arm in a clinical trial that reflects the usual care of the participating physicians.

CONFLATION OF THERAPY AND MONITORING

The fundamental goal of monitoring is to guide a clinician in management decisions. Thus, monitoring is inextricably linked to treatment. A monitoring device on its own never cured anyone. It can improve outcome only if it leads to more effective therapy. This link is not always recognized. Yet it hovers over all assessments of a monitoring device. The conflation of monitoring with therapy differs from the evaluation of diagnostic techniques in other areas of medicine; a test is judged by its diagnostic accuracy, not on the expectation that it will improve outcome.

Consider the use of hemodynamic monitoring in an unstable patient with septic shock. Therapeutic options include fluids, vasopressors, or inotropic agents. None of these agents directly correct the underlying problem. Each may also cause harm. When a supranormal cardiac index was used as a target for hemodynamic management in 762 critically ill patients, survival was no better than with usual care.[157] When high-dose dobutamine was used to achieve a high cardiac index, Hayes et al[164] found that treated patients had a higher mortality than the usual care group: 54% versus 34%. In a complex patient with septic shock, when initial hemodynamic therapy is unsuccessful, it is common to undertake invasive monitoring (often involving a PA catheter) to guide more aggressive therapy. An unsuccessful outcome in such patients may be the result of ineffective pharmacologic agents or complications caused by them. Yet, the results of such trials are commonly interpreted as evidence that hemodynamic monitoring is not effective.

PATIENT RESPONSE TO THERAPY

In medicine, we treat patients, not diseases. Patients have varying responses to therapy depending on their disease. Although the right therapy may be chosen (e.g., cefotaxime for meningococcemia), a patient may have an undesired response to the therapy that worsens outcome. A PA catheter may be inserted in a patient in septic shock to guide therapy. The patient may develop cardiogenic pulmonary edema (with fluid resuscitation), a life-threatening arrhythmia (with dobutamine), or digital ischemia (with norepinephrine). These adverse reactions can outweigh beneficial effects of the monitoring device (the PA catheter) itself. No monitoring modality is likely to improve outcome unless it is combined with a therapeutic intervention that has a good benefit-to-risk ratio.

Final Outcome

An outcome event is an occurrence (such as death) that may be modified after implementing some intervention (monitoring wedge pressure with a PA catheter). Outcomes research is defined by the statistical analysis of clinical data to determine whether particular interventions are associated with particular results. To discriminate between benefits and risks of an intervention, an adequate sample size is necessary. Sample size is calculated on the basis of baseline event rate, expected benefit, level of significance (α), and the power to detect a difference ($1-\beta$).[165] Studies evaluating the effect of monitoring on patient outcome often lack statistical power. Statistical power is especially important when complications are rare and the expected impact (of an intervention) is small. If the outcome under evaluation occurs frequently, fewer patients will be needed than if the outcome occurs infrequently. Moller et al[129,166] conducted a prospective, randomized trial of the effect of pulse oximetry on the rate of postoperative complications in 20,802 surgical patients. Hypoxemia (defined as a $Sp_{O_2} < 90\%$) was detected nineteen times more often in the oximeter group than in the control group ($p < 0.0001$). The primary goal of the study, however, was to determine whether the rate of postoperative complications was decreased. For this goal, statistical significance was not reached. The investigators concluded that it would take at least 500,000 patients to show a reduction in a rare event such as myocardial infarction and 1,900,000 patients to show a reduction in anesthesia-related deaths.

The American Society of Anesthesiologists introduced monitoring standards that mandated use of pulse oximetry in every patient undergoing anesthesia. Subsequently, Eichhorn[167] observed a threefold reduction in the incidence of major preventable intraoperative injury (ten in 757,000 vs. one in 244,000 anesthetics), yet the reduction did not reach statistical significance. Because the incidence of serious adverse events is low, it is estimated that an additional 6,545,605 cases would be needed to detect a significant reduction in major preventable intraoperative injury.[24,168] Given the necessary effort, would anyone suggest that it makes sense to undertake such a study to find out if pulse oximetry is helpful during anesthesia? If the study were negative, would anesthesiologists stop using this monitoring device? Unlikely.

When anesthesiologists were surveyed in the study of Moller et al,[129,166] 80% felt more secure when they used a pulse oximeter. Of 104 anesthesiologists, nineteen believed that the pulse oximeter helped them avoid serious complications (such as esophageal intubation, tracheal tube disconnection or displacement, anesthesia machine failure, and respiratory problems immediately after extubation). It is this mindset that has established pulse oximetry as an essential component of the standard of care despite a failure to achieve a $p < 0.05$ level of proven efficacy. The lack of concurrence between proof of efficacy in randomized trials of pulse oximetry and its requirement as part of the standard of care has major ramifications for all monitoring techniques.

When researchers evaluate the usefulness of a monitoring device, the selected outcome measure (mortality or complication rates) may be unrealistic. If benefit is expected to be small, an outcome based on mortality may not be sufficiently sensitive to detect it. Undertaking inappropriately designed studies may cause valuable tools to be discarded. At face value, the outcome of the study of Moller et al[129] should lead physicians to stop using pulse oximetry—at least in the operating room.

Authors commonly cite examples where intermediate outcomes (prevention of hypertension, hypoxemia, or ischemia; or suppressing premature ventricular contractions following myocardial infarction) were misleading. A widely cited study is the Cardiac Arrhythmia Suppression Trial (CAST) study. This consisted of a randomized trial to test the hypothesis that suppression of asymptomatic or mildly symptomatic premature ventricular contractions (PVCs) with antiarrhythmic agents in patients who have suffered a myocardial infarction improves survival.[169–172] It was believed that suppression of PVCs would prevent ventricular tachycardia and ventricular fibrillation and thus decrease mortality. Patients treated with antiarrhythmic agents (flecainide, encainide, or moricizine), however, had a higher mortality (8.0%, sixty-three of 755) than patients receiving placebo (3.5%, twenty-six of 743).

The increased mortality in the intervention arm of the CAST study is often interpreted as evidence that physiologic reasoning is unreliable, and that mortality is the only study outcome that reliably captures truth of efficacy.[49] Before accepting that conclusion, the data need to be closely scrutinized. A number of concerns arise. Mortality in the placebo group (3.5%) was much lower than expected.[173] The low mortality was partly a consequence of study design.[174,175] Only patients whose ventricular arrhythmias were suppressed during an open-label titration phase of the study were randomized to the active drug or placebo. Patients whose ventricular arrhythmias were not suppressed or who did not tolerate the pharmacologic agent were not randomized to either arm.[169,172] Thus, patients randomized into the study had a low risk for death for two reasons: The exclusion of patients who had died and exclusion of patients in whom arrhythmias could not be suppressed (with drugs) during the open-label titration (prerandomization) phase.[175] Of patients in the placebo arm, 80% had PVCs alone without having nonsustained ventricular tachycardia; moreover, more than half had a near-normal ejection fraction (above 40%).[172] There is further evidence that mortality in the placebo group is not generalizable. The CAST investigators undertook a subsequent analysis in the 318 patients who survived the open-label titration phase but who were not randomized to either arm of the study and the 942 patients who were randomized to the placebo arm.[176] Occurrence of death or a resuscitated cardiac arrest was higher in the nonrandomized patients (8.5%, twenty-seven of 318) than in the placebo group (4%, thirty-eight of 942).[176] In summary, the adverse effects of the antiarrhythmic agents in the CAST study may largely reflect the failure of the investigators to recruit representative patients into the placebo arm, insofar as the investigators excluded patients in whom they could not suppress their arrhythmias (a marker of increased mortality).[171,177–179] Certainly, it is inappropriate to use data from the CAST study to conclude that therapy guided by ECG monitoring (that is, physiologic reasoning) is not helpful.

CONCLUSION

Patients receiving mechanical ventilation are vulnerable to a host of complications and it is essential to spot these problems at the earliest possible time. Such complications are commonly associated with alterations in physiologic functions in different organ systems. By continuously recording many physiologic variables in real time, monitoring systems offer the possibility of alerting a physician to a significant change in a patient's status. The hope is that such a warning will provide an opportunity to interrupt a cascade of events sufficiently early in their evolution to avert a lethal catastrophe. Accordingly, expertise in the operation of monitoring systems plays a vital part in the intelligent use of mechanical ventilation. This expertise involves more than familiarity with the touch pads and screens of the machinery. Physicians must know the physiologic principles on which each monitor is based, appreciate the responsiveness and fidelity of the charted variables, be facile in troubleshooting a system, and evaluate monitored data in accordance with the canons developed for interpreting diagnostic tests. All these skills play a vital part in minimizing the ills that the ventilated patient is heir to—they form a consummation devoutly to be wished.

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XIII

MANAGEMENT OF VENTILATOR-SUPPORTED PATIENTS

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49

PRONE POSITIONING IN ACUTE RESPIRATORY FAILURE

Luciano Gattinoni
Paolo Taccone
Daniele Mascheroni
Franco Valenza
Paolo Pelosi

Approximately 35 years ago, the use of the prone position was proposed to improve arterial oxygenation in patients with acute respiratory failure (ARF).[1–3] The prone position, however, may have variable effects on gas exchange. Moreover, it has been suggested that, independent of gas exchange, the prone position may decrease the harm of mechanical ventilation, improving the outcome of patients with ARF. This chapter discusses the mechanisms affecting the changes in gas exchange consequent to the prone position in patients with ARF, and the effects of prone positioning on outcome of critically ill patients.

EFFECTS OF PRONE POSITIONING ON GAS EXCHANGE

The effects of prone positioning on gas exchange may result from a combination of the following mechanisms: (a) changes in regional lung inflation, (b) redistribution of ventilation, and (c) redistribution of perfusion. These three mechanisms apply to both the normal and diseased lung. In the diseased lung, however, these mechanisms are also affected by the underlying pathology. Moreover, because the underlying pathology is an evolving process, it is likely that the effects of positioning on arterial oxygenation will vary with time.

Regional Lung Inflation

METHODS OF INVESTIGATION

Most of the studies dealing with regional lung inflation in normal subjects were performed with radioactive xenon.[4,5] We used computed tomography (CT) to quantify regional lung inflation.[6,7] The CT scan provides a computer-reconstructed image that is composed of several hundred elementary units (voxels). Each voxel is characterized by a given level of absorption of X-rays, which mainly reflects the density of the material being studied. The density is usually expressed in CT numbers or Hounsfield units (H).[8] A density equal to 0 H characterizes a voxel composed of water, while a voxel with a density of −1000 H is composed of gas. A voxel with a CT number equal to −500 H has a composition of 50% gas and 50% tissue. By analysis of the CT numbers, we quantitatively describe the regional lung inflation of a single CT section, at the level of the lung base, that is representative of the entire lung.[6] The CT section is divided into ten levels along the vertical axis, each level including approximately 300 to 400 voxels (Fig. 49-1). The gas-to-tissue ratio, which is our index of regional lung inflation, was computed from the average CT number at each lung level.

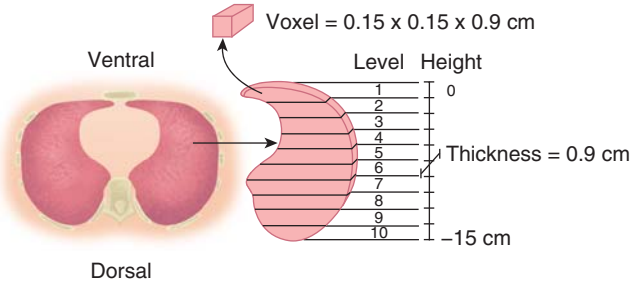

FIGURE 49-1 Regional analysis of the CT scan image. The vertical distance from ventral to dorsal surface (height) is divided into ten equal intervals. Ten lung levels are then obtained. Each level is composed of 300 to 400 elementary units (voxels), each characterized by a given CT number expressed in Hounsfield units (H). (Used, with permission, from Pelosi et al.[16])

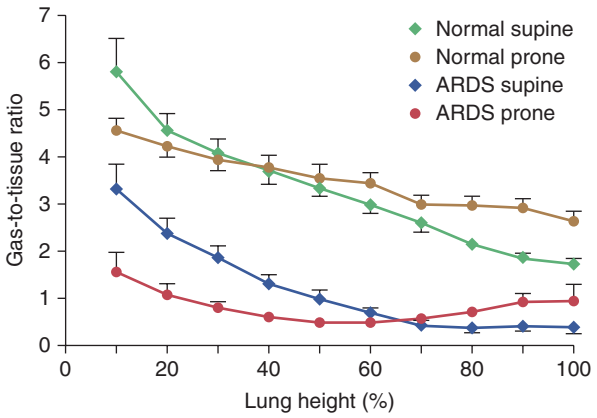

FIGURE 49-2 The gas-to-tissue ratio as a function of lung height in the supine (*diamonds*) and prone (*circles*) positions. The *green* and *brown* symbols refer to normal lungs ($N = 14$) and the *blue* and *red* symbols refer to lungs of patients with acute respiratory distress syndrome (*ARDS*) ($N = 20$). It is important to note that "height = 0" refers to the ventral surface in the supine position and to the dorsal surface in the prone position. The height scale direction is from nondependent (0) to dependent (100).

NORMAL LUNGS

Regional Inflation in the Supine Position. As shown in Figure 49-2, the regional inflation, expressed as the gas-to-tissue ratio, decreases along the vertical axis (from ventral to dorsal). Because the decrease is exponential, the rate of change of regional lung inflation with height may be characterized by a decay constant (K_d). The lower the value of the K_d, the higher the rate of the decrease of regional lung inflation along the vertical axis. The K_d in normal subjects is 13.6 ± 2.5 cm. At this distance from the ventral surface, the gas-to-tissue ratio is 37% of the gas-to-tissue ratio value computed at the ventral surface. In other words, the alveolar dimensions, in the dorsal regions, should be approximately one-third of those at the ventral surface.

Regional Inflation in the Prone Position. When a normal subject is shifted from supine to prone, the regional inflation distribution changes, increasing in the dorsal regions and decreasing in the ventral regions (see Fig. 49-2). The regional inflation decreases exponentially from dorsal to ventral for both supine and prone positions; however, the K_d is higher in the prone position compared with the supine position (K_d prone, 26.2 ± 2.2 cm; K_d supine, 13.6 ± 2.5 cm). This indicates that the regional inflation distribution is more homogeneous in the prone than in the supine position, and therefore the prone position does not simply reverse the regional inflation distribution. We confirmed these concepts in animal studies by means of CT scan.[9]

Mechanism of Vertical Inflation Gradient. The regional inflation is believed to depend on the local transpulmonary pressure (i.e., the absolute difference between pressure in the alveoli and pressure at the pleural surface [Ppl]). At functional residual capacity, alveolar pressure equals atmospheric pressure; thus, changes in transpulmonary pressure are caused by regional differences in Ppl. The Ppl gradient in normal subjects is approximately 0.2 to 0.3 cm H_2O/cm.[10] The nature of this pressure gradient, however, is still controversial and is mainly attributed to the following factors: (a) lung weight, (b) shape and mechanical properties of the chest wall, and (c) shape and mechanical properties of the lung.

The role of lung weight in normal subjects is considered a predominant mechanism by some investigators.[11–14] It was first stressed by Krueger et al,[15] who found that the normal Ppl gradient was very similar to the normal density of the lung (0.22 g/L). The lung-weight theory assumes that the lung behaves as a fluid and that the hydrostatic pressures are transmitted through the lung parenchyma as in a liquid (i.e., at a given lung height, the superimposed pressure [SP_L] is equal to the product of the height of the lung column and density). Estimating the SP_L with the CT scan, in normal subjects, we found an average SP_L gradient of 0.23 cm H_2O/cm,[16] which is similar to the Ppl gradient classically reported in physiology. Factors other than lung weight, however, may play a substantial role in determining Ppl. In fact, in the prone position, the decay of the regional inflation with height is less than in the supine position (i.e., the Ppl gradient is probably lower in the prone than in the supine position; see Fig. 49-2). If the SP_L was the only determinant of Ppl, the decay of the regional lung inflation would be similar in prone and supine positions. As shown in Figure 49-2, however, the regional inflation distribution, along the vertical axis, was different in the supine and prone positions. Our findings are in keeping with those of Mutoh et al[17] in normal dogs, in which the Ppl gradient was directly measured. Factors such as the thoracic lung shape and compliance should then be involved in determining the regional inflation changes with positioning. In addition, the prone position eliminates the compression of the lungs by the heart, which also contributes to a more homogeneous distribution of lung inflation.[18,19]

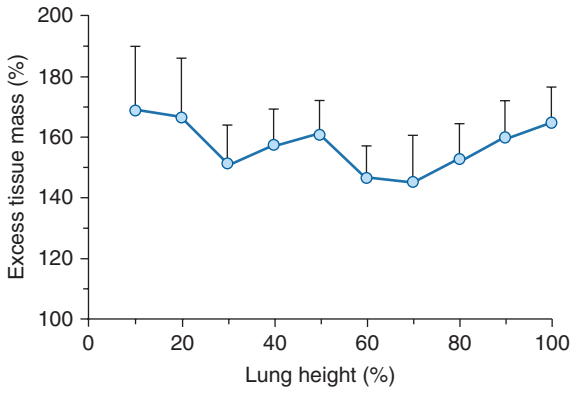

FIGURE 49-3 The distribution of excess tissue mass (i.e., the mass in excess of the expected normal mass) as a function of lung height. Data refer to thirty-four ARF lungs studied in the supine position. Zero on the abscissa refers to the ventral lung surface. (Used, with permission, from Gattinoni et al.[51])

LUNGS IN ACUTE RESPIRATORY FAILURE

Anatomic Changes during Acute Respiratory Failure. The early phases of ARF are characterized by lung edema. The edema causes a large increase in "lung tissue" and therefore in lung weight. In ARF patients, we found that lung weight, as measured by the CT scan technique, was two to three times greater than normal,[20] and this is consistent with the lung weight values reported in autopsy series.[21] We also found that edema (i.e., the amount of tissue mass in excess of normal [excess tissue mass]) does not accumulate preferentially in the dependent regions, and it is quite evenly distributed at each lung level (Fig. 49-3). The nongravitational distribution of edema was reported in a series of animal experiments using different techniques.[22,23] This homogeneous increase in lung edema has two important consequences for regional inflation. First, although ARF is characterized by a marked decrease in lung gas volume,[20] the total lung dimensions are similar to normal secondary to the increase in lung tissue mass (edema).[16] Second, the increased lung tissue mass leads to a dramatic increase in SP_L, which may be as high as 10 to 15 cm H_2O in the most dependent regions.[6,7,16]

Regional Inflation in the Supine Position. Figure 49-2 shows the behavior of regional inflation in patients with ARF in the supine position. As in the normal lung, the regional inflation decreases exponentially along the ventral–dorsal axis.[16] Two important differences, however, must be stressed. First, the regional inflation at the ventral surface is only half that of the normal lung. Second, the decay constant in the regional inflation with height (K_d) is almost half that of normal; that is, the rate of the decrease of regional inflation from the ventral to dorsal region is double that of the normal lung (K_d ARF = 6.9 ± 1.2 cm vs. K_d normal = 13.6 ± 2.5 cm). This suggests that in supine ARF patients at 0 cm H_2O positive end-expiratory pressure (PEEP), there is almost total alveolar collapse in the posterior half of their lungs, as confirmed by the CT scan image (Fig. 49-4).

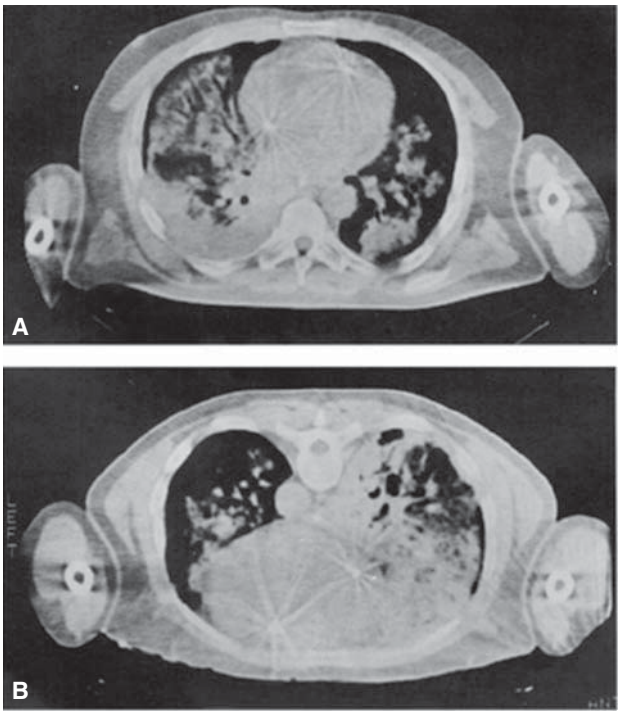

FIGURE 49-4 A representative CT scan image in supine (**A**) and in prone (**B**) positions. Note the typical redistribution of lung densities. Images taken 10 minutes apart, and at end-expiration apnea, with 10 cm H_2O PEEP. (Used, with permission, from Gattinoni et al.[6])

Regional Inflation in the Prone Position. Figure 49-2 shows the behavior of regional inflation in the prone position. As with normal subjects, the inflation gradient is reversed, and the regional inflation is greater in dorsal regions and lower in ventral regions. Once again, the dependent lung regions (ventral) are collapsed (see Fig. 49-4). As with normal subjects, regional inflation is more homogeneously distributed than in the supine position; however, exponential fitting of the experimental data did not reach a level of significance in all patients.

Mechanism of Vertical Inflation Gradient. The main difference in regional inflation between normal subjects and patients with ARF is the greater rate of decrease of regional inflation along the vertical axis in ARF lungs. This suggests that the Ppl gradient is higher in patients with ARF than in normal individuals.[16] The most likely explanation of the increased Ppl in ARF is increased lung weight; the overall lung shape, in fact, is not different between normal individuals and patients with ARF.[16] The thoracic–lung shape modifications when the patients are turned prone, however, probably change the Ppl gradient (i.e., the modifications of the lung and the chest wall shape may redistribute the forces acting at the pleural surface).

The relationships between lung shape modifications and distribution of regional lung inflation in ARF patients is discussed in "Mechanisms Involved in Arterial Oxygenation Changes in the Prone Position" below.

SUMMARY

In patients with ARF, lung densities redistribute from the dorsal to the ventral region when turned prone. Regional inflation decreases exponentially from the nondependent to the dependent lung region in both the supine and prone positions. The decay in regional inflation, both in normal individuals and in patients with ARF, is greater in the supine than in the prone position. This indicates that regional inflation is usually more homogeneously distributed in the prone position. The regional inflation gradient is secondary to the Ppl gradient. Lung weight is probably a major determinant in increasing the Ppl gradient in ARF. Thoracic–lung shape modifications from supine to prone, however, may produce a more homogeneous distribution of regional inflation in the prone position.

Distribution of Ventilation

As a general rule, ventilation relates to applied pressures, flows, and resistances according to the following equation:

$$DV = C \times (DP_{tp} - \dot{V} \times R)$$

where DV is variation in volume, C is compliance, DP_{tp} is transpulmonary pressure, $\dot{V}$ is flow, and R is resistance. It follows that regional ventilation depends on regional compliances, regional transpulmonary pressure swings, regional flow rates, and regional resistances.

NORMAL LUNGS

Distribution of Ventilation in the Supine Position. When a bolus of radioactive gas is inhaled by spontaneously breathing subjects in the supine position, ventilation is predominantly distributed to the dependent lung regions.[24] From available data, the major determinants of the distribution of ventilation appear to be: (a) the regional inflation distribution and (b) the pattern of diaphragmatic movement (active or passive).

Mead et al,[25] Otis et al,[26] and Pedley et al[27] proposed a lung model divided into two compartments: upper and lower. Regional inflation is greater in the upper (ventral) compartment and smaller in the lower (dorsal) compartment. The upper lung regions are closer to the flat portion of their pressure–volume curve, while the lower regions are on the steeper portion of the curve. Consequently, for a given applied pressure, ventilation is greater in the lower lung regions than in the upper regions.

In the supine position, a large portion of the lung is close to the diaphragm, which may vary its tension, shape, and position. During tidal spontaneous breathing, there is a greater displacement of the dependent hemidiaphragm, with consequent greater ventilation of the dependent lung.[28–30] Accordingly, in spontaneously breathing subjects, both regional inflation and diaphragmatic movement cooperate to distribute ventilation preferentially to the dependent lung. There are, however, three major conditions in which the ventilation is greater in the nondependent lung: (a) ventilation at low lung volume, (b) ventilation at high inspiratory flow rate, and (c) mechanical ventilation during anesthesia and muscle paralysis. The preferential ventilation of the upper compartment at a low lung volume is easily explained by the work of Otis et al[26] (i.e., at a low lung volume, the upper lung regions are probably shifted on the steeper part of the pressure–volume curve). At a high inspiratory flow rate, the accessory respiratory muscles appear to play a determining role in the redistribution of ventilation to the upper compartment.[31,32] During mechanical ventilation, particularly during anesthesia and paralysis, the diaphragm appears to play a major role in the distribution of ventilation.[33–35] In this situation, the diaphragm behaves as a flaccid membrane, which is faced with the vertical pressure gradient of the abdominal contents. The upper, nondependent part of the diaphragm moves passively and faces a lower abdominal pressure; thus, ventilation is greater in the nondependent lung regions.

Distribution of Ventilation in the Prone Position. Distribution of ventilation in prone position is still controversial. Indeed, some authors found a uniform vertical distribution of ventilation in spontaneously breathing subjects,[36] whereas others found a vertical gradient with either greater ventilation in the dependent (ventral) regions[4] or in the nondependent lung regions.[37]

No data are available concerning ventilation at low lung volumes or at a high inspiratory flow rate in the prone position. During mechanical ventilation in anesthetized paralyzed normal individuals in the prone position, Rehder et al[37] found that the distribution of ventilation was greater in the nondependent lung regions, where the passive upper position of the diaphragm faced a lower abdominal pressure.

Recently, in an animal study, we confirmed that the distribution of ventilation in the prone position is more homogeneous than in the supine position, and that in the prone position there is less lung strain once tidal volume is delivered.[9]

LUNGS IN ACUTE RESPIRATORY FAILURE

Distribution of Ventilation in the Supine Position. CT scan studies in patients with ARF have shown that ventilation is distributed preferentially to the nondependent lung because the dependent lung is usually collapsed and/or consolidated (see Fig. 49-4). We obtained CT scans at both end-expiration and end-inspiration in ten patients during the early phase of ARF.[38] In these patients, we, indeed, found that "ventilation" was preferentially distributed to the nondependent (ventral) lung regions. The pattern was in part modified by application of PEEP. With an increase in PEEP and reopening of the dependent lung regions, "ventilation" was more uniformly distributed (gas could reach the recruited dependent regions).

Distribution of Ventilation in the Prone Position. Few data have been published on the distribution of ventilation in patients with ARF placed in the prone position. Because regional inflation is more uniform in the prone position, similarly to the pattern in normal lungs, however, one would expect that ventilation should be more uniform in this posture. Vieillard-Baron et al showed that the prone position does improve homogenization of tidal ventilation by reducing time-constant inequalities.[39]

SUMMARY

In spontaneously breathing normal subjects, when supine, ventilation is preferentially distributed to the dependent lung regions, although prone position data are controversial. During mechanical ventilation, this pattern is reversed with preferential distribution of ventilation to the nondependent lung in both supine and prone positions. Accordingly, the main determinant of ventilation distribution is the regional inflation gradient and transdiaphragmatic pressures. In mechanically ventilated patients with ARF at low PEEP level, ventilation is preferentially distributed to the nondependent lung regions. In the prone position, we expect a similar pattern of ventilation distribution, because the collapsed areas move from the dorsal to the ventral regions. Tidal volume, however, is more homogeneously distributed in the prone position, because of a reduction in the slow compartment zones of the lung, and possibly because of a more homogeneous distribution of regional inflation.

Distribution of Perfusion

NORMAL LUNGS

Distribution of Perfusion in the Supine Position. The most widely accepted model that describes the pulmonary perfusion pattern is that described by West et al.[40] According to these investigators, the relationship between blood flow and pulmonary artery pressure, alveolar pressure, and venous pressure can be modeled as in a Starling resistor, where a collapsible tube traverses a closed chamber (the gas compartment) in which pressure (the alveolar pressure) may be varied at will. When the inflow pressure (pulmonary artery pressure) is lower than the chamber pressure (alveolar pressure), blood flow stops (zone 1). When the inflow pressure is higher than the chamber pressure, the flow through the system is governed by either the difference between pulmonary artery pressure and alveolar pressure (zone 2) or the difference between pulmonary artery pressure and venous pressure, when the outflow pressure (venous pressure) exceeds the chamber pressure (zone 3).

According to this "gravitational" view, perfusion should progressively increase down the lung. In the supine position, the lung should be characterized by perfusion in zone 2 and zone 3, increasing from ventral (zone 2) to dorsal (zone 3), because zone 1 conditions do not occur. Several authors, suggesting that factors other than gravity can determine the perfusion heterogeneity, have challenged the model of West et al.[41–45]

Distribution of Perfusion in the Prone Position. According to the gravitational theory, a perfusion gradient should exist from dorsal to ventral. Few data confirm this pattern in human subjects.[4] A perfusion gradient, however, could not be observed in the prone position in dogs;[44,46] regional pulmonary blood flows were positively correlated when measured in supine and prone position (and not negatively correlated, as expected according to the gravitational theory).

LUNGS IN ACUTE RESPIRATORY FAILURE

Distribution of Perfusion in the Supine Position. Whatever the determinants of perfusion in the normal lung, several physiologic and anatomic factors are likely to alter the perfusion distribution in ARF. Among these are (a) hypoxic vasoconstriction, (b) vessel obliteration, and (c) extrinsic vessel compression.

The effects of hypoxic vasoconstriction were evaluated in the lateral position using separate lung ventilation.[47] The inspiration of a hypoxic gas mixture by the dependent lung failed to redirect blood flow toward the nondependent lung, whereas diversion occurred in the supine position. This suggests that hypoxic vasoconstriction alone is not able to counteract the effects of posture on pulmonary blood flow.

Both macrothrombi and microthrombi have been found at various stages of ARF.[48] These anatomic alterations were associated with the appearance of filling defects when selective angiography was performed.[49] Unfortunately, data are not available regarding the distribution of these defects (homogeneous, dependent, or nondependent?), but obviously the presence of vessel obliteration will alter perfusion distribution. Nonthrombotic obliterative vascular disease may also occur in the early stage of ARF secondary to congestion or compression of vessels, and in the intermediate or late stages of ARF secondary to focal obstruction of small arteries and veins as a result of fibrosis.

Increased SP_L in ARF could also cause extrinsic vessel compression: The radiologic equivalent would be the "pruning" of vessels on selective angiography. In early ARF, we found (unpublished observation) that selective angiography was usually positive (filling defects and/or pruning) when the tip of the catheter was positioned in the dependent lung regions (dense areas on CT scan), and negative when it was in the nondependent lung regions. Moreover, we occasionally found changes in the selective angiography findings (from positive to negative) when the patients were turned from supine to prone, and the angiography was repeated in the same lung region.

All these data suggest that the pulmonary flow distribution is altered in ARF. If the compression mechanism and hypoxic vasoconstriction are operating, both should act mainly in the dependent lung regions (less aeration and higher SP_L), and the blood flow should partly be diverted toward the nondependent regions, as observed in cardiogenic pulmonary

edema.[50] This would partly protect against hypoxemia. In fact, it is not unusual to find 60% to 70% of airless lung (in the dependent regions) with a shunt fraction of 30% to 40%.[51] This indirectly proves that, in the supine position, part of the pulmonary blood flow is redistributed to the nondependent lung.

Distribution of Perfusion in the Prone Position. To our knowledge, few data are available regarding the distribution of pulmonary blood flow in patients with ARF mechanically ventilated in the prone position. Experimental evidence in dogs suggests that perfusion to the dorsal regions is greater than to the ventral regions in the prone position.[46] This occurrence might lead to a more even distribution of blood flow.[52] Endogenous nitric oxide plays a role in the regulation of regional pulmonary perfusion. In fact, after the inhibition of nitric oxide synthase by N(G)-monomethyl-L-arginine infusion, nitric oxide synthase messenger RNA expression and nitric oxide production were significantly higher in dorsal region as compared with ventral lung regions. In the supine position, lung perfusion was shifted to ventral regions during nitric oxide synthase inhibition, whereas in the prone position lung perfusion remained unchanged.[53] Moreover, acute changes of oxygenation consequent to positioning in patients with acute respiratory distress syndrome (ARDS) do not induce any short-term effect on pulmonary endothelin-1 net clearance or angiotensin-II net formation.[54] These data suggest that mechanisms other than gravity or hypoxic pulmonary vasoconstriction operate in the prone position to distribute blood flow.

SUMMARY

In the normal lung, blood flow is distributed according to gravity. Factors other than gravity, however, may play a role in governing regional perfusion. These factors seem prevalent in the prone position, where the vertical perfusion gradient may disappear. In the edematous ARF lung, available data suggest that pulmonary blood flow is partly diverted toward the nondependent, more aerated, regions. Vessel compression and hypoxic vasoconstriction may play a role in this pattern of blood flow distribution. In the prone position, during ARF, the nondependent, dorsal regions seem more perfused than the ventral regions. Consequently, in ARF, perfusion seems less dependent on gravity than in normal conditions.

Ventilation–Perfusion Matching

In the past, a number of investigators have used the multiple inert gas technique to study ventilation–perfusion ($\dot{V}_A/\dot{Q}$) relationships in different forms of ARF.[55–57] The general conclusions of these studies can be summarized as follows: although ventilation and perfusion are usually well matched in ARF lungs, a consistent portion of pulmonary flow traverses airless regions (true shunt), and low $\dot{V}_A/\dot{Q}$ compartments are scarcely represented.

The effect of prone positioning on regional shunt and aeration was studied in an animal model of acute lung injury using $^{13}N_2$ injection and positron emission tomography.[58] This study confirmed that supine position is associated with a high shunt fraction in the dorsal region (i.e., high perfusion and poor aeration), whereas prone positioning leads to a decrease of shunt fraction in the dorsal region, without a concomitant impairment of gas exchange in the ventral region. These effects were related to an increase in total gas content and a more uniform distribution of aeration in the prone position, because the increase in aeration in the dorsal region was not offset by loss of aeration in the ventral region. Moreover, in the prone position, perfusion resulted in less gravity dependence, because a substantial fraction of pulmonary blood flow was maintained in the dorsal region. In summary, this study demonstrated that prone positioning restores aeration while it preserves perfusion in the dorsal region of the lung, decreasing the regional and total shunt secondary to an increase in gas-exchanging pulmonary blood flow.

EFFECT OF PRONE POSITIONING ON CLINICAL OUTCOME OF PATIENTS WITH ACUTE RESPIRATORY FAILURE

Effects on Arterial Oxygenation

Over the last 35 years a series of reports appeared in the literature dealing with the use of the prone position as a tool to improve arterial oxygenation in patients with ARF. Over the years, several clinical studies on prone positioning have been conducted, including many retrospective studies,[1,3,59,60] prospective observational studies,[6,39,61–76] randomized clinical trials,[77–81] and meta-analyses.[82–86]

From these published data some generalizations may be made.

1. There is strong evidence that prone positioning is effective in improving oxygenation of patients with ARF. For this beneficial effect, the use of prone positioning is currently considered in the treatment of patient requiring injurious levels of fractional inspired oxygen concentration ($F_{I_{O_2}}$) and plateau pressure[87] or as a "rescue maneuver" for life-threatening hypoxemia. It must be pointed out, however, that (a) the degree of improvement is highly variable (from a few to hundreds of millimeters of mercury change in partial pressure of arterial oxygen (Pa_{O_2}), (b) a small fraction of patients do not show any improvement or even show a deterioration in arterial oxygenation while prone, and (c) the individual response to the prone position is hard to predict.
2. In the patients who respond, the improvement in gas exchange is usually progressive, and it may take hours to appear; moreover, some of these patients show a progressive decrease in arterial oxygenation if the prone position is maintained for long periods of time.

Thus, the long-term response to the prone position ranges from deterioration to great improvement, and it may be time dependent (slow improvement and slow deterioration).

3. The issue is further complicated when analyzing the effects of returning the patients to the supine position after they have been prone. Three different responses have been observed in patients who exhibited improved oxygenation in the prone position: (a) most of the patients display better oxygenation than in the original supine position, although the values are lower than in the prone position; (b) some patients return to basal supine oxygenation values when returned to the supine position (these patients are then considered "prone dependent"); and (c) some patients display improved oxygenation compared to both the previous supine and prone values.
4. When the same patient is turned several times, the effects of the maneuver may change in time (no improvement, whereas previous positioning in the prone position produced marked improvement or the reverse).

From the above description, it is obvious that the effects of positioning depend on the individual patient (i.e., the underlying pathology and pathophysiologic status, which may vary over time). Over the years, several authors have described the response to prone position in specific categories of ARDS[67,75] and patients without ARDS[76,88] and the improvement in oxygenation induced by inhaled nitric oxide.[61,62,64,65,70,74] The predictability of the oxygenation response to prone positioning, however, remains uncertain.[71]

MECHANISMS INVOLVED IN ARTERIAL OXYGENATION CHANGES IN THE PRONE POSITION

We can attempt to infer the mechanisms involved in arterial oxygenation changes when patients are turned to the prone position. We first discuss the mechanisms that may operate in the early period after positioning and then the mechanisms that are possibly time related.

Early Effects. An increase or decrease in Pa_{O_2} is caused by changes in regional lung inflation, ventilation distribution, and perfusion distribution. The effects on oxygenation (improvement or deterioration) are likely explained by a varying interaction between the mentioned factors in the different postures.

As previously discussed in the section "Regional Lung Inflation" regional inflation decreases from ventral to dorsal in the supine position, and from dorsal to ventral in the prone position. The rate of decrease in regional inflation, however, is steeper in the supine position than in the prone position (see Fig. 49-2). Because the decrease in inflation may be expressed in exponential form, this is equivalent to saying that the decay rate of regional inflation along the vertical axis (K_d) is lower in the supine position than in the prone position. This, however, refers to average values. In an individual patient, the pattern may be substantially different.

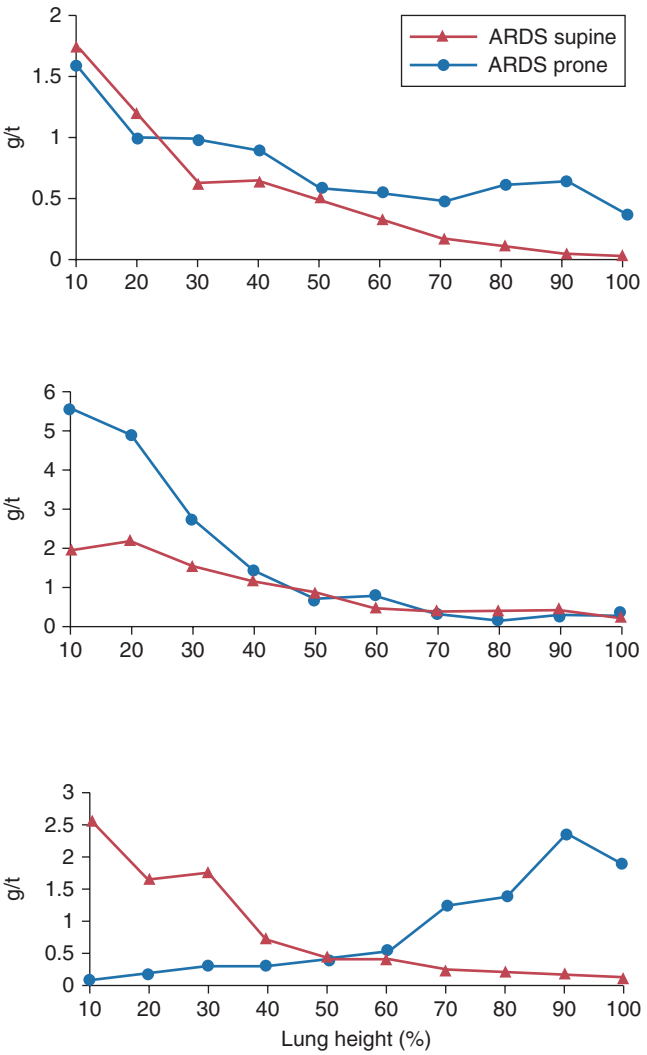

FIGURE 49-5 Different behaviors of regional inflation (gas-to-tissue ratio [*g/t*]) as a function of lung height in the supine (*red triangles*) and prone (*blue circles*) positions in three acute respiratory distress syndrome (*ARDS*) patients. Zero on the height scale refers to the ventral lung surface in the supine position and to the dorsal lung surface in the prone position. As such, the direction of the lung scale is always from the nondependent to dependent lung region (see text for further explanation).

In Figure 49-5, we report three ARDS patients who showed different patterns of regional inflation in the supine and prone positions. In the first patient (*upper panel*), regional inflation behaves as for the average population (see Fig. 49-2). The exponential fitting of the decay of regional inflation ($r = 0.91$) showed a K_d of 4.2 cm in the supine position. In the prone position, the decay of regional inflation was smoother, as reflected by the higher value of K_d, 14 cm (exponential fitting, $r = 0.97$). In this patient, Pa_{O_2} improved by 65 mm Hg on moving from the supine to the prone position.

The *middle panel* in Figure 49-5 shows the regional inflation pattern of a patient in which the decay of regional

inflation was significant in both the supine and prone positions ($r = 0.96$ and $r = 0.98$, respectively). In this case, however, K_d was lower in the prone position than in the supine position (4.3 and 9.4 cm, respectively). In this case, Pa_{O_2} deteriorated when the patient was turned from supine to prone (101 mm Hg when supine and 71.5 mm Hg when prone).

The *bottom panel* in Figure 49-5 refers to a very unusual patient. In this case, the low regional inflation areas in the supine position did not redistribute on switching to the prone position, and the pattern of regional inflation remained the same in the two positions. In this case, Pa_{O_2} did not change with alteration in position (61 mm Hg when supine and 68 mm Hg when prone).

We then tested the hypothesis that, in the individual patient, improvement in Pa_{O_2} on switching from supine to prone occurs when the decay in regional inflation is smoother (i.e., a higher K_d) in the prone position, whereas a deterioration in Pa_{O_2} occurs on switching from the supine to the prone position when the decay in regional lung inflation is steeper in the prone position (lower K_d). Plotting the individual K_d differences between prone and supine positions (DK_d) and the individual changes in Pa_{O_2} (DPa_{O_2}), we found a significant correlation between DK_d and DPa_{O_2} (Fig. 49-6). This suggests that the response in Pa_{O_2} is associated with a change in regional inflation: The position in which regional inflation is more homogeneous (higher K_d) is associated with a better Pa_{O_2}. When the regional inflation gradient along the vertical axis does not differ between the prone and supine positions (i.e., equal decrease from nondependent to dependent lung regions, whatever position is assumed), the Pa_{O_2} does not change. To state that the Pa_{O_2} changes are caused by regional inflation changes and not simply associated with them, however, we must assume that (a) ventilation behaves like regional inflation (i.e., it is more homogeneously distributed when inflation is more homogeneously distributed), and (b) perfusion is not changed when the position is changed (i.e., the relative perfusion of the dorsal and ventral regions does not change with position).

The question remains as to why in some patients regional inflation is more homogeneous in the prone position (and oxygenation improves in this position), while in other patients regional inflation is more homogeneous in the supine position (and oxygenation is better in this position). As previously discussed, regional inflation is dictated by Ppl, and this may, in turn, be influenced by SP_L and lung shape. Because SP_L is similar in the supine and prone positions,[6] it is possible that the postural changes in regional inflation are caused by the associated lung-shape variations. We attempted to quantify the variation in lung shape on switching from the supine to the prone position by dividing the lung area into two compartments (at 50% of the ventral–dorsal distance), the upper (U) and the lower (L) compartments, and calculating the upper-to-lower (U/L) ratio in the prone and supine positions. The difference in U/L ratio between the prone and supine positions (DU/L ratio) gives a quantitative estimate of lung-shape change. For example, when the DU/L ratio is zero, lung shape is unmodified, and the greater the DU/L ratio, the greater the upper compartment is in the prone position. We found that the DU/L ratio significantly correlated with both DK_d (Fig. 49-7) and DPa_{O_2} (Fig. 49-8).

This indicates that, when the U/L ratio is much lower in the supine position and much higher in the prone position, oxygenation will improve in the prone position. Consequently, we suggest that, according to these data, lung-shape modifications, as well as the modifications in regional inflation, may be predictive, in individual patients, of the early effects of positioning on arterial oxygenation.

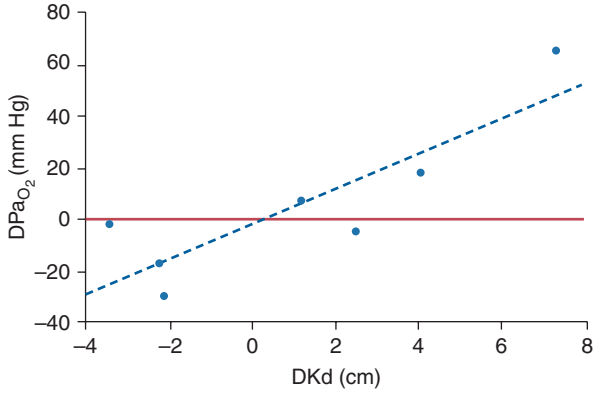

FIGURE 49-6 Relationship between changes in Pa_{O_2} (DPa_{O_2}) and changes in the regional lung decay constants (DK_d) between the prone and supine positions. Data are from seven patients with ARF (regional inflation was computed as weighted mean of the two lungs). Positive values of DPa_{O_2} indicate that the Pa_{O_2} is higher in the prone position, while negative Pa_{O_2} values indicate that Pa_{O_2} is higher in the supine position. When DK_d is close to zero (i.e., the decrease of regional inflation is similar in the prone and supine positions), the DPa_{O_2} is close to zero ($DPa_{O_2} = -1.7 + 6.6 \times DK_d$; $r = 0.86$; $P < .05$).

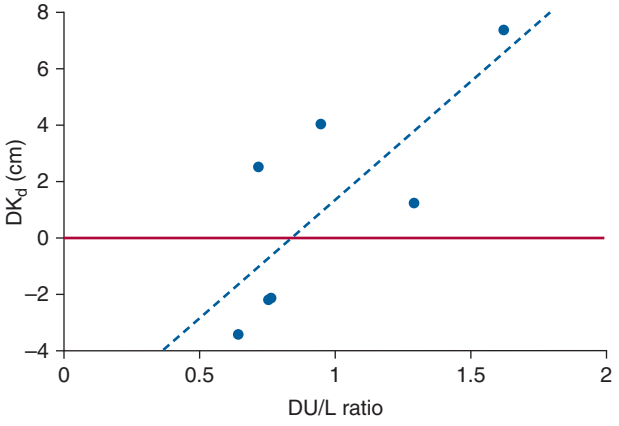

FIGURE 49-7 Changes in the regional lung inflation decay constants (DK_d) as a function of the changes of upper-to-lower lung ratio (*DU/L* ratio) between the prone and supine positions. ($DK_d = -7 + 8.3 \times$ DU/L ratio; $r = 0.77$; $P < .05$).

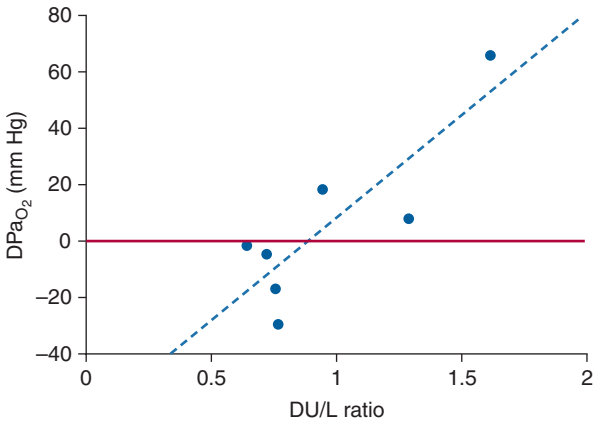

FIGURE 49-8 DPa_{O_2} as a function of the changes in upper-to-lower lung ratio (DU/L ratio) between the prone and supine positions ($DPa_{O_2} = -63 + 71.2 \times$ DU/L ratio; $r = 0.85$; $P < .05$).

Late Effects. When the positioning maneuvers are prolonged over time or are repeated several times during the course of ARF, the oxygenation response may be highly variable. No data are available with which to speculate on the possible mechanisms. We know, however, that with time edema may redistribute, lung pathology may progress from edema to fibrosis, and vascular characteristics may change. Further studies are needed to understand the time-related effects of positioning on arterial oxygenation.

Effects on Arterial CO_2. Recently there has been a paradigmatic shift of attention from changes in Pa_{O_2} to changes in partial pressure of arterial carbon dioxide (Pa_{CO_2}) consequent to prone positioning in patients with ARF. According to Pa_{CO_2} change, patients may be divided into two categories: those who show a decrease of Pa_{CO_2} secondary to prone position, and those whose Pa_{CO_2} does not change or even increases.

Before discussing the meaning of Pa_{CO_2} change, it is worth remembering that expected changes in Pa_{CO_2} are relatively smaller than changes in Pa_{O_2} because of the different slopes of the content/tension relationship. For a similar change in content, the change in tension of CO_2 (partial pressure of the gas) is expected to be approximately 12% of the change in Pa_{O_2}. This would result, for instance, in a change in Pa_{O_2} of 5 mm Hg versus a change in P_{O_2} of 40 mm Hg, implying not only more controlled measurements, but also greater accuracy.

That Pa_{CO_2} increases during the course of ARDS, in association with structural changes of the lung, has been known for many years.[77,78] Kallet et al found that an increase in dead space is a prognostic marker of ARDS mortality.[89]

We found that patients who display a decrease in Pa_{CO_2} in the prone position experience a greater survival (dose dependent) than do patients who do not show a decrease, or even show an increase in Pa_{CO_2}.[90] Moreover, we recently reported the decrease in Pa_{CO_2} during prone ventilation is associated with a higher lung recruitability as measured with CT scan.[91] Accordingly, the Pa_{CO_2} response to prone positioning may be associated to the underlying pathology: predominant recruitment in Pa_{CO_2} responders versus blood-flow diversion in nonresponders. Interestingly, only the changes in Pa_{CO_2} were associated with survival in this study, not the changes in Pa_{O_2}.

The Impact of Prone Positioning on Mortality

RATIONALE

Since the first report dating back to the 1970s,[1–3] the prone position has been proposed and used to improve oxygenation. The progressive recognition of the mechanism underlying this effect, however, led to the hypothesis that the prone position may decrease the danger associated with mechanical ventilation (ventilator-induced lung injury).[92] The hypothesis is based primarily on the observation that in the prone position there is a more homogeneous distribution of inflation, suggesting indirectly a more homogeneous distribution of stress and strain, which are likely the first triggers of ventilator-induced lung injury. In fact, in several animal models, it has been shown that the prone position decreases ventilator-induced lung injury or at least delays its progression.[9,93,94] CT scan studies in animals documented a decrease in regional strain in the prone as compared with the supine position.[9] Indeed, the possible favorable effects of prone positioning on outcome of patients with ARF should not be related to oxygenation changes, which were not found to be associated with outcome, but, instead, to changes in regional lung mechanics, by which forces applied by the ventilator should be more evenly distributed throughout the lung parenchyma.

RANDOMIZED CLINICAL TRIALS ON PRONE POSITIONING

To date, four major randomized, controlled trials (RCTs) have addressed the effect of prone positioning on outcome of adult patients with hypoxemic ARF.[77–80] Other minor published trials will not be discussed here, because they were characterized by major limitations (e.g., small sample size, inclusion criteria other than adult hypoxemic respiratory failure, application of prone positioning for less than 48 hours, patients cotreated with nonconventional ventilator modalities, and so on).[76,81,95–100] Table 49-1 lists the main characteristics of the four largest published trials. As shown, these trials exhibit large variations in term of enrollment criteria (acute lung injury or ARDS vs. hypoxemic respiratory failure vs. ARDS only), intensity of intervention ("early phase strategy" in the trials published earlier vs. "prolonged strategy" in the latest trials), and use of relevant cointervention (i.e., protective mechanical ventilation strategy). Despite the incorporation of the successively acquired scientific evidence into the newer protocols, none of these trials showed any benefit of prone positioning on the mortality of the general population of patients with

TABLE 49-1: CHARACTERISTICS OF THE LARGEST RANDOMIZED, CONTROLLED TRIALS INVESTIGATING THE EFFECT OF PRONE POSITIONING ON THE OUTCOME OF PATIENTS WITH HYPOXEMIC ACUTE RESPIRATORY FAILURE

	Taccone et al[80]	Mancebo et al[79]	Guérin et al[78]	Gattinoni et al[77]
Patients (n)	344	142	802	304
Enrollment period (years)	2004 to 2008	1998 to 2002	1998 to 2002	1996 to 1999
Enrollment criteria	ARDS with PEEP ≥5 cm H_2O	ARDS with four-quadrant infiltrates on CXR	Hypoxemic acute respiratory failure (413 ALI/ARDS pts)	ALI/ARDS with PEEP ≥5 cm H_2O
Stratified randomization for ARDS severity	Yes	No	No	No
Time after meeting enrollment criteria	<72 hours	<48 hours	>12 to 24 hours	Not prespecified
Last follow-up	6 months	Hospital discharge	90 days	6 months
Planned duration of prone positioning (average)	20 hours/day for 28 days	20 hours/day until weaning criteria	≥8 hours/day until weaning criteria	6 hours/day for 10 days
Actual duration of prone positioning (average)	18 hours for 8.3 days	17 hours for 10.1 days	9 h for 4.1 days	7 hours for 4.7 days
Protective mechanical ventilation	Yes (V_T ≤8 mL/kg of PBW)	Yes (V_T ≤10 mL/kg of PBW or ABW)	No	No
Trial ended early	No	No	Yes (slow enrollment)	Yes (slow enrollment)

Abbreviations: ABW, actual body weight; *ALI*, acute lung injury; *ARDS*, acute respiratory distress syndrome; *CXR*, chest X-ray; *PBW*, predicted body weight; *PEEP*, positive end-expiratory pressure; V_T, tidal volume.

acute lung injury or ARDS. In a post hoc analysis, however, of one of the first RCTs evaluating prone positioning,[77] we reported a reduction in 10-day mortality in the subgroup of patients with severe hypoxemia or with higher severity of illness. This finding was reinforced in the most recent RCT,[80] where the subgroup of patients with the most severe ARDS (stratified at randomization according a Pa_{O_2}/FI_{O_2} below 100) exhibited a trend toward a reduction in absolute 6-month mortality in the treatment arm of approximately 10%, a signal that did not reach statistical significance because of the small number of patients included in this subgroup. Notably, patients treated with prolonged prone ventilation demonstrated an increase in the rate of adverse events in this study (e.g., dislodgment of chest tube or endotracheal tube, desaturation, need for increased sedation and muscle relaxants, hypotension, or arrhythmias).

META-ANALYSES ON PRONE POSITIONING

A major limitation of the reported RCTs on prone positioning is the relatively small sample size, which could result in an underpowered study, particularly in the case of subgroup analysis. Because of the low incidence of ARDS, especially in its most severe form, several years of data collection are required, which prolongs the time needed to conduct an RCT on prone positioning.[101] Consequently, several meta-analyses have been performed to evaluate the effect of prone positioning in a larger population of patients.[82,84–86,102] Of note, most of these meta-analyses were conducted on a study level, reporting inconclusive results on primary and secondary outcomes in the unselected population of patients with hypoxemic ARF. This kind of meta-analysis, however, does not permit any subgroup stratification, whereas the body of knowledge derived from RCTs clearly suggests that prone positioning could be beneficial only in the subset of the most severely ill patients. To overcome this issue, two meta-analyses[83,103] with different trial inclusion criteria, have been conducted at a patient level, in collaboration with prone trialists, to determine whether prone positioning has a different impact on mortality depending on the extent of hypoxemia. In both of these studies, a threshold of Pa_{O_2}-to-FI_{O_2} ratio of 100 mm Hg was chosen, in line with the most recently published RCT.[80] Both meta-analyses support the hypothesis that prone positioning decreases mortality of patients with severe hypoxemia, whereas it has no beneficial effect in patients with less-severe hypoxemia (Fig. 49-9). Interestingly, a post hoc analysis using varying Pa_{O_2}-to-FI_{O_2} thresholds suggested improved mortality in the most severely hypoxemic group, using a Pa_{O_2}-to-FI_{O_2} ratio of up to 140 mm Hg to define this subgroup.[83]

We speculate that patients with severely hypoxemic ARDS derive benefit from prone positioning because it is only this subgroup of patients who have the physiologic prerequisites for prone positioning to work: They have a greater amount of edema, more widespread alveolar collapse, and higher lung recruitability.[104] In fact, the benefit of prone positioning on the respiratory system is greater recruitment of the dorsal region, which could lead a more homogeneous distribution of the stress and strain forces of mechanical ventilation, potentially decreasing the risk of alveolar injury by mechanical ventilation. This phenomenon is best observed when the aerated portion of the lung is small and when lung recruitability is high.[105]

Summary

The evidence derived from RCTs and recent meta-analyses clearly indicate that prone positioning should not be

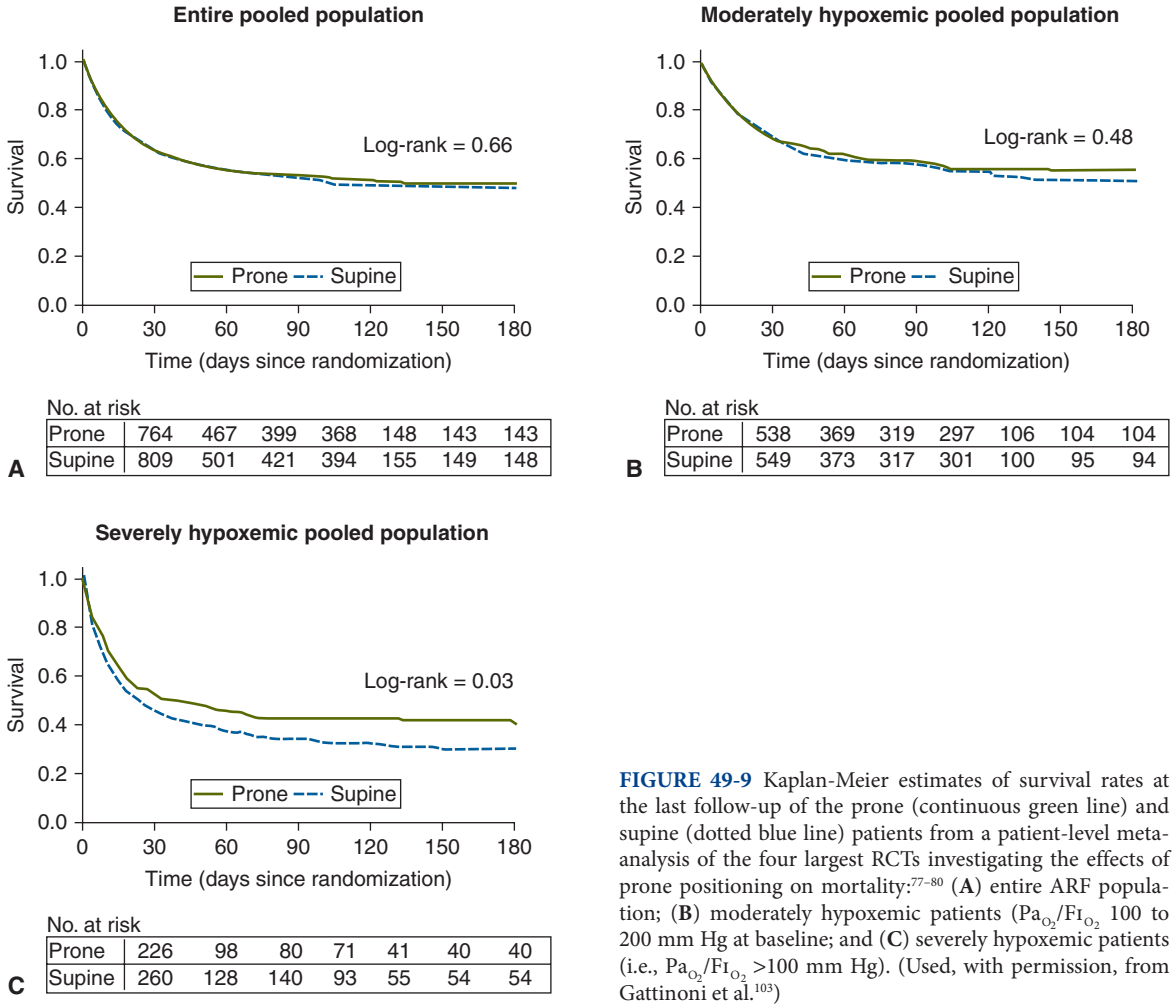

FIGURE 49-9 Kaplan-Meier estimates of survival rates at the last follow-up of the prone (continuous green line) and supine (dotted blue line) patients from a patient-level meta-analysis of the four largest RCTs investigating the effects of prone positioning on mortality:[77–80] (**A**) entire ARF population; (**B**) moderately hypoxemic patients (Pa_{O_2}/FI_{O_2} 100 to 200 mm Hg at baseline; and (**C**) severely hypoxemic patients (i.e., Pa_{O_2}/FI_{O_2} >100 mm Hg). (Used, with permission, from Gattinoni et al.[103])

implemented in patients with less-severe hypoxemic respiratory failure, a situation in which therapy produces useless and potentially harmful effects. Prone positioning, however, should be considered for the treatment of patients with severe hypoxemia, although great care and experienced personnel are required when performing this intervention. Future studies are needed to clarify practical questions facing the clinicians using prone positioning, such as the optimal duration of the therapy,[85] the validity of the Pa_{O_2}-to-FI_{O_2} threshold[83] in guiding therapy, and the real impact of adverse events. A currently ongoing trial targeting the enrollment of 460 patients with Pa_{O_2}/FI_{O_2} less than 150 mm Hg will provide additional data.[106]

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PAIN CONTROL, SEDATION, AND NEUROMUSCULAR BLOCKADE

John P. Kress
Jesse B. Hall

Mechanically ventilated patients often require sedatives and analgesics, and in some circumstances may even require the addition of neuromuscular blockade. The myriad disease processes causing respiratory failure frequently elicit a sense of respiratory distress in these patients. In addition, therapies such as endotracheal intubation and positive-pressure ventilation bring about discomfort to a significant number of patients in the intensive care unit (ICU), and patients often receive these life support treatments after surgical interventions or medical conditions that themselves carry a burden of pain. Accordingly, most patients receive analgesics and/or sedatives while undergoing mechanical ventilation. Although many drugs are available to carry out the goals of pain control and, if necessary, sedation in the ICU, studies of the use of these agents were initially performed in other settings such as the operating room or procedure suite. However, accumulation of evidence directed at ICU patient outcomes—specifically patients undergoing mechanical ventilation—has increased over recent decades, and awareness of the complex pharmacology of sedatives and analgesics in critical care is now well established. At the same time, heightened awareness of the complications associated with the use of neuromuscular blocking agents has relegated their use to mostly short-term indications, such as general anesthesia in the operating room, with ICU use now reserved for a small population of patients, typically suffering from severe acute respiratory distress syndrome. The drugs used to achieve analgesia and sedation of mechanically ventilated patients are necessarily potent; however, the enduring effects when these drugs are used without discretion has impacted strategies for their administration.

RATIONALE

Recognition of the fundamental pathophysiologies of respiratory failure and the interaction of the mechanical ventilator and patient will allow goals of pain control, sedation, and neuromuscular blockade to complement the supportive goals of mechanical ventilation. An individualized strategy can then be executed, recognizing goals unique to each patient. This chapter discusses principles and goals of pain control, sedation, and neuromuscular blockade in mechanically ventilated patients, as well as review the drugs currently available to achieve these goals.

PAIN CONTROL

We begin our discussion with the analgesic agents because many patients experience pain to some degree, because inadequate control of pain is unfortunately a memory patients may have after ICU management, and because the ability of the patient to clearly indicate and quantify pain may be significantly impaired by respiratory failure and the devices employed to treat it. This last fact can lead to the unfortunate circumstance of pain in the mechanically ventilated patient presenting as agitation, which, if treated with sedatives alone, is often inadequately managed and leads to excessive drug administration.

Indications

The indications for analgesia during mechanical ventilation come directly from the multiple reasons for pain in these patients. Pain from surgical incisions or trauma is self-evident, but other indications for pain control are subtler. These include endotracheal suctioning or placement of invasive catheters such as arterial or venous lines. Preexisting problems such as skeletal fractures from metastatic cancer and prolonged immobility during bed rest[1] should be considered as other potential causes of pain. The mere presence of an endotracheal tube causes pain in some patients.

Pain may cause many adverse effects, including increased endogenous catecholamine activity, myocardial ischemia, hypercoagulability, hypermetabolic states, sleep deprivation, anxiety, and delirium.[2] Treating pain diminishes some of these detrimental effects.[3]

Assessing Adequacy

It is undeniable that pain occurs in some mechanically ventilated patients.[4–6] Failure to recognize that pain can cause agitation that may lead to inappropriate administration of nonanalgesic sedatives. Accordingly, an aggressive approach to managing pain has been strongly recommended by consensus opinions regarding sedation of mechanically ventilated patients.[7,8] Indeed, it is prudent to actively inquire for the presence of pain and begin the assessment of mechanically ventilated patients by postulating that pain is present as a symptom. The ability to accurately discern pain may be difficult because many ventilated patients are unable to convey its presence and clinical parameters such as changes in vital signs are often not reliable indicators.

In spite of such recommendations and vigilance, the management of pain in ventilated patients is inadequate in some cases.[5] Ineffective communication with patients may be at the root of this problem, because delirium in the ICU is common.[9] Concern over addiction to opiates,[10] adverse cardiopulmonary effects of analgesics, and arbitrary dose limits are other reasons for inadequate analgesia in ventilated patients.

Although attention to analgesia is important, it is similarly important to recognize that not all ventilated patients experience pain. A recent prospective observational study of 171 ICU patients described their self-reported experiences while in the ICU (34% of these were mechanically ventilated).[4] Only 40% of patients reported pain. The important message from this study is that pain, although common and distressing, is not universal. Accordingly, a concerted effort to determine whether or not a patient has pain is extremely important, lest unnecessary withholding or administration of analgesics occur.

Tools to categorize pain, such as scales or scoring systems, may be beneficial. In general, simpler scales are more effective because communication for many ventilated patients is limited. The visual analog scale, although not specifically evaluated in critically ill, mechanically ventilated patients, has very good reliability and validity.[11,12] This scale uses a self-reported measure of pain intensity that consists of a 10-cm line on paper with verbal anchors of "no pain" and "severe pain." A similar scale is the numeric rating scale. This scale also consists of a horizontal line with numeric markings 1 and 10 anchoring either extreme of the pain-intensity scale.[13]

Previous studies have shown that benzodiazepines may enhance the analgesic effects of opiates[14,15] and that opiate requirements are decreased in patients sedated with benzodiazepines compared with propofol.[16,17] Notwithstanding this interesting observation, it is imperative that sedative agents are not used in the place of analgesics.

Selection of Agent

Nonpharmacologic analgesic strategies are worth considering. For example, malpositioning of invasive catheters (an endotracheal tube impinging on the main carina) is a problem that may be easily remedied. Likewise, optimal patient positioning in bed may at least partially relieve low back pain, pain from chest tubes, and so on. In spite of appropriate attention to nonpharmacologic approaches, most patients require administration of pharmacologic agents. Opiates are given in most circumstances and are discussed below.

Opiates

Opiate receptors are ubiquitous, being found in the central nervous system as well as peripheral tissues. The two most clinically important opiate receptors are μ and κ. There are two subtypes of μ receptors, μ_1 and μ_2. Of these subtypes μ_1 receptors mediate analgesia, while μ_2 receptors mediate respiratory depression, nausea, vomiting, constipation, and euphoria. The κ receptors are responsible for such effects as sedation, miosis, and spinal analgesia. Several opiate drugs are available for clinical use and are discussed in detail below.

MORPHINE

Morphine is a commonly used opiate agent and is the drug with which all other opiates are typically compared. Administered intravenously, it has a relatively slow onset

of action (typically 5 to 10 minutes) because of its low lipid solubility, which delays movement of the drug across the blood–brain barrier. The duration of action after a single intravenous dose of morphine is approximately 4 hours. When given repeatedly, accumulation in tissue stores may prolong the effect. It is metabolized in the liver, undergoing glucuronide conjugation, and its active metabolite, morphine-6-glucuronide, may accumulate, particularly in renal failure. Elimination occurs in the kidney, so effects may be prolonged in renal failure. The primary central effect of all opiates is analgesia, which is mediated through the μ and κ receptors. Opiates have some anxiolytic properties, but no reliable amnesia.

FENTANYL

Fentanyl is a synthetic opiate. It has a very high lipid solubility, unlike morphine, leading to rapid movement across the blood–brain barrier and rapid onset of action. Redistribution into peripheral tissues leads to short duration of action after a single dose (0.5 to 1 hour). When fentanyl is given repeatedly and tissue stores become saturated, its clinical effect can be prolonged. Fentanyl has no active metabolites and does not release histamine.[18]

HYDROMORPHONE

Hydromorphone has pharmacologic properties similar to morphine with regard to onset of action. Because it has no active metabolites, however, the duration of action after long periods of hydromorphone administration may be less than that of morphine.

MEPERIDINE

Meperidine is a lipid-soluble opiate with rapid movement across the blood–brain barrier and a rapid onset of action (3 to 5 minutes). The higher lipid solubility leads to peripheral redistribution so that duration after a single dose may be shorter as compared with morphine (1 to 4 hours). Meperidine undergoes hepatic metabolism and renal elimination. Because metabolites of meperidine may accumulate secondary to the common organ dysfunctions that accrue in critically ill patients, and because these metabolites have neurotoxic effects that may cause seizures, there seems no reason to ever use this agent in the ICU patient (see below).[19]

REMIFENTANIL

Remifentanil is another synthetic, lipid-soluble drug with a rapid onset of action. It is quickly metabolized via hydrolysis by nonspecific blood and tissue esterases. As such, its pharmacokinetic profile is not affected by hepatic or renal insufficiency. It is given by continuous infusion because of its rapid metabolism and recovery time. When remifentanil is used during general anesthesia, available data suggest that postoperative respiratory failure is reduced, presumably because patients wake up more rapidly. It provides reliable short-term analgesia in patients with postoperative respiratory failure,[20] and may reduce ICU admissions by allowing extubation in the operating room.[21] Because of remifentanil's unique pharmacology, there is a potential for rapid tolerance to the drug.[22] This has been referred to as *hyperalgesia*.[23] Because remifentanil is eliminated from the body so rapidly and completely, it may lead to a circumstance where patients are left with no analgesia. Although further research is needed to more fully address this issue, it is important to acknowledge this potential problem when using remifentanil in the ICU patient.

Methods of Delivery

For most patients, intravenous injection of opiate analgesics is the preferred route. Intramuscular injections are discouraged because of pain related to the injection itself and unpredictable absorption in critically ill patients. Dosing strategies for intravenous administration of opiates include continuous infusions and intermittent dosing strategies. Intermittent dosing can be further divided into scheduled administration, administration on an *as needed* or *PRN* basis, and patient-controlled analgesia. Dosing given as needed may lead to fluctuations between inadequate and excessive analgesia. Patients alert enough to respond to their own pain needs may benefit from patient-controlled analgesia strategies,[24] although most ventilated patients are not alert enough to utilize a patient-controlled analgesia device. Transdermal opiates may be continued in patients who are chronically receiving such medications, although transcutaneous absorption is unpredictable during critical illness. Certainly, this route should not be used for treating acute pain in mechanically ventilated patients.

Toxicity

All opiates induce respiratory depression, which is centrally mediated and dose dependent. Depression is mediated by the μ_2 receptors in the brainstem medulla; the typical pattern is one of reduced respiratory rate but preserved tidal volume. The response to hypercapnia is decreased and the ventilatory response to hypoxia is obliterated. The depressed respiratory property of these drugs can be exploited in ventilated patients suffering from subjective dyspnea or coughing.

The hemodynamic effects of opiates in euvolemic patients are typically minimal. Hypovolemic patients with blood pressure sustained by sympathetic hyperactivity may suffer hypotension after the administration of opiates. Most opiates cause a decrease in heart rate because of decreased sympathetic activity. Although morphine causes histamine release, this does not usually cause hemodynamic compromise. Remifentanil may cause bradycardia and hypotension, particularly when administered concurrently with drugs having vasodilating properties, such as propofol. Hypertension after remifentanil, though described, is uncommon.

TABLE 50-1: COMMONLY USED OPIATES

	Morphine	Fentanyl	Remifentanil	Methadone
Typical starting dose	2 to 5 mg	25 to 50 mcg	0.025 to 0.1 mcg/kg/min infusion	5 to 10 mg
Onset	10 minutes	0.5 to 1 minute	3 to 5 minutes	10 to 20 minutes
Duration after single dose	4 hours	0.5 to 1 hour	NA; 5 minutes after 4-hour infusion	6 to 24 hours
Metabolism	Hepatic	Hepatic	Nonspecific tissue and plasma esterases	Hepatic
Elimination	Renal	Renal	Renal	Renal
Anxiolysis	+	++	++	+
Analgesia	++++	++++	++++	++++
Hypnosis	No reliable effect	No reliable effect	No reliable effect	No reliable effect
Amnesia	No reliable effect	No reliable effect	No reliable effect	No reliable effect
Seizure threshold	No effect	No effect	No effect	No effect
Reducing dyspnea	++++	++++	++++	++++
Cardiovascular effect	Venodilation	Venodilation	Venodilation	Venodilation
Respiratory effect	Hypoventilation	Hypoventilation	Hypoventilation	Hypoventilation
Common side effects	Ileus, nausea and vomiting, itching	Ileus, nausea and vomiting, itching	Ileus, nausea and vomiting, itching	Ileus, nausea and vomiting, itching

+, minimal effect; ++, mild effect; +++, moderate effect; ++++, large effect.

Gastrointestinal dysfunction in the form of pharmacologic ileus is common with the use of opiates in mechanically ventilated patients. Methylnaltrexone, a specific antagonist of μ_2 receptors in the gut, has been reported to attenuate opiate-induced gastrointestinal ileus in humans.[25,26] The utility of methylnaltrexone in critically ill, mechanically ventilated patients has not been tested.

Seizures are a toxicity unique to meperidine and occur as a result of its metabolite normeperidine, which is a central nervous system stimulant. Patients with renal failure and/or with prolonged use are especially prone to normeperidine accumulation. Because meperidine offers no significant advantage over other available opiates, its side-effect profile should largely preclude its use in critically ill patients.

Muscle rigidity occasionally occurs with synthetic opiates such as fentanyl and remifentanil. It is not seen with naturally occurring opiates like morphine. It is usually seen when high doses of these drugs are injected rapidly and may affect chest wall muscles. The mechanism of opiate-induced skeletal muscle rigidity, although not fully understood, is thought to involve supraspinal activity of the drugs in the striata and substantia nigra. In the most extreme cases, respiratory muscle rigidity makes ventilation impossible. Neuromuscular blockade, typically with succinylcholine, reverses this problem. Fortunately, this problem is extremely rare with the doses of opiates used in the management of ventilated patients in the ICU.

Dependence and withdrawal can be seen in patients receiving opiates for extended time periods when the drugs are discontinued. Patients who abuse opiates are at risk for this when hospitalized during critical illness. The signs and symptoms seen in withdrawal syndromes are mostly nonspecific and include pupillary dilation, sweating, lacrimation, rhinorrhea, piloerection, tachycardia, vomiting, diarrhea, hypertension, yawning, fever, tachypnea, restlessness, irritability, increased sensitivity to pain, nausea, cramps, muscle aches, dysphoria, insomnia, symptoms of opioid craving, and anxiety. Patients without previous illicit drug use may also experience opiate withdrawal when pharmacologically administered opiates given for extended time periods are suddenly stopped. Whether any preemptive strategies, such as downward titration or regular interruption of dosing, will attenuate or prevent opiate withdrawal is not known. Although apparently logical, use of long-acting opiates (e.g., methadone, transdermal fentanyl) to overcome this problem has not been studied in the ICU. Table 50-1 summarizes the pharmacologic properties of commonly used opiates.

SEDATION

Indications

Sedation needs vary widely in mechanically ventilated patients. Although nonpharmacologic approaches such as comfortable positioning in bed and verbal reassurance are reasonable initial considerations, treatment with sedative agents is frequently needed. Effective use of sedatives and analgesics in critically ill patients begins with an understanding of their various indications. Effective *analgesia* (discussed above) is extremely important and should be considered concurrently with sedation.

Anxiety occurs frequently in ventilated patients and is one of the most common indications for sedation. Anxiety may result from (a) uncertainty of one's surroundings, diagnosis,

or prognosis; (b) uncomfortable experiences such as the presence of an endotracheal tube or invasive diagnostic or therapeutic procedures; or (c) isolation from family and friends. Sedatives may be required to facilitate routine nursing care of ventilated patients. Procedures such as endotracheal suctioning, dressing changes, and repositioning regularly elicit distress requiring sedatives.

Dyspnea is common in ventilated patients and may be a source of distress requiring sedation. Excessive coughing may contribute to patient–ventilator dyssynchrony in some patients. Many patients requiring mechanical ventilation suffer from cardiopulmonary instability and impaired gas exchange. Abnormal elevations in oxygen consumption and carbon dioxide production may compromise such patients. Reduction of oxygen consumption can stabilize the balance between oxygen supply and demand.[16] Autonomic instability and elevated endogenous catecholamine activity are common in ventilated patients and may lead to hemodynamic changes (e.g., tachycardia or hypertension) that may elicit myocardial ischemia in some patients, particularly those at risk for coronary artery disease.[27]

Amnesia is often cited as an indication for sedation of ventilated patients. Certainly, for those patients mechanically ventilated during surgical procedures, the importance of amnesia is indisputable.[28] On the contrary, in ICU patients, the necessity of continuous amnesia is far less certain. Although amnesia for certain portions of critical illness requiring mechanical ventilation may seem logical (e.g., during invasive procedures), complete amnesia for extended periods during mechanical ventilation in the ICU has never been proven to confer benefit. Indeed, some data suggest that prolonged ICU amnesia may be detrimental to long-term neuropsychiatric recovery from critical illness.[29–31] It is clear, however, that complete amnesia is mandatory whenever neuromuscular blocking agents are administered.

The relationship between *delirium* and sedation is indisputable. Delirium—defined as an acutely changing or fluctuating mental state, inattention, disorganized thinking, and an altered level of consciousness that may or may not be accompanied by agitation—has been noted to have a wide incidence range in critically ill patients.[9,32,33] Hyperactive or agitated delirium may occur with anxiety as well as sepsis, fevers, encephalopathy (e.g., hepatic or renal), withdrawal syndromes (alcohol, tobacco, or other illicit drugs), or medications. Such hyperactive delirium is frequently treated with neuroleptic medications such as haloperidol.[34] A substantial fraction, however, of ventilated ICU patients exhibit an insidious, hypoactive form of delirium. Currently, it is unclear whether this form of delirium is an indication for any pharmacologic therapy.

Assessing Adequacy

The assessment of sedation adequacy requires a thorough awareness of the indications for sedation. Even when indications are clear, adequacy assessment is challenging because of its subjective nature. As such, a reliable instrument to categorize level of sedation is an important initial step. In view of that, several sedation scales such as the Ramsay Sedation Score,[35] the Sedation Agitation Scale,[36] and the Richmond Agitation-Sedation Scale (RASS)[37] have been developed. The Ramsay scale, described nearly 40 years ago, is often referenced in clinical investigations of sedation, even though it has never been objectively validated.[38] Accordingly, other sedation scales such as the Sedation Agitation Scale and RASS have been developed and tested for validity and reliability.[39] The RASS is perhaps the most extensively evaluated scale. It has been validated for ability to detect changes in sedation status over consecutive days of ICU care, as well as against constructs of level of consciousness and delirium. Because of their more precise scientific evaluations, the RASS and Sedation Agitation Scale should be viewed as preferable to the traditional Ramsay scale.

Ultimately, the evaluation of sedation adequacy is an individualized bedside maneuver. Guidance from nurses is useful, because they are often the first to notice changes in level of sedation. Theoretically, the optimal level of sedation would result in a state in which all indications for sedation are attended to, and the patient is fully communicative with bedside caregivers. This state of being awake and communicative while sedatives are being administered is ideal, and is possible in many patients. Unfortunately, for some, the stresses of respiratory failure and mechanical ventilation do not permit such a state.

Objective monitors of sedation level would be attractive tools for ventilated patients. The bispectral index monitor processes raw electroencephalogram signals into a discrete scaled number from 0 (absence of cortical activity) to 100 (fully awake). This monitor has been shown to track the level of consciousness under general anesthesia. There are some data that suggest a good correlation between the bispectral index and the sedation agitation scale[40] as well as the RASS;[39] however, problems such as electromyographic interference[41] have undermined the utility of this device for widespread use in the ICU.

Selection of Agent

After indications for sedation are established, the clinician must choose one or more agents to administer. This section outlines the various agents currently available and discusses the pharmacologic properties of each agent.

BENZODIAZEPINES

Benzodiazepines act by potentiating γ-aminobutyric acid (GABA) receptor-mediated inhibition of the central nervous system. The GABA receptor complex regulates a chloride channel on the cell membrane, and, by increasing the intracellular flow of chloride ions, neurons become hyperpolarized, with a higher threshold for excitability. The GABA receptor can be competitively antagonized with the

synthetic agent flumazenil, thereby reversing the pharmacologic effects of benzodiazepines. Midazolam, lorazepam, and diazepam are the three available parenteral benzodiazepines.

The onset of action of midazolam is rapid (0.5 to 5 minutes) and the duration following a single dose is short (approximately 2 hours). All parenteral benzodiazepines, including midazolam, are lipid soluble with a large volume of distribution, and are therefore widely distributed throughout body tissues. For all benzodiazepines, the duration of action after a single bolus depends mainly on the rate of redistribution to peripheral tissues, especially adipose tissue. Midazolam undergoes hepatic metabolism and renal excretion. One metabolite of midazolam (α-hydroxymidazolam) has active pharmacologic properties and is renally excreted. Accordingly, there seems little point to using midazolam in ICU patients who have kidney dysfunction. In the presence of normal renal function, α-hydroxymidazolam has a half-life of 1 hour. The pharmacokinetics of midazolam are very different when it is administered to critically ill patients, especially when given by continuous infusion for prolonged periods. Under these circumstances there is preferential accumulation of the drug in peripheral tissues, where metabolism is not possible. When drug infusions are stopped, the peripheral tissue stores release midazolam back into the bloodstream, leading to prolongation of clinical effect.[42] Obese and elderly patients may be even more prone to prolonged effects.

Intravenous lorazepam has a slower onset of action when compared to midazolam (5 minutes). This is the result of a lower lipid solubility that slows the drug's ability to cross the blood–brain barrier. The duration of action following a single dose is long (6 to 10 hours) and is proportional to the dose given. Because these data refer to healthy volunteers, applicability to critically ill patients is difficult. Lorazepam's longer duration of action is caused by lower lipid solubility with decreased peripheral tissue redistribution. The absence of renally excreted metabolites makes it the benzodiazepine of choice in patients with kidney failure.

Intravenous diazepam has a rapid onset of action (1 to 3 minutes) and a limited duration of action following a single dose (30 to 60 minutes). Like midazolam, these pharmacologic properties are caused by the high lipid solubility, which leads to rapid peripheral redistribution of diazepam and extended duration of action. As such, there is little point to ever using diazepam for ICU sedation.

The parenteral benzodiazepines have similar pharmacodynamic effects. All cause dose-dependent suppression of awareness along a spectrum from mild depression of responsiveness to obtundation. They are potent anxiolytic drugs and reliably produce amnesia;[43] lorazepam appears to produce the longest duration of antegrade amnesia. Another common feature of these drugs is their reliable anticonvulsant effect.[44] Rarely, benzodiazepines cause agitation. This paradoxical response typically accelerates as additional benzodiazepine is given; although rare, it has a propensity to affect elderly patients. All benzodiazepines induce dose-dependent depression of respiratory drive. This ventilatory depression, while less extreme than that seen with opiates, behaves in a synergistic manner with opiate-induced respiratory depression. A pattern of reduced tidal volume and slightly increased respiratory rate may help to discern a benzodiazepine effect from the pattern of slow, deep breathing typically seen with opiates. Benzodiazepines, like opiates, can obliterate the hypoxic ventilatory drive. They have minimal effects on the cardiovascular system of euvolemic patients, typically causing slight decreases in blood pressure without a significant change in heart rate. The effect is exacerbated in the presence of relative hypovolemia. In patients with elevated endogenous sympathetic drive, more profound decreases in blood pressure can be seen. Table 50-2 summarizes the pharmacologic properties of the parenteral benzodiazepines.

TABLE 50-2: PROPERTIES OF COMMONLY USED BENZODIAZEPINES

	Midazolam	Lorazepam	Diazepam
Typical starting dose	1 to 2 mg	0.5 to 1 mg	5 to 10 mg
Onset	0.5 to 2 minutes	3 to 5 minutes	1 to 3 minutes
Duration after single dose	2 hours	6 to 10 hours	1 to 6 hours
Metabolism	Hepatic	Hepatic (less influenced by age and liver disease)	Hepatic
Elimination	Renal	Renal	Renal
Anxiolysis	++++	++++	++++
Analgesia	No effect	No effect	No effect
Hypnosis	++++	++++	++++
Amnesia	++++	++++	++++
Seizure threshold	+++	++++	+++
Reducing dyspnea	+	+	+
Cardiovascular effect	Venodilation	Venodilation	Venodilation
Respiratory effect	Hypoventilation	Hypoventilation	Hypoventilation
Common side effects	Paradoxical agitation	Paradoxical agitation	Paradoxical agitation

+, minimal effect; ++, mild effect; +++, moderate effect; ++++, large effect.

PROPOFOL

Propofol is an intravenous anesthetic with an alkylphenol molecular structure. Like benzodiazepines, it appears to act on the GABA receptor, although not at the same site as the benzodiazepines. The drug is hydrophobic and is prepared as a lipid emulsion, so it rapidly crosses the blood–brain barrier, leading to a rapid onset of sedation. High lipid solubility also allows for rapid redistribution to the peripheral tissues with a duration of action measured in minutes.[45] With prolonged infusions, duration may be increased slightly, although it is rare for the effect to last beyond 60 minutes from the time of infusion discontinuation. When the infusion is stopped, the peripheral tissue stores redistribute the drug back into the plasma, but usually not to clinically significant levels because of the drug's high lipid affinity. Propofol is ultimately metabolized predominantly in the liver. It has an elimination half-life of 4 to 7 hours and no active metabolites.

Propofol has predictable pharmacodynamic effects, acting as a hypnotic agent causing a dose-dependent depression of responsiveness and awareness. It is also a potent anxiolytic and amnestic agent.[45] Indeed, at high infusion rates, propofol is commonly used for general anesthesia. It appears to have effective anticonvulsant properties.[46] Propofol has no detectable analgesic activity and is not recommended as a sole agent for the initial management of mechanically ventilated patients, because pain control is important in some of these patients. The drug causes ventilatory depression and even apnea in some patients. Because apnea with propofol is unpredictable and not always dose dependent, it should not be used without readiness to secure the airway. The respiratory pattern with propofol is a decrease in tidal volume and a slight increase in respiratory rate. Propofol can cause significant decreases in blood pressure, especially in hypovolemic patients. Hypotension is mainly caused by preload reduction from dilation of venous capacitance vessels. There is mild myocardial depression that also contributes to hypotension.[47] The hemodynamic effect is generally more pronounced than with the benzodiazepines and it should be given cautiously to patients with cardiac disease. Hyperlipidemia is a unique side effect of propofol.[48]

As noted above, the drug is delivered in an intralipid carrier, and propofol 1% solution has 1.1 kcal/mL.[49] Therefore, parenteral lipid feedings must be adjusted to account for the calories administered with this drug. Triglyceride levels should be checked frequently and the drug stopped if hypertriglyceridemia is noted. Strict aseptic technique and frequent changing of infusion tubing is essential to prevent iatrogenic transmission of bacteria and fungi because propofol can support their growth.[50] A "propofol infusion syndrome," manifesting as dysrhythmias, heart failure, metabolic acidosis, hyperkalemia, and rhabdomyolysis, is a rare complication. It appears to be more likely to occur when high doses and/or concentrations of propofol are used.[51] An unpublished randomized, controlled trial of propofol in 327 pediatric patients reviewed by the Food and Drug Administration described a concentration-dependent increase in 28-day mortality in propofol-treated patients versus patients treated with other sedatives (4% mortality with sedatives other than propofol, 8% mortality with 1% propofol, and 11% mortality with 2% propofol).[52] Propofol has received media attention because of problems with national shortages[53] and reports of use of this agent as a drug of abuse[54,55]

FOSPROPOFOL

Fospropofol is a prodrug of propofol that has been introduced as a potential alternative agent for ICU sedation. The Food and Drug Administration approved the drug in 2008. It is metabolized in vivo to the active drug propofol, but the parent drug is water soluble with a much smaller volume of distribution than propofol.[56] The onset of action is on the order of minutes, just slightly longer than propofol. The potential implications of this characteristic include a lower propensity for accumulating in adipose stores during prolonged infusions, although thus far it has only been studied in Phase III clinical trials for colonoscopy, bronchoscopy,[57] or minor surgical procedures.[58] Contamination of fospropofol is less of a concern than propofol because of its water-soluble nature. Further study is needed to evaluate its utility in the ICU.

BUTYROPHENONES

Butyrophenones such as haloperidol may be used for sedation of mechanically ventilated patients. These drugs induce a state of tranquility, and patients often behave with a detached affect. Butyrophenones appear to antagonize dopamine, especially in the basal ganglia, although their exact site of action is not known.

The onset time of intravenous haloperidol is 2 to 5 minutes and the half-life is 2 hours. Starting doses of 1 to 10 mg are typically used with titration depending on the desired end point. The drug is metabolized in the liver.

These drugs are typically reserved for patients who are acutely agitated and hyperactive. A state of cataleptic immobility is occasionally seen. Haloperidol provides no amnesia, no effect on seizure activity, and minimal analgesia. Butyrophenones such as haloperidol are the drugs of choice for agitated delirium. A retrospective study reported an association between haloperidol in ventilated patients and a reduction in mortality,[59] but there are no confirmatory prospective trials. Currently, there is no convincing evidence for the use of antipsychotics in the treatment of ICU delirium. A small pilot study comparing haloperidol, ziprasidone, and placebo given to delirious patients in a preemptive manner found no differences in outcomes, although this study may have been underpowered to detect a difference.[34] A randomized trial comparing haloperidol to olanzapine showed similar reductions in delirium, but fewer extrapyramidal side effects with olanzapine.[60]

Haloperidol causes no significant respiratory depression.[61] This is an attractive feature of haloperidol, because most sedative or analgesic drugs cause respiratory depression.

Haloperidol is known to prolong the QT interval in some patients; it has been reported to result in torsades de pointes,[62]

although this problem is rare. The drug also mildly antagonizes the α_1 receptor and may decrease the neurotransmitter function of dopamine, resulting in mild hypotension.

Extrapyramidal effects are occasionally seen with these drugs, but are much less common with intravenous than with oral butyrophenones. When these complications occur, treatment with diphenhydramine or benztropine may be necessary. The neuroleptic malignant syndrome is another extremely rare problem, thought to result from central dopaminergic blockade leading to extrapyramidal side effects, muscle rigidity, and excess heat generation. It is a life-threatening complication, manifested by "lead pipe" muscle rigidity, fever, and mental status changes. Although data are limited, dantrolene, bromocriptine, and benzodiazepines are listed as possible treatment options.[63]

DEXMEDETOMIDINE

Dexmedetomidine is a selective α_2 agonist with both sedative and analgesic properties.[64] Patients receiving this drug are sedated when undisturbed, but they may arouse easily with minimal stimulation, particularly if they are not receiving opiates or other sedatives concurrently and do not have encephalopathy related to their critical illness. Dexmedetomidine is unique in that some patients transition from sedated to alert states quickly and easily without needing to discontinue the drug infusion, which permits frequent neurologic examinations. The drug is approved for short-term use (<24 hours) in patients initially receiving mechanical ventilation. Dexmedetomidine is analgesic sparing in postoperative patients.[65] Because it causes no respiratory depression, it can be continued after discontinuation of mechanical ventilation and extubation. Because it does not produce respiratory depression, it is not a desirable agent when this property is beneficial, such as the initial management of a ventilated patient in whom permissive hypercapnia is sought.

Side effects include bradycardia (on rare occasions of a severe nature[66]) and hypotension,[67] especially with hypovolemia or high endogenous sympathetic tone. Vasoconstriction and hypertension with increasing doses of dexmedetomidine also have been described.[68] Early studies with dexmedetomidine evaluated postoperative ICU patients[69]; however, more recent studies have targeted other types of patients receiving dexmedetomidine for longer periods of time. Pandharipande et al reported that dexmedetomidine resulted in more days alive without delirium or coma and more time at the targeted level of sedation than lorazepam.[70] Riker et al studied dexmedetomidine for longer-term ICU infusions and found that, compared to midazolam, it resulted in less ICU delirium and fewer days on the ventilator.[71] Table 50-3 summarizes the pharmacologic properties of the other commonly used sedative agents: propofol, haloperidol, and dexmedetomidine.

KETAMINE

Ketamine has a molecular structure similar to phencyclidine. Patients experience a state of mind in which perception is separated from sensation, a "detached from surroundings" or so-called dissociative state. While appearing unaware of their surroundings, patients keep their eyes open and maintain a protective cough reflex. They may behave with coordinated

TABLE 50-3: PROPERTIES OF OTHER SEDATIVE AGENTS

	Propofol	Fospropofol	Haloperidol	Dexmedetomidine
Typical starting dose	1 to 2 mg/kg	2 to 6 mg/kg	0.5 to 1 mg	0.5 to 1.0 mcg/kg over 10 minutes; 0.2 to 0.7 mcg/kg/hour infusion
Onset	0.5 to 1 minutes	4 to 12 minutes	2 to 5 minutes	5 to 10 minutes
Duration after single dose	2 to 8 minutes	2 to 8 minutes	2 hours	30 to 60 minutes
Metabolism	Hepatic, renal	Hepatic, renal	Hepatic	Hepatic
Elimination	Renal	Renal	Renal	Renal
Anxiolysis	++++	++++	+++	+++
Analgesia	No effect	No effect	No effect	++
Hypnosis	++++	++++	++	+++
Amnesia	++++	++++	No effect	+
Seizure threshold	Increases	Increases	No effect	No effect
Reducing dyspnea	+	+	No effect	No effect
Cardiovascular effect	Venodilation, arteriolar dilation, myocardial depression	Venodilation, arteriolar dilation, myocardial depression	Venodilation, arteriolar dilation	Venodilation, arteriolar dilation, bradycardia, occasional hypertension
Respiratory effect	Hypoventilation	Hypoventilation	No effect	No effect
Common side effects	Increased triglycerides	Increased triglycerides	Neuroleptic malignant syndrome (rare), extrapyramidal effects (rare)	Hypotension, bradycardia

+, minimal effect; ++, mild effect; +++, moderate effect; ++++, large effect.

movements that appear to be without purpose. The drug has profound analgesic properties without producing respiratory depression. The circulatory effects of hypertension and tachycardia, typically seen, reflect increased activity of the sympathetic nervous system. Some, but not all patients, experience amnesia after receiving ketamine. A recent study found ketamine to be an effective alternative to etomidate to facilitate intubation in the ICU. There was a significantly lower incidence of adrenal insufficiency with ketamine.[72] The side effects of emergence delirium and severe hallucinations limit ketamine as a mainstream agent for sedation and analgesia in mechanically ventilated patients. Indeed, this phencyclidine derivative is popular as an illicit drug of abuse.

BARBITURATES

Barbiturates such as thiopental and pentobarbital are potent agents that cause amnesia and unconsciousness. They have no role as sedatives in ICU patients because of a propensity to cause hemodynamic instability and prolonged accumulation in peripheral tissues secondary to lipid solubility. Thiopental is sometimes used to induce anesthesia to facilitate endotracheal intubation. These drugs may be used to induce a pharmacologic coma in patients with severe brain injury.

INHALATIONAL ANESTHETICS

Inhalational anesthetics are used often in the operating room to maintain general anesthesia in mechanically ventilated patients. These agents have analgesic, amnestic, and hypnotic sedating properties. These exhaled gases must be effectively scavenged because they are not metabolized to any significant degree. Delivery and scavenging are technically challenging problems, which has limited greatly the use of these agents outside of the operating room. While there are devices that can be attached to ventilator circuitry to recycle inhalational anesthetics,[73,74] these agents are largely restricted to the research setting and more data are needed before their widespread use in the ICU.

Strategies for Delivery of Sedatives in Critically Ill Mechanically Ventilated Patients

Because no single drug can achieve all of the indications for sedation and analgesia in the ICU, a combination of drugs, each titrated to specific end points, may be more effective. This strategy can allow lower doses of individual drugs and reduce drug accumulation. Both continuous intravenous infusion and intermittent bolus techniques have been advocated. Intermittent bolus strategies may lead to fluctuations in level of sedation and increase demands on nursing time, potentially distracting attention away from other patient care issues. The perceived benefits of continuous sedative infusions include a more consistent level of sedation with better patient comfort, though convenience is likely the greatest reason for its popularity.

Ideally, strategies for sedation and analgesia in critically ill patients should adhere to pharmacokinetic and pharmacodynamic principles. Unfortunately, ICU patients frequently exhibit unpredictable alterations in pharmacology so that precise guidelines for drug administration are not possible. For instance, when short-acting benzodiazepines such as midazolam and lorazepam are administered in the ICU, these drugs accumulate in tissue stores with consequent prolonged clinical effect. Other circumstances that confound prediction of pharmacologic behavior of sedatives and analgesics include altered hepatic and/or renal function, polypharmacy in the ICU with complex drug–drug interactions, altered protein binding, and circulatory instability. The multicompartmental pharmacokinetics typical in critically ill patients defy simple bedside pharmacokinetic profiling.[75] As such, titration of sedatives and analgesics against discernible clinical end points, while imprecise, is the most commonly utilized tool. Further confounding administration of sedatives in the ICU is the dramatic difference between extremes of sedation. Because oversedated patients are easier to manage than undersedated patients, clinicians may be heavy handed when sedating agitated patients.

The occasional ICU patient may require extraordinarily high doses of sedatives to achieve tranquility; such doses may be much greater than those quoted in the literature and recommended by drug manufacturers. Indeed, as discussed below in "Neuromuscular Blocking Agents," occasional patients may even require pharmacologic paralysis to achieve synchrony with mechanical ventilation.[76]

As sicker patients demonstrate improved outcomes in the ICU,[76–80] aggressive levels of sedation and analgesia are sometimes necessary. This is particularly likely for patients managed with unconventional ventilator strategies (e.g., permissive hypercapnia, low tidal volumes, prone positioning, and pressure-controlled ventilation), because these strategies may be inherently distressing to many patients. For selected patients, deep sedation may be the only practical option.

The use of deep sedation, however, carries a high price, because the neurologic examination is severely limited. Ideally, a head-to-toe daily assessment for the presence of organ failures should be routine for every critically ill patient. This is particularly so during resuscitative phases of care, when assessing the adequacy of end-organ perfusion and function is vital. The mental status examination is an important gauge of brain perfusion. Because brain injury is a devastating complication of critical illness,[81] acute cerebral dysfunction must be detected quickly and corrected if possible before permanent injury takes place. The veil of sedation severely handicaps clinicians' ability to serially follow a patient's neurologic condition.

A protocol-driven approach to sedation has been shown to alleviate many of the problems mentioned above.[82] Such protocols assure adequate analgesia and sedation using frequent assessments of patient needs with goal-directed titration of analgesics and sedatives. Alternatively, a routine protocol of daily interruption of continuous sedative infusions can reduce many of the complications of sedation in the ICU

setting, including duration of mechanical ventilation and ICU length of stay.[17] Such a strategy allows patients to spend some of their ICU time awake and interactive. This can allow earlier mobilization of intubated patients leading to improved independence of function and reduced ICU delirium,[83] as well as reduced drug administration and reduced diagnostic neurologic evaluations. Such protocol-driven sedation strategies allow a focused downward titration of sedative infusion rates over time, streamlining administration of these drugs and minimizing the tendency for accumulation.

Initially, the thought of decreasing or stopping sedatives in a critically ill patient who has been agitated may be unsettling. As such, clinicians may aggressively sedate patients early in their ICU course, and maintain the same level of deep sedation indefinitely. A daily holiday from sedatives can eliminate the tendency to "lock in" to a high sedative infusion rate. When sedative infusions are decreased or stopped, tissue stores can redistribute drug back into the circulation. Sometimes interruption of sedative infusions can lead to abrupt awakening and agitation. This must be anticipated by the ICU team to avoid complications such as patient self-extubation; if excessive agitation is noted, sedatives should be restarted. Although the attempt at waking and communication may fail on a given day, this does not portend inevitable failure on all subsequent days. When awakening patients from sedation, reaching the brink of consciousness, without precipitating excessive agitation may be ideal for some. Once objective signs of consciousness are demonstrated, restarting sedatives at half the previous dose and *as needed* is reasonable. Adjustments from this starting point can be individualized to patient needs.

It is clear that sedatives may impact the duration of mechanical ventilation.[17,84] Pairing sedation strategies, such as daily sedative interruption with spontaneous breathing trials, results in shortened ventilator, ICU, and hospital days[85] (Fig. 50-1).

Literature evaluating long-term consequences of recovery from respiratory failure and sedation suggests that post-ICU depression is common in patients who require mechanical ventilation during critical illness.[86] Posttraumatic stress disorder following recovery has been reported as well.[29,31] Some data suggest that lack of awareness related to sedation and/or underlying illness is associated with development of this disorder, and that preservation of awareness during mechanical ventilation may reduce this problem.[29,31,87]

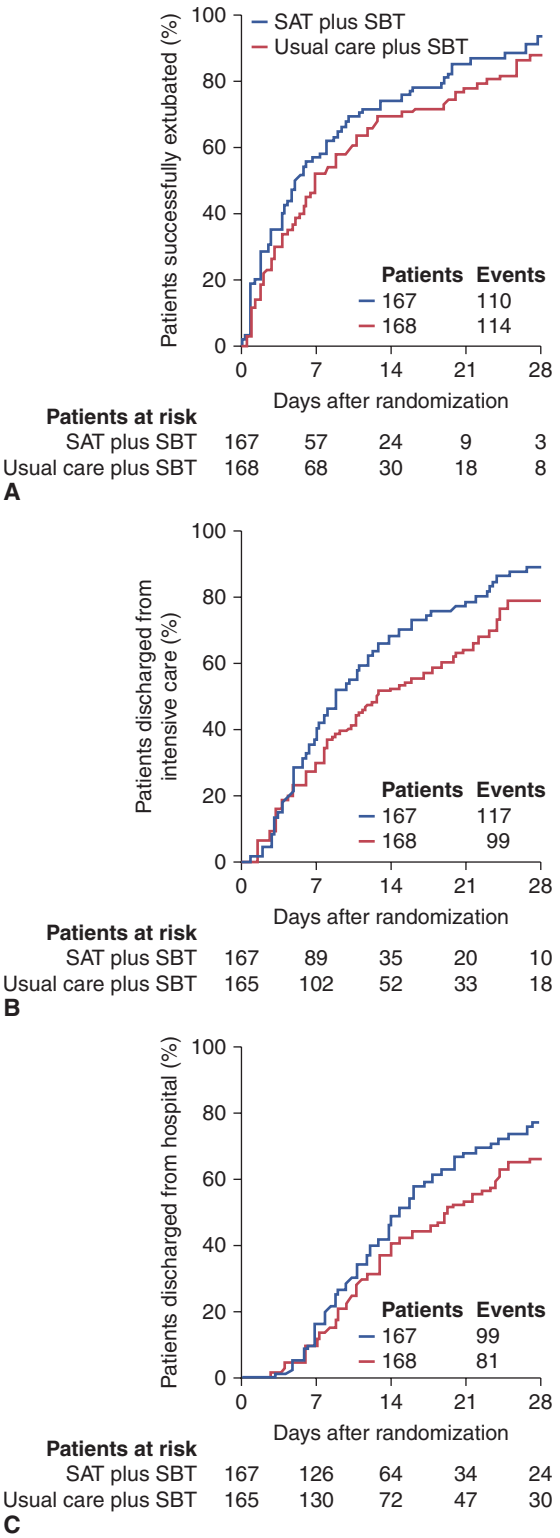

FIGURE 50-1. Probability of successful extubation (**A**), discharge from intensive care (**B**), and hospital discharge (**C**) during the first 28 days after randomization. *SAT*, spontaneous awakening trial; *SBT*, spontaneous breathing trial. (Used, with permission, from Girard et al.[85])

NEUROMUSCULAR BLOCKING AGENTS

Indications

The use of neuromuscular blocking agents (NMBAs) during mechanical ventilation has decreased considerably in the last two decades. These agents remain a common tool to facilitate endotracheal intubation and assure immobility

during surgical procedures. The need for these drugs beyond their use to facilitate procedures is relatively rare in the ICU. Complications related to the use of NMBAs during critical illness have relegated these agents to use as a last resort, usually only for extreme derangements in cardiopulmonary physiology.

Indications for neuromuscular blockade include facilitation of mechanical ventilation in the rare patient who continues to have extreme *ventilator dyssynchrony* despite aggressive administration of sedatives and analgesics. Occasionally, a patient remains so dyssynchronous with the ventilator that effective ventilation is not possible and *severe derangements in gas exchange* ensue, leading to a need for neuromuscular blockade.

Papazian et al conducted a randomized trial in patients with severe acute respiratory distress syndrome (partial pressure of arterial oxygen-to-fractional inspired oxygen concentration ratio [Pa_{O_2}/FI_{O_2}] <150), in which patients received cisatracurium versus placebo in a double-blinded manner. Those receiving cisatracurium had a better adjusted 90-day mortality (hazard ratio [HR] 0.68 [0.48 to 0.98]; $P = 0.04$).[76] The mechanism(s) behind the survival benefit in this study is not known, but may relate to patients being more synchronous with the ventilator and hence avoiding alveolar overdistension or opening–closing cycles that lead to ventilator-associated lung injury.

Patients with *tetanus* may require neuromuscular blockade because of chest wall rigidity, which may prohibit effective chest wall excursion and ventilation. As mentioned above in the discussion of opiate toxicities, the rare occurrence of *skeletal muscle rigidity with high-dose synthetic opiates* may require neuromuscular blockade to permit ventilation. This problem is rare and muscle rigidity short-lived, so that neuromuscular blockade is necessary for only a short time. Lastly, circulation in patients with *severe hemodynamic instability* may become more compromised when respiratory distress demands even greater blood flow to the respiratory muscles from a circulation that cannot accommodate such demands. It is mandatory that patients given NMBAs receive drugs to assure amnesia while they are pharmacologically paralyzed.

Assessing Level of Blockade

Acetylcholine is released from synaptic vesicles at the terminal end of the motor nerve and binds to the postsynaptic end plate, propagating an electrical signal and leading to muscle contraction. Pharmacologic NMBAs bind to the acetylcholine receptor at the terminal end of the motor nerve. These agents can activate the acetylcholine receptor (depolarizing agents) or competitively inhibit the receptor without activating it (nondepolarizing agents). The depth of neuromuscular blockade from nondepolarizing agents is most accurately monitored with the use of a peripheral nerve stimulator. The use of a peripheral nerve stimulator in the ICU has been shown to reduce the amount of neuromuscular blocking drug used and shorten recovery of neuromuscular function and spontaneous ventilation;[88] however, with cisatracurium as the preferred ICU neuromuscular blocking agent (see below the section of Agents–Non depolarizing neuromuscular blocking agents), such monitoring may be unnecessary given the reliable clearance of this drug.[89]

Selection of Agent

DEPOLARIZING NEUROMUSCULAR BLOCKING AGENTS

Succinylcholine. Succinylcholine is the only available depolarizing NMBA. It has the most rapid and reliable onset of neuromuscular blockade, with paralysis sufficient to permit endotracheal intubation within 60 seconds of dosing. As such, succinylcholine is used only to facilitate endotracheal intubation but is not indicated for ongoing neuromuscular blockade in critically ill patients.

NONDEPOLARIZING NEUROMUSCULAR BLOCKING AGENTS

A number of nondepolarizing NMBAs are currently available. The pharmacology of the drugs commonly used during mechanical ventilation in the ICU is discussed below.

Pancuronium. Pancuronium is an older NMBA used during general anesthesia. It has a long half-life, with a duration of action between 60 and 90 minutes after a single intravenous bolus dose of 0.1 mg/kg. Its vagolytic side effect (typically results in a heart rate increase of approximately 10 beats/min), active metabolite (3-hydroxypancuronium), and reliance on renal clearance limit its attractiveness in critically ill patients.

Vecuronium. After the usual loading dose of 0.1 mg/kg, vecuronium typically lasts 30 minutes. Half of the drug is excreted in bile, so prolonged action may be seen in patients with liver dysfunction. In addition, one-third of the drug is excreted in the kidneys, so that accumulation in the setting of renal insufficiency may be seen. The active metabolite 3-desacetylvecuronium may lead to prolongation of effect with repeated dosing, particularly in patients with renal failure.[90]

Rocuronium. Unlike the other aminosteroidal nondepolarizing NMBAs, rocuronium has a rapid onset of action, typically within 60 to 90 seconds. It may be used to facilitate endotracheal intubation, as a substitute for succinylcholine, when the latter is contraindicated (e.g., burns, muscle tissue injury, and upper motor neuron lesions). The usual bolus dose is 0.6 to 1.0 mg/kg, with a duration of effect of 30 to 45 minutes, similar to vecuronium. The metabolite, 17-desacetylrocuronium, has minimal neuromuscular blocking activity.

Atracurium. Atracurium is a benzylisoquinolinium compound with a duration of action between 20 and 45 minutes. The initial loading dose is 0.4 to 0.5 mg/kg. The drug is usually given by continuous infusion in critically ill, mechanically ventilated patients at a dose of 10 to 20 mcg/kg/min. Atracurium is inactivated in plasma by ester hydrolysis and Hofmann elimination so that renal or hepatic dysfunction do not impact its duration of blockade. Atracurium may cause histamine release, and its breakdown product, laudanosine, has been associated with central nervous system excitation and seizures. Currently, it is rarely used in the ICU.

Cisatracurium. Cisatracurium is an isomer of atracurium and it has a similar pharmacologic profile to atracurium. The initial loading dose is 0.1 to 0.2 mg/kg and the duration of action is approximately 25 minutes. Like atracurium, this drug is inactivated in plasma by ester hydrolysis and Hofmann elimination. Cisatracurium does not cause histamine release. Because of its short half-life, it requires administration by continuous infusion. The usual dose is 2.5 to 3 mcg/kg/min. This drug is currently the most frequently used for neuromuscular blockade in mechanically ventilated ICU patients. Apart from succinylcholine and rocuronium use to facilitate endotracheal intubation, there seems little reason to ever use a neuromuscular blocking agent other than cisatracurium in the ICU.

Toxicity

In normal individuals, depolarization of skeletal muscle beds after administration of depolarizing NMBAs such as succinylcholine leads to release of intracellular potassium, typically resulting in an increase in serum potassium of approximately 0.5 mEq/L. Denervation of skeletal muscle from tissue injury, such as with burns or upper motor neuron lesions, may result in more dramatic rises in serum potassium with administration of succinylcholine.

The major toxicity with nondepolarizing NMBAs is prolonged weakness, which occurs by two separate mechanisms. The accumulation of a NMBA parent drug or its metabolites is seen with some agents (e.g., pancuronium and vecuronium), especially in patients with renal and/or hepatic dysfunction.[91] The second cause of weakness associated with NMBAs is known as *acute quadriplegic myopathy syndrome*. Patients with this syndrome manifest acute paresis, myonecrosis with increased creatine phosphokinase concentration, and abnormal electromyography. Electromyographic findings are consistent with denervation of skeletal muscle, which may progress to muscle atrophy and even muscle necrosis.

Complications of NMBAs have reduced, but not eliminated, their use in the ICU.[92] This is particularly noteworthy when corticosteroids are used in conjunction with NMBAs. Several studies suggest this combination is associated with a significant incidence of myopathy.[93] Table 50-4

TABLE 50-4: PROPERTIES OF COMMONLY USED NEUROMUSCULAR BLOCKING AGENTS

	Succinylcholine	Pancuronium	Vecuronium	Rocuronium	Atracurium	Cisatracurium
Type	Depolarizing	Nondepolarizing	Nondepolarizing	Nondepolarizing	Nondepolarizing	Nondepolarizing
Typical loading/ intubation dose	1.0 to 1.5 mg/kg	0.1 mg/kg	0.1 mg/kg	0.6 to 1.0 mg/kg	0.5 mg/kg	0.1 to 0.2 mg/kg
Continuous infusion? (dose)	No	No	No	No	Yes (10 to 20 mcg/kg/min)	Yes (2 to 3 mcg/kg/min)
Onset	60 seconds	3 to 5 minutes	3 to 5 minutes	1 to 2 minutes	3 to 5 minutes	3 to 5 minutes
Duration after loading dose	7 to 9 minutes	60 to 90 minutes	30 to 40 minutes	30 to 45 minutes	20 to 45 minutes	25 minutes
Metabolism	Plasma cholinesterase	Hepatic	Hepatic/biliary	Hepatic	Ester hydrolysis/ Hoffman elimination	Ester hydrolysis/ Hoffman elimination
Elimination		Renal	Renal/biliary	Biliary clearance of parent molecule from plasma		
Active metabolite?	No	Yes	Yes	Yes (minimal)	No	No
Cardiovascular effect	Supraventricular and ventricular rhythm disturbances with hyperkalemia	Vagolytic—tachycardia	None	None	Histamine release	No histamine release
Common side effects	Hyperkalemia	None	None	None	Histamine release	None

summarizes the pharmacologic properties of commonly used NMBAs.

IMPORTANT UNKNOWNS AND THE FUTURE

Currently available drugs for pain control, sedation, and neuromuscular blockade in mechanically ventilated patients all have important limitations. Given the availability of agents with fewer propensities to accumulate and impair neurologic evaluations or liberation from mechanical ventilation, the use of benzodiazepines in the ICU is falling out of favor. Novel approaches, such as inhalational agents and fospropofol, will require more research before they move into the mainstream.

Protocol-driven management of sedation and pain control can clearly improve patient outcomes, regardless of the agent administered. More experience with protocols and better understanding of potential limitations is needed to continue to optimize patient outcomes, both short-term and long-term. As such, further expansion of protocol-driven administration of sedation and analgesia should be evaluated, particularly in different ICU environments, such as general surgery, trauma, or neurologically injured patients.

Use of sedation scales and titration of drugs based upon goals described by these objective scales should allow optimization of sedation and analgesia. The impact of sedation and analgesia on delirium during critical illness must be further studied, given the magnitude of this problem in terms of prevalence and associated morbidity. The impact of neuromuscular blockade, sedation, and pain control on recovery following respiratory failure is poorly understood. Patients who require mechanical ventilation during critical illness suffer psychological and physical complications, and recovery may be slow and incomplete.[94–96] With recognition of psychological maladjustment, a few strategies achieving improved outcomes have been reported,[31,87,97] but more studies in this area are needed. Physical debilitation after respiratory failure and critical illness is well described, with most studies focusing on recovery from acute respiratory distress syndrome. Many of these patients suffer from critical illness-related polyneuropathy and myopathy.[98,99] Sedation strategies can allow patients to be more interactive in the ICU environment; this can encourage the opportunity for very early mobilization in the ICU[83,100,101] and reductions in functional impairment and deconditioning.

SUMMARY AND CONCLUSION

Pain control, sedation, and neuromuscular blockade are important components of the treatment of mechanically ventilated patients. Directing treatment to specific and individualized goals will assure that patient needs are met. All currently available agents for use in ventilated patients have limitations and complications related to their use. Rather than seeking an ideal drug, strategies of drug administration that focus attention on principles of sedative pharmacology in critical illness should be utilized. When these drugs are given to individual patients, recognition of specific goals will allow rational administration strategies to be implemented, which should lead to improvement in short- and long-term outcomes.

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HUMIDIFICATION

51

Jean-Damien Ricard
Didier Dreyfuss

Humidification issues are overlooked by many clinicians in the intensive care unit (ICU). Because the need to heat and humidify inspired gases during mechanical ventilation is unanimously accepted, this process is considered the basic, supportive standard of care, about which there is no real debate. Yet, considerable controversy has surrounded central issues concerning humidification such as the level of adequate humidification and how to provide it, the influence of humidification devices on the incidence of ventilator-associated pneumonia, and certain patients and clinical situations and their requirements, such as the need for humidification during noninvasive ventilation. This may account for important differences in the practice of humidification between countries.[1,2] Fortunately, renewed interest has emerged over the past decade, as indicated by several clinical studies that have helped settle some controversies. This chapter will review the reasons for conditioning inspired gases by recalling the normal process of heating and humidifying air during spontaneous breathing, the physical principles of humidification, and the consequences of inappropriate conditioning. Devices to achieve this conditioning are covered and their advantages and potential drawbacks discussed. Finally, practical guidelines are provided.

RATIONALE

As mentioned in the next section, the upper respiratory tract is responsible for most of the conditioning of the inspired gases. Important features of this conditioning (reviewed by Irlbeck[3]) include heat, humidification, and filtration, in order to deliver to the lower respiratory tract a warm (32°C [89.6°F]), humid (95% relative humidity), and pathogen-free and particle-free gas. The last step is achieved in the lower respiratory tract. During invasive mechanical ventilation, the endotracheal tube bypasses the upper respiratory tract. This places the burden of supplying heat and humidity to the cold and dry medical gases on the lower respiratory tract, a task for which it is poorly suited.[4]

ANATOMY AND PHYSIOLOGY OF THE UPPER AIRWAY

The upper respiratory tract (nose, mouth, nasopharynx, oropharynx, laryngopharynx, and larynx, but mainly the nose) is responsible for most of the conditioning of inspired gas. Anatomic structure and physiologic function of the nose are

intimately linked. The highly vascular mucosa of the nose is ciliated and rich in mucosal glands and goblet cells. Three curved bony plates on the lateral side of each nasal cavity (the superior, middle, and inferior concha or turbinate bones), covered with a mucous membrane, ensure the important function of satisfactorily conditioning inspired gases. Their large surface area and position in relationship with the air current enable sufficient contact with the inspired gas. This mucous membrane also lines the paranasal sinuses, trachea, and bronchi but not the pharynx, which does not take part in the air-conditioning process.

PHYSICAL PRINCIPLES OF HUMIDIFICATION

Humidity can be defined as the moisture content of the atmosphere and by extension, water present as vapor in a gas mixture. Vaporization indicates the change of a liquid (or a solid) to a gas or vapor. There is no strict difference between the terms *gas* and *vapor,* although gas is generally used to describe a substance that appears in the gaseous state under standard conditions of pressure and temperature, and vapor to describe the gaseous state of a substance that appears ordinarily as a liquid or solid. Such a change of state requires a certain amount of energy or heat to overcome the van der Waals forces that bind the molecules together in the liquid state. They then escape the liquid as individual molecules of vapor. This amount of heat, specific for each substance, is known as the latent heat of vaporization of the substance.

Importantly, liquids can change to gases at temperatures below their boiling points. Vaporization of a liquid below its boiling point is called evaporation, and can occur at any temperature when the surface of a liquid is exposed in an unconfined space. Molecules of liquid that leave the surface of the liquid (because of sufficient kinetic energy) turn to vapor. They do so with their latent heat; the loss of heat causes the liquid's temperature to decrease. These molecules of vapor exert a certain amount of pressure known as vapor pressure. Vapor pressure is substance and temperature specific (i.e., each substance has a specific vapor pressure for each given temperature). At its boiling point, the vapor pressure of a liquid is equal to the atmospheric pressure. Therefore, vapor pressure of water at 100°C (212°F) is 760 mm Hg.

Measurements of humidity include absolute humidity and relative humidity. Absolute humidity is the mass of water vapor per unit volume of the gas mixture and is measured in milligrams of water per liter of gas (mg H_2O/L). Importantly, at any given temperature, a gas may contain only up to a certain amount of water vapor, corresponding to its maximal capacity at that temperature. Any extra water vapor will condense back into a liquid state. Relative humidity indicates the ratio of the actual water vapor content of the gas mixture to its total capacity at the given temperature. The amount of water vapor a gas can contain is directly proportional to the temperature of the gas (Fig. 51-1). For example, air with 50% relative humidity contains 22 mg of H_2O at 37°C (98.6°F), but only 8.5 mg of H_2O at 20°C (68°F).

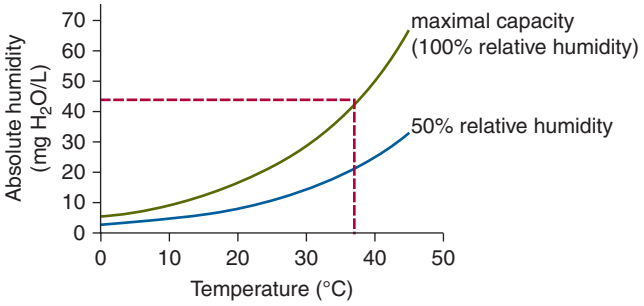

FIGURE 51-1 Absolute humidity (mass of water vapor) of air as a function of temperature at two relative humidities (100% and 50%). The *dotted lines* indicate the value of absolute humidity (44 mg H_2O/L) at core body temperature (37°C [98.6°F]) when air is fully saturated (100% relative humidity).

PHYSIOLOGIC PRINCIPLES OF HUMIDIFICATION

Physiologic humidification delivers inspired air at 37°C (98.6°F) and saturated with water vapor (100% relative humidity) to the lungs. Figure 51-1 indicates that in these conditions, the gas mixture contains 44 mg of H_2O per liter. The principle of humidification lies in the heat and humidity gradient that exists between the inspired gas and the respiratory tract.

As indicated above, humidification occurs first and mainly in the nose, then in the trachea and up to the second-generation bronchi. The large surface area of the turbinates, in combination with their irregular shape and protrusion into the nasal cavity that create a turbulent flow, enables a rapid transfer of heat from the mucosa to the inspired air. This heat gain is sufficient to allow water to evaporate from the mucosa into the inspired gas, enabling its humidification. As a result, inspired gas is warmed and humidified and nasal mucosal temperature decreases from 37°C (98.6°F) to 31°C (87.8°F).

During expiration, the opposite occurs. The gas leaves the alveolus at 37°C (98.6°F) with 44 mg/L of H_2O, and transfers heat to the cooler upper airway. As its temperature decreases, so does its maximal water content capacity. Condensation on the mucosa then occurs. At the end of expiration, approximately one-third of the heat and humidity has been transferred back to the mucosa.

Until the inspired gas has reached 37°C (98.6°F) with 44 mg/L water content, heat and water are lost from the respiratory tract. The point at which inspired gas reaches core temperature and 100% relative humidity is called the isothermic saturation boundary. It is usually situated in the second-generation bronchi. After this point, temperature and humidity of inspired gas remain constant, to ensure adequate gas exchange in the alveolus. Depending on climatic

conditions, the isothermic saturation boundary may move up or down the respiratory tract.

PATHOPHYSIOLOGY OF THE UPPER AIRWAY

Underhumidification

Underhumidification results from the bypassing of the upper airway that follows tracheal intubation and from the absence or inadequacy of conditioning of the dry, compressed, medical gas. Delivery to the lower respiratory tract of insufficiently warmed and humidified gas displaces the isothermic saturation boundary further down the bronchial tree. Moisture and heat loss ensues, inducing structural damages of the respiratory tract that may lead to physiologic and functional impairments with clinical repercussions.

EFFECTS OF MOISTURE LOSS

Moisture loss from the respiratory tract is, under normal conditions, a physiologic phenomenon (approximately 150 mL water) and contributes to the body's insensible water loss. The loss may be much greater if minute ventilation is increased, or if the gradient between the water content of inspired and expired air is large or both. This situation is encountered during mechanical ventilation and was first described during general anesthesia. In one of the first comprehensive studies on this topic, Burton described the reduction of mucociliary function after several hours of dry gas ventilation. When heat and humidity were added, mucociliary function was restored.[5] Numerous studies have been performed subsequently and exhaustively reviewed.[4] The adverse effects of inadequate humidification comprise structural damages such as loss of ciliary function, cilia destruction, damage to mucus glands, cytoplasmic and nuclear degeneration, cellular desquamation, mucosal ulceration, changes in tracheal cytology, and loss of surfactant. Such structural damage has functional repercussions: destruction of the mucociliary escalator, increase in sputum viscosity, increased airway resistance, decreased pulmonary compliance, reduced functional capacity, and increased pulmonary shunting. Clinical consequences include retained secretions, mucus plugging, atelectasis, increased work of breathing, hypothermia, and hypoxemia.[3] In clinical practice, the worst and most feared adverse effect of underhumidification is life-threatening endotracheal tube occlusion, which requires urgent endotracheal tube replacement (see section on effectiveness and outcome, below).

EFFECT OF HEAT LOSS

During general anesthesia, the amount of heat loss through the respiratory tract is very small in comparison with that of other sources (e.g., the operative field and skin). Two mechanisms may account for this loss. Heat is transferred from the respiratory mucosa to the inspired gases, and the amount depends on the patient's minute ventilation, the temperature gradient between the respiratory tract and the inspired gas, and the latter's specific heat. Given the very low specific heat of air, minimal heat is required to raise its temperature. The second and major mechanism by which heat is lost is vaporization (change of liquid water of the respiratory mucosa into vapor and its transfer to the inspired gas). Given the high specific heat of water, a significant amount of heat is required to raise the relative humidity of inspired gases. The amount of heat is further increased when the relative humidity of the inspired gas is very low (i.e., dry medical gas). These considerations may be important during prolonged surgery in infants and young children, keeping in mind that skin, operative site, and fluid administration are the major contributors to the heat loss.

Overhumidification

Because heat and moisture exchangers (HMEs) act passively (see below), they cannot deliver excessive heat or water to the respiratory tract. Consequently, the adverse effects described below are only possible with heated humidifiers and aerosol humidifiers and are now seldom encountered.[6]

EXCESS WATER

The volume of water that can be added to the airway mucosa depends on the state it is in. With heating and humidifying devices, water is in a molecular form (vapor) and is therefore unlikely to result in overhumidification, given the amount of water vapor contained in inspired gases. To significantly increase this amount would require excessive heating of the inspired gas (way above body temperature), thus causing thermal injury before overhydration. Effects of excess water have been reported in the past with the use of aerosol humidifiers,[7] but clinicians are now well aware of these side effects.

EXCESS HEAT

Reports of lung injury secondary to excessive heat are rare[6] and are related to the misuse of heated humidifiers.[8]

METHODS OF HUMIDIFICATION

Although many different types of humidifiers have been developed in the past, clinicians mainly use two types of devices to condition inspired gas during mechanical ventilation: heated humidifiers and HMEs.

Heated Humidifiers

The general working principle of heated humidifiers is to heat water contained in a humidification chamber that humidifies

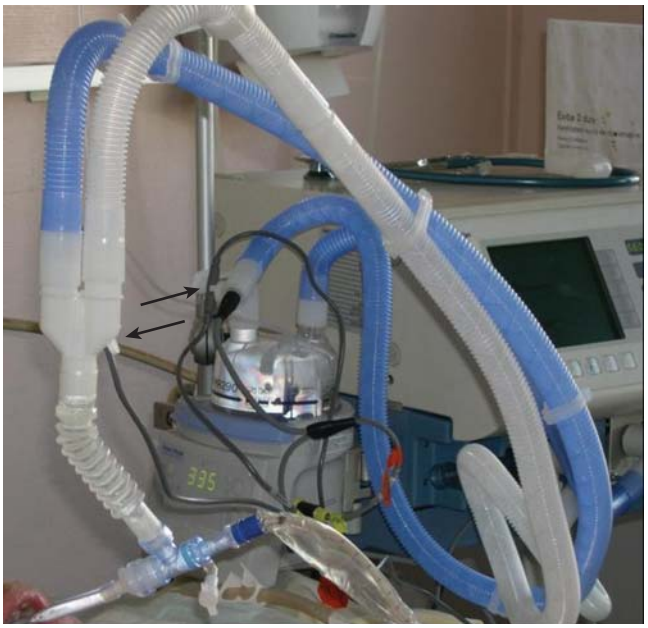

FIGURE 51-2 Heated humidifier with a heated breathing circuit. Two temperature probes monitor gas temperature at the exit of the humidifier chamber and at the Y-piece before the endotracheal tube (*black arrows*).

inspired gas passing through it (Fig. 51-2).[9] Heating the water enables evaporation to occur, and the gas leaves the chamber saturated with water vapor. Evaporation depends on the surface area over which it occurs, the temperature of the liquid water, and the magnitude of the vapor pressure above the water surface. It can therefore be increased by augmenting the contact of inspired gas and water (larger humidification chamber), by raising the temperature of the liquid water, and by increasing the mass flow of gas above the water surface so as to decrease the vapor pressure. Once the inspired gas has left the humidifier, it cools along the breathing circuit before reaching the patient. Thus, the temperature one wished to achieve at the patient's level will not be reached. There are two ways to help overcome this problem. Inspired gas can be heated in the chamber to above the temperature one wishes to deliver to a patient, to take into account the heat loss across the circuit. Abundant condensation, however, will occur inside the tubing, providing an ideal reservoir for bacterial colonization[10,11] and will need to be drained, exposing health care workers to contaminated fluids and placing other patients at risk of cross-contamination.[12] To prevent this condensation (that results from the decrease in the temperature of the gas whose maximum vapor-carrying capacity is therefore reduced), breathing circuits can be heated by placing electric heater wires either in the wall or in the lumen of the circuit.

New devices are now servocontrolled by means of temperature sensors placed at the exit of the humidification chamber and just before the catheter mount (or flex tube). Because only the temperature is monitored (and not the humidity), however, these devices may become faulty in certain circumstances (see below).[13,14]

Heat and Moisture Exchangers

HMEs have undergone considerable development since their first description in the mid-1950s.[15] The basic principle of all HMEs lies in their capacity to retain heat and moisture during expiration and deliver these to the incoming dry medical gas during subsequent inspiration (Fig. 51-3).[16] This passive function has been achieved by different mechanisms. Metal elements of the first condensers were replaced by disposable foam, plastic, or paper. Increased moisture output was further achieved by coating the condenser element with a hygroscopic chemical (calcium or lithium chloride), which chemically adsorbs expired water vapor that is then returned to the inspired gas. These HMEs were called hygroscopic condensers. Derived from the field of filtration, hydrophobic HMEs were also used to heat and humidify inspired gas. The very large surface area of pleated, water-repellent ceramic of the first hydrophobic HMEs along with its low thermal conductivity enabled an important temperature gradient to develop within the HME that favored heat and moisture retention. Finally hygroscopic and hydrophobic elements were used in a single HME to create a "combined" HME. Hygrometric performance of these various HMEs differ considerably,[17] with hydrophobic HMEs exhibiting the lowest humidity outputs (with the attendant risk of endotracheal tube occlusion) and combined HMEs the highest, although recent measurements indicate that some purely hygroscopic HMEs provide levels of absolute humidity comparable

FIGURE 51-3 A combined (hydrophobic and hygroscopic) heat and moisture exchanger. *Dark arrows* indicate the presence of dripping wet condensation in the flexible tubing (the bright reflection seen on the wall of the tubing) suggesting that adequate humidity is being delivered by the heat and moisture exchanger (see text for details). Note that the heat and moisture exchanger is positioned vertically above the endotracheal tube, thus limiting the amount of secretions refluxing from the tube to the heat and moisture exchanger.

to those of combined HMEs.[18,19] New devices have been designed to boost the humidifying performance of HMEs,[20] although their actual clinical benefit is uncertain.

APPLICATION

Based on the above principles, supplying heat and humidity to inspired gases is mandatory when the upper airway is bypassed during tracheal intubation. This supply must be provided as soon as the patient is connected to the ventilator, either by an HME or by a heated humidifier. Apart from certain specific situations (see "Practical Steps" below), both HMEs and heated humidifiers serve equally well. Despite this, practices differ considerably among countries.[1,21] Rationalizing the choice of a given humidifying device should help decrease costs in mechanical ventilation without impeding quality of care.

EFFECTIVENESS AND OUTCOME

Several important aspects must be taken into account when analyzing the effectiveness and outcomes of inspired gas conditioning, including:

- The avoidance of endotracheal tube occlusion (the worst and most feared complication of inadequate gas conditioning). This aspect is directly linked to the performance of the humidifying device in terms of heat and humidity delivery;
- The avoidance of spreading microorganisms (especially multidrug-resistant organisms). This is directly linked to the humidifying device's capacity to prevent contamination of the respiratory tubing (Fig. 51-4 and Fig. 51-5);
- The addition of minimal resistance and dead space;
- The practicability of use of the device;
- The minimal maintenance necessary to ensure optimal use of the device; and
- The minimal cost associated with the purchase and the long-term use of the device.

Using this list, one can define the characteristics of the ideal humidifier: a device that provides adequate levels of humidification whatever the ventilator and patient conditions; one that does so automatically; one that is safe to operate (i.e., is electric-shock free, with no or a limited number of connections that can become faulty); one that protects the environment from the patient's pathogens; one that is easy to use; and one that requires low maintenance and is inexpensive.

Ensuring Adequate Humidification

The adequate level of humidification can be defined as a level at which there is no excessive heat or water loss by the respiratory tract. The difficulty arises when one tries to set the minimum value of absolute humidity a device should deliver.

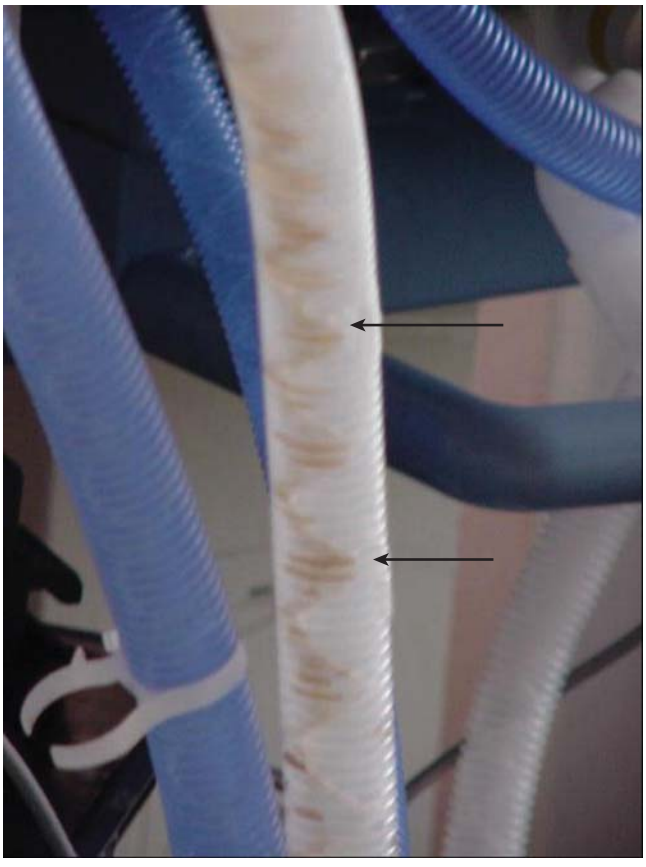

FIGURE 51-4 A heavily contaminated breathing circuit.

This may be useful when selecting and comparing different devices. Although ranges as wide as 25 to 35 mg H_2O/L have been suggested in the past,[22] the figure of 30 mg H_2O/L is recommended today.[24] That is, a clinician wishing to select an appropriate humidifying device should make sure that the device delivers at least 30 mg H_2O/L of absolute humidity.

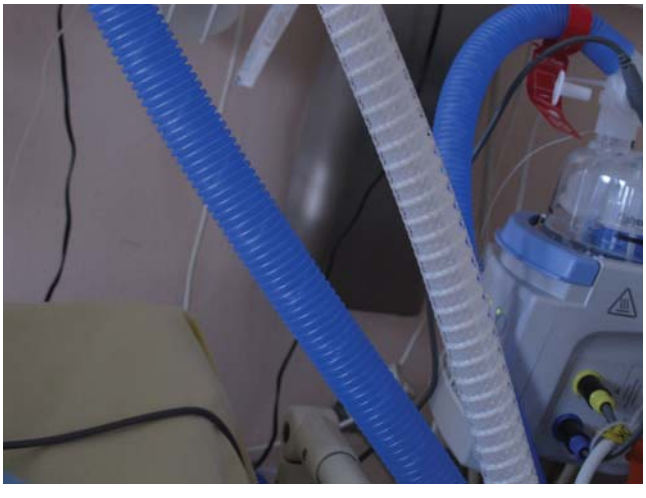

FIGURE 51-5 A dual heated respiratory circuit. The new generation expiratory limb (*white tubing*) allows water vapor to diffuse through the tubing wall, thus minimizing condensate formation in the limb.

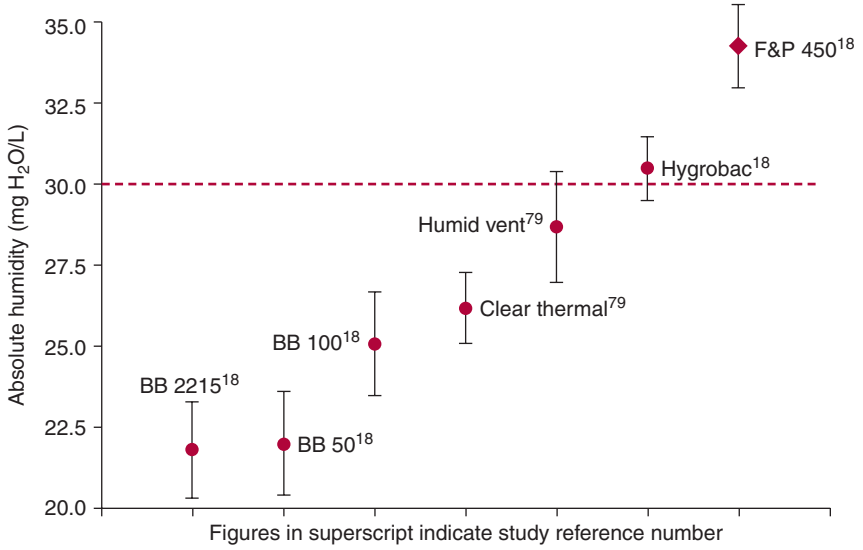

FIGURE 51-6 Values of absolute humidity delivered by several heat and moisture exchangers and one heated humidifier. The *dotted horizontal line* delineates the minimum value of humidity (30 mg H_2O/L) a device should deliver. Note the discrepancies that exist among heat and moisture exchangers (*red circles*). The HMEs exhibiting the lowest values of absolute humidity are those most strongly associated with endotracheal tube occlusions. The heated humidifier (*red diamond*) exhibited the highest value for absolute humidity.

A recent study indicates that this output is not achieved by all available HMEs.[23]

In the past, HMEs and heated humidifiers were not equivalent in terms of humidity output. Back in the late 1980s, several studies alerted clinicians to the risk of endotracheal tube occlusions associated with the use of HMEs.[24–27] These studies, however, all used purely hydrophobic HMEs, whose measured performance displayed low values of absolute humidity.[17,18,28,29]

Although heated humidifiers indisputably deliver greater values of absolute humidity than HMEs[17,28,29] (Fig. 51-6), there is to date no evidence of any benefit of these greater values in terms of clinical outcome, including endotracheal tube occlusion. Table 51-1 displays the incidence of endotracheal tube occlusion reported in recently published studies. It is important to note that: (a) endotracheal tube occlusion rates have drastically dropped in comparison with earlier studies;[25–27] (b) endotracheal tube occlusion is also reported with the use of heated humidifiers; and (c) the incidence of endotracheal tube occlusion no longer appears to be greater with HMEs than with heated humidifiers. In one study, the incidence was greater with heated humidifiers than with HMEs.[30]

The reasons for this unusually high rate of endotracheal occlusions deserve particular attention. As indicated above (see "Methods of Humidification" above), new heated humidifiers are servocontrolled. Because the temperature of the incoming gas mixture has a direct effect on the heating mechanism of the plate that warms the humidification chamber, if the temperature is too high, the plate no longer heats, resulting in very low levels of absolute humidity,[13,14] sometimes below 20 mg H_2O/L.[13,14] These very low values, well below the 44 mg H_2O/L expected with these devices, are encountered when the temperature of the gas exiting the ventilator is high and/or when the ambient temperature is high.[13,14] It is notable that depending on the type of ICU ventilator, the output ventilator temperature may vary from 26°C to 35°C (78.8°F to 95°F).[13,14] An automatic compensation system has been designed that seems to be effective in overcoming this worrisome problem.[14,31] This system is available on some, but not all, heated humidifiers. If not, HMEs should be used.

TABLE 51-1: ENDOTRACHEAL TUBE OCCLUSION RATES IN STUDIES COMPARING HEATED HUMIDIFIER AND HEAT AND MOISTURE EXCHANGERS

Reference	No. of Patients	No. of ETT Obstructions	
		HH	HME
Branson et al 1993[75]	120	0	0
Dreyfuss et al 1995[54]	131	0	1
Branson et al 1996[76]	200	0	0
Villafane et al 1996[31]	23	1	0
Boots et al 1997[57]	116	0	0
Hurni et al 1997[78]	115	1	0
Kollef et al 1998[58]	310	0	0
Thomachot et al 1998[74]	29	0	0
Kirton et al 1998[56]	280	1	0
Lacherade et al 2002[32]	370	5	1
Jaber et al 2004[93]	60	2	1

Abbreviations: ETT, endotracheal tube; *HH*, heated humidifier; *HME*, heat and moisture exchanger.

Resistance

Both types of humidifying devices (HMEs and heated humidifiers) marginally increase resistance to flow in the respiratory circuit[32–35] with no impact on auto–positive end-expiratory pressure, even in patients with chronic obstructive pulmonary disease (COPD).[36] Thus, resistance to flow of humidifying devices during invasive mechanical ventilation is not a major problem clinically.

Dead Space

Because of their internal volume, HMEs increase dead space in the ventilator circuit.[35,37,38] This increase is directly proportional to the internal volume of the HME, which may vary between 30 mL and 95 mL.[38] The impact of dead space on work of breathing and arterial CO_2 depends on the mode of ventilation and tidal volume used. During volume-assist control ventilation, internal dead space will only influence Pa_{CO_2} and pH: the smaller the tidal volume used (in combination with an HME with a large internal volume), the greater the impact on arterial CO_2 and pH.[39,40] During invasive and noninvasive pressure-support ventilation, use of HMEs may increase work of breathing in COPD and in difficult-to-wean patients.[34,41–45] This increase in work of breathing, however, is easily overcome by increasing the level of pressure support by 5 to 10 cm H_2O.[34,41,43,44]

Microbiologic Outcome

NOSOCOMIAL PNEUMONIA

The problem of nosocomial infection related to respiratory equipment is not new, and older inhalation therapy equipment posed a considerable challenge in ICUs in the past.[46–49] Similarly, it has been suggested that contamination of respiratory tubing used with heated humidifiers may be a risk factor for ventilator-associated pneumonia.[11,50] This hypothesis stemmed from the rapid and considerable bacterial colonization of respiratory tubing encountered with use of heated humidifiers.[10–12,51] Because HMEs prevent bacterial contamination of respiratory tubing,[52,53] the question arose as to whether, or not, the incidence of ventilator-associated pneumonia was greater with heated humidifiers.[54] There is now overwhelming evidence that the method of humidification does not influence occurrence of ventilator-associated pneumonia.[30,52,55–58] This is not very surprising considering the pathogenesis, mainly the silent aspiration of contaminated gastric and oropharyngeal secretions.[59] Consistent with this reasoning, the incidence of ventilator-associated pneumonia is not affected by the duration of use of HMEs, whether changed every 48 hours,[60] 72 hours,[18] or only once a week.[61] Similarly, the type of HME does not influence the rate of ventilator-associated pneumonia.[62,63] Despite these facts, some have recently recommended they be preferred to heated humidifiers to prevent nosocomial pneumonia.[64]

CROSS-CONTAMINATION

Although use of heated humidifiers is not associated with a greater incidence of ventilator-associated pneumonia, these devices do have the potential for cross-infection.[12] Craven et al studied ventilator-circuit colonization during the first 24 hours after a circuit change. They found a rapid colonization: 33% of circuits were colonized at 2 hours, 64% at 12 hours, and 80% at 24 hours. The median level of colonization at 24 hours was 7×10^4 organisms/mL.[11] Bacteria isolated in respiratory tubing condensates correlate with the microorganisms found in patients' tracheobronchial secretions.[11,51,55] These highly contaminated condensates should therefore be handled as infectious waste and regularly emptied.[11] Repeating these septic maneuvers several times a day increases the risk of cross-infection, especially when patients are colonized with multidrug-resistant bacteria.[65]

Preventing respiratory tubing contamination confers on HMEs a great advantage over heated humidifiers.[19,52,55] Attempts have been made to reduce formation of condensation in the circuits by heating both the inspiratory and the expiratory limb of the circuit. Such equipment needs to be evaluated in the clinical setting. A preliminary report found that condensation still occurred in up to 50% of patients ventilated with these heated circuits,[65] leading to substantial bacterial colonization (see Fig. 51-4). A modified expiratory limb enabling evaporation through the wall of the circuit considerably decreases occurrence of condensation in the circuit (see Fig. 51-5).

Practicability and Maintenance

For obvious reasons, HMEs are far easier to handle than heated humidifiers. They require no maintenance and several studies indicate that they reduce staff work load.[52,56,66] Several technical improvements brought to the new heated humidifiers (servocontrol, automatic water-filling system, heated respiratory circuits, and so on) have considerably reduced the time required to check and operate them.

Safety

Clinicians are well aware of the hazards associated with HMEs (mainly endotracheal tube occlusion),[1] but may be less aware of the hazards associated with heated humidifiers. Some recently described hazards deserve particular attention. Burns to the patients and breathing circuit meltdowns have occurred in the past because of heated wires.[67–69] More frequent and more recent is the risk of ventilator shutdown because of rain out from heated humidifiers.[70–72]

Costs

Several studies have compared the costs of humidification with HMEs with those of heated humidifiers.[52,54–56,66,73,74] All conclude that considerable cost savings can be achieved by using HMEs, not only because heated humidifiers are

expensive to buy, but also because they are expensive to run (especially because of the price of heated respiratory tubing). Costs can be further reduced by extending the use of HMEs; several studies indicate that these devices may be used without change for up to a week (see below).[56,61,75]

PRACTICAL STEPS

Invasive Mechanical Ventilation

An algorithm for heating and humidifying inspired gases during invasive mechanical ventilation is proposed in Figure 51-7.

WHICH DEVICE FOR WHICH PATIENTS

There are very few and rare contraindications to the use of HMEs. Because they act passively, the amount of heat and moisture they deliver to the inspired gases depends on the amount of heat and moisture they retain during expiration. Therefore, patients with profound hypothermia or important bronchopleural fistulas should preferably be ventilated with a heated humidifier. In addition, a heated humidifier may be preferable in patients ventilated for acute asthma or acute respiratory distress syndrome, in whom a drastic decrease in tidal volume induces extreme respiratory acidosis (to avoid increased dead space with HMEs).[39,40] A heated humidifier can be used until the patient's respiratory condition improves sufficiently to enable the use of an

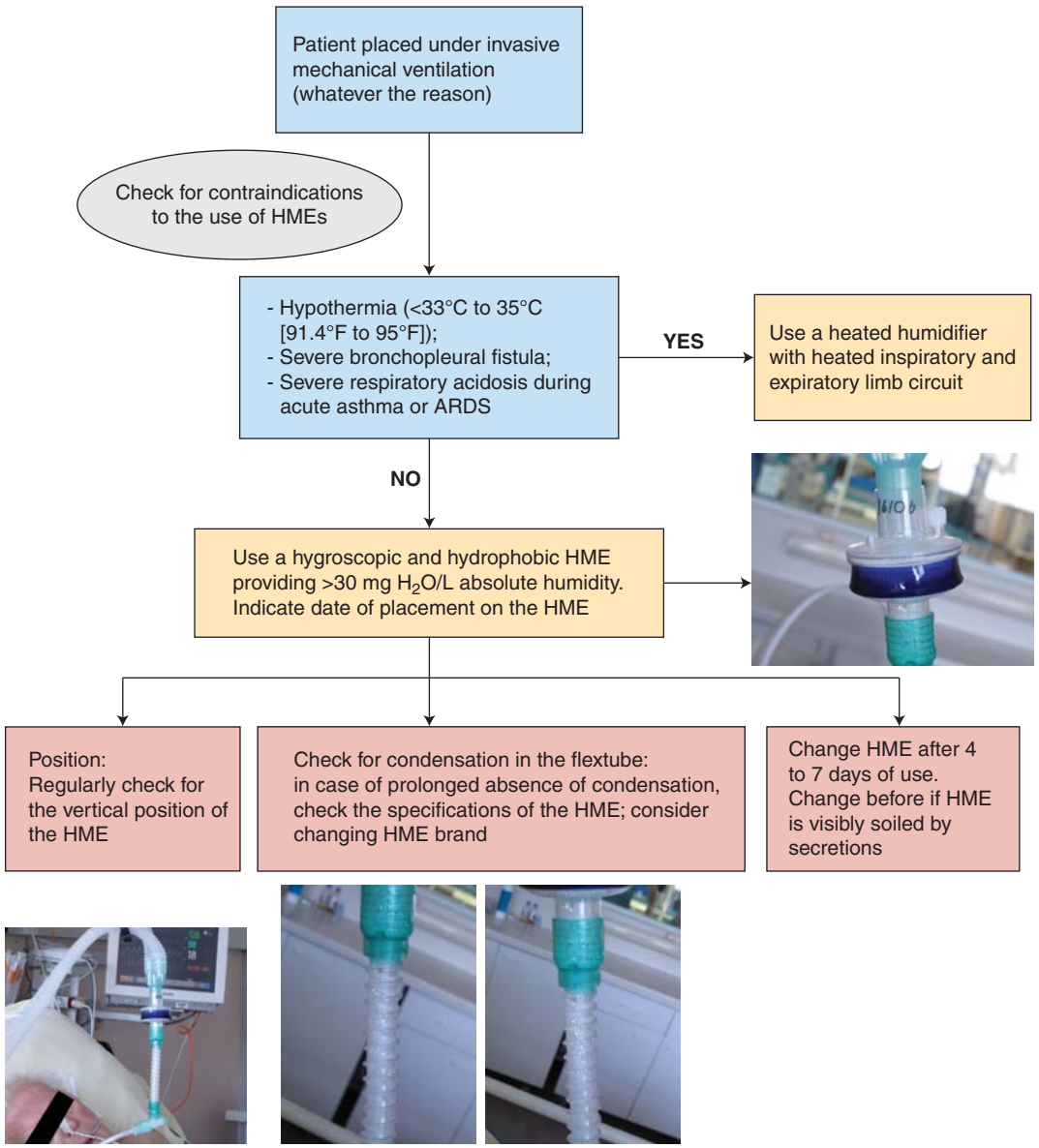

FIGURE 51-7 Algorithm for heating and humidifying inspired gases during invasive mechanical ventilation. *ARDS,* acute respiratory distress syndrome; *HME*, heat and moisture exchange.

HME. Apart from these specific situations, HMEs should be considered first to heat and humidify inspired gases of all ventilated patients. They are as effective as heated humidifiers, and are much cheaper and much easier to use. Importantly, medical as well as surgical patients can benefit from them.

Despite the former practice of restricting their use to patients without a history of respiratory disease and only for the first 5 days of mechanical ventilation,[74,76] several studies have clearly shown that they may be used in any ventilated patient, even in patients with COPD and for any length of mechanical ventilation. Because patients with COPD represent the most important subgroup of ventilated patients in the United States,[77] and because their duration of ventilation is longer than that of other patients,[77] adequate humidification is probably more critical in such patients than in patients ventilated for shorter periods. Numerous studies show that long-term mechanical ventilation can be safely conducted in such patients with HMEs.[19,55,56,75,78–80] Three studies have specifically compared humidity output of HMEs in patients with and without COPD and consistently found that the measured values for absolute humidity were very similar (Fig. 51-8).[19,75,80]

FREQUENCY OF HEAT AND MOISTURE EXCHANGE REPLACEMENT

There is now considerable evidence that HMEs may be used for longer than the 24 hours recommended by manufacturers.[18,19,56,60,61,73,75,79–82] Compelling results stem from rigorous clinical evaluation[56,60] or extensive bedside measurement of humidity delivery.[18,19,61,75,79–81] Figure 51-9 shows that humidity delivery of a combined HME (Hygrobac, DAR, Mirandola, Italy) used for 7 days without change was remarkably stable throughout this period. Progressive clogging of the device with tracheal secretions (that seriously increase resistance to airflow) could have been a drawback. Repeated measurements of the resistance of the HME over 7 days indicate that this phenomenon did not occur (Fig. 51-9).[75]

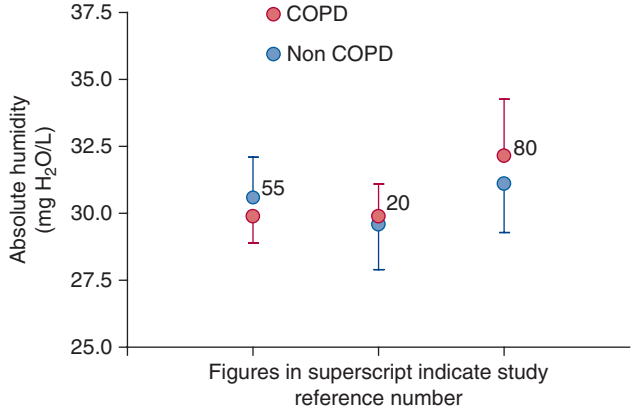

FIGURE 51-8 Comparison of the absolute humidity delivered by heat and moisture exchangers in patients with and without chronic obstructive pulmonary disease (COPD). Values are similar, indicating that these devices are suitable for patients with COPD undergoing mechanical ventilation.

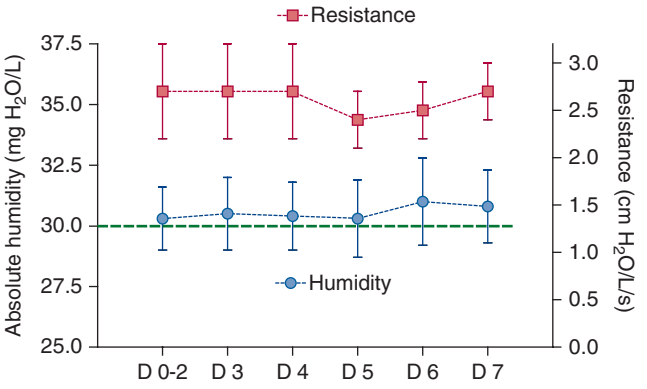

FIGURE 51-9 Absolute humidity (*left Y axis*) and resistance (*right Y axis*) measured over time in combined heat and moisture exchangers used for 7 days without change. Note the perfect stability of the humidity output and the lack of increase in resistance over time. (Adapted, with permission, from Ricard et al.[53])

Keeping the HME vertically above the tracheal tube (see Fig. 51-3) (and having nurses and doctors repeatedly check the position of the HME) prevents secretions from refluxing from the tracheal tube and obstructing the HME.[19,75] Use of HMEs may be extended in both medical patients (including those with COPD[19,75,79,80]) and surgical patients.[18,61,73,82] This practice is now widely accepted,[83] and recommendations have been made to change HMEs only once a week.[64] In our own published[75] and unpublished experience,[75] we have been changing HMEs only once a week since 1997, and have not encountered endotracheal tube occlusions.

Noninvasive Mechanical Ventilation

The question of heat and humidification requirements during noninvasive ventilation has gone unanswered until very recently. The 2001 International Consensus Conference on Noninvasive Ventilation made no recommendation as to whether a humidifying device should be used or not.[84] This absence stems from the uncertainties regarding the level of humidification required during noninvasive ventilation (given the fact that the upper airways are not bypassed) and that can be achieved during noninvasive ventilation with HMEs and heated humidifiers.

This aspect has received attention in a recent study that compared the water content of gas delivered obtained during noninvasive ventilation with either an HME or a heated humidifier, and the comfort or discomfort experienced by healthy subjects.[85] In the absence of humidification, water content was very low when an ICU ventilator was used (5 mg H_2O/L), but equivalent to ambient air hygrometry with a turbine ventilator at minimal fractional inspired oxygen concentration (FI_{O_2}) (13 mg H_2O/L). HME and heated humidifier had comparable performances (25 to

30 mg H_2O/L) although HME's effectiveness was reduced with leaks (15 mg H_2O/L). During continuous positive airway pressure, dry gases (5 mg H_2O/L) were less tolerated than humidified gases. Gases humidified at 15 or 30 mg H_2O/L were equally tolerated. These data indicate that in favorable conditions, HME and heated humidifiers provide equivalent comfort to the patient through similar water content to the inspired gases.

This study contrasts with some physiologic studies of the influence of the humidifying device on respiratory variables. In a randomized crossover study in nine patients receiving noninvasive ventilation for moderate to severe acute hypercapnic respiratory failure, a significant increase in work of breathing was found with HMEs in comparison with heated humidifiers), although this did not significantly impact the partial pressure of arterial carbon dioxide (Pa_{CO_2}).[44] The dead space of HMEs is obviously responsible for these observations and a recent study showed that use of an HME with a very small dead space does not alter respiratory variables, compared with heated humidifiers.[86]

The question that arises is whether the choice of a given humidifying device during noninvasive ventilation affects outcome, especially the intubation rate. To address this issue, a large multicenter randomized trial tested the hypothesis that the use of HMEs would increase intubation rates.[87] During 13 months, 247 patients were randomized to noninvasive ventilation either with an HME or a heated humidifier. The intubation rate (failure of noninvasive ventilation) was higher with a heated humidifier than with an HME, although the difference did not reach statistical significance (37.6% vs. 30.6%; $p = 0.31$). Mortality tended to be higher in the heated humidifier group (21.5% vs. 14.1%; $p = 0.18$). Pa_{CO_2} tended to be lower in the heated humidifier group (66 vs. 72 mm Hg; $p = 0.08$).[87] These preliminary results suggest that the observed increases in work of breathing, minute ventilation, and Pa_{CO_2} in carefully conducted physiologic studies (but on a small number of selected patients) may only play a marginal role in the clinical setting. Taken together, it can now be stated that noninvasive ventilation can be safely and efficiently performed with HMEs, provided attention is given to minimize leaks and that a small internal volume HME is chosen.

Adjustments at the Bedside and Troubleshooting

Assessing humidification at the bedside is desirable, if not essential, for at least two reasons: (a) a life-threatening tracheal tube occlusion[24] may occur without any precursory clinical signs of insufficient humidification; and (b) devices may not deliver, in some instances, the heat and humidity that is expected of them, because they are either malfunctioning[14] or performance in the clinical setting does not attain that stated by the manufacturer.[14,80]

Such assessment raises two questions: (a) Is the device delivering enough heat and humidity (according to the standards)? (b) Is the amount of heat and moisture delivered appropriate for a given patient?

ASSESSING HEAT AND MOISTURE EXCHANGERS AND HEATED HUMIDIFIERS AT THE BEDSIDE

A simple means of evaluating the humidity delivered by a given device is to assess the amount of condensation seen in the flexible tubing that connects either the Y-piece (when using a heated humidifier) or the HME to the endotracheal tube.[14,17,88] Indeed, the amount of condensation seen in the flexible tubing is positively correlated with the absolute humidity measured at the bedside.[14,17] If the tubing remains constantly dry over time, or only very few droplets of water are seen, then absolute humidity delivered by a device is probably below 25 mg H_2O/L, and the patient is at risk of endotracheal tube occlusion. When numerous droplets are seen in the tubing or if it is dripping wet, the device is probably delivering sufficient absolute humidity to prevent endotracheal tube occlusion.[17]

ASSESSING ADEQUACY OF INSPIRED GAS CONDITIONING

Although it is conceivable that some patients have special humidification needs, the prevailing literature indicates that heated humidifiers and HMEs equally meet humidification requirements in the vast majority of ventilated patients. Therefore, monitoring the characteristics of secretions (thick and tenacious, or watery and abundant) as a guide to insufficient or excessive humidification may be of limited value, because changes in mucus characteristics may be entirely caused by the patient's condition (respiratory status, fluid balance, and so on), and not a consequence of the humidifying device. It has been shown that air humidification with either an HME or a heated humidifier has similar effects on mucus rheologic properties, contact angle, and transportability by cilia in patients undergoing mechanical ventilation.[89]

IMPORTANT UNKNOWNS

The preliminary results showing a trend toward higher intubation and mortality rates following noninvasive ventilation with a heated humidifier[87] strongly bring into question the use of these devices during noninvasive ventilation, at least in patients for whom Pa_{CO_2} is not the main problem. A question unanswered until recently was whether a humidification device was necessary in every single patient undergoing noninvasive ventilation. The above-mentioned study by Lellouche et al[85] provides some important clues. If an ICU ventilator is used, then additional heat and moisture is essential to ensure subject comfort, and this can be achieved equally by an HME or a heated humidifier. When a turbine ventilator is used, the hygrometry obtained is close to that of ambient air, and one should ask whether inspired gases are too dry or not. Unfortunately, because this study was conducted in healthy

subjects, it remains unknown if its results are applicable to the clinical setting. One can legitimately hypothesize that the level of humidification that provides comfort to a healthy subject differs from that required for a patient with COPD suffering from acute respiratory failure.

THE FUTURE

In the field of acute respiratory failure management, underhumidification is no longer the main threat associated with invasive or noninvasive mechanical ventilation. The challenge now facing clinicians is the appropriate management (in terms of humidification) of a much larger population of patients that breathe spontaneously but require additional oxygen. Despite the millions of patients receiving external oxygen every day around the world, little data are available on their needs in terms of humidification. If very low flows of oxygen do not seem to be associated with marked discomfort, recent data indicate that cold-water bubble humidifiers perform poorly during oxygen therapy.[90] Additional heat and moisture, provided by a heated humidifier, only partially relief the dryness of mouth provoked in patients by dry oxygen.[90] Little is known when higher flows are used with a face mask. A new technique, called *high-flow nasal cannula oxygen*, has arisen from the neonatal and pediatric experience with very high-flow oxygen therapy. It combines a heated humidifier and an air-oxygen blender allowing flows up to 60 L/min with 100% FI_{O_2} (Optiflow, Fisher & Paykel, Auckland, New Zealand). One must bear in mind that patients' inspiratory flow during respiratory distress may exceed 60 L/min.[91] Thus, conventional oxygen therapy, even at its maximum flow (15 L/min), will cover only a small fraction of a patient's inspiratory flow in terms of oxygen and humidification. With a high-flow nasal cannula, better matching between an adequately heated and humidified oxygen flow and a patient's inspiratory demand is obtained. Promising results have been reported with this technique in ICU patients in acute respiratory failure,[92,93] as well as in patients presenting to the emergency department with hypoxemic respiratory failure.[94]

SUMMARY AND CONCLUSION

Adding heat and moisture to the inspired gas during invasive mechanical ventilation is mandatory. This can be efficiently achieved either by heated humidifiers or by HMEs. Although hygrometric performance of combined HMEs is slightly lower than that of heated humidifiers, they are clinically as efficient and do not cause more endotracheal tube occlusions. They may be used in the vast majority of medical (including COPD) and surgical ICU patients and for the entire duration of mechanical ventilation. Specific situations, however, such as menacing respiratory acidosis during mechanical ventilation of patients with acute asthma or very severe acute respiratory distress syndrome, require the use of a heated humidifier until the respiratory condition improves sufficiently to enable the use of an HME. Use of heated humidifiers does not increase the risk of ventilator-associated pneumonia, nor does prolonged use of HMEs. However, because circuits get rapidly contaminated with heated humidifiers (unlike HMEs), they carry the potential for cross contamination. Finally, costs of mechanical ventilation are greatly reduced with the use of HMEs.

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AIRWAY SECRETIONS AND SUCTIONING

Gianluigi Li Bassi

Retention of airway secretions in patients on invasive mechanical ventilation constitutes a common problem associated with several complications. Therefore, secretion management represents a great challenge for respiratory therapists, nurses, and physicians, particularly in the patient with underlying airways disorders. This chapter discusses management of airway secretions in mechanically ventilated patients, focusing on physiology of mucus production, clearance, and the most common treatments, both pharmacologic and nonpharmacologic, to enhance removal of retained secretions. Although adequate humidification of the inspired gas plays a primary role on mucus clearance, the reader is referred to Chapter 51 for a comprehensive discussion of this topic.

PHYSIOLOGY OF AIRWAY SECRETION AND CLEARANCE

The lungs are exposed daily to 10,000 to 12,000 L of inhaled air, which potentially carries pathogens and noxious particles. Nevertheless, airways are efficiently protected by the airway lining fluid, which constitutes a physical barrier and a medium with antimicrobial and immunomodulatory properties. The airway lining fluid is a biphasic layer formed by a gel-phase (mucus), mainly consisting of water (97%), with proteins, lipids, electrolytes, and cellular debris making up the remaining 3% of its weight. By contrast, the inner layer is a low-viscosity sol-phase that mainly provides lubrication for continuous ciliary beating.

The main components of mucus are mucins. These are large (up to 3×10^6 Daltons per monomer) heavily glycosylated proteins that provide a tangled network necessary to entrap any particles inhaled during ventilation. Two different types of mucins have been identified: (a) cell-tethered and (b) secreted mucins. Cell-tethered mucins present several functions in cellular adhesion, pathogen binding, and cellular transduction. We focus on secreted mucins, because detailed description of membrane-bound mucins goes beyond the scope of this chapter.

Four genes coding for airway-secreted mucins have been identified and map to chromosome 11p15.5[1] and 12q12.[2] As depicted in Table 52-1, the genes can be found in different

TABLE 52-1: GENES CODING FOR SECRETED MUCINS IN THE AIRWAYS

Gene	Chromosomal Locus	Tissue Distribution	Airways Predominant Distribution
MUC2	11p15	Lung, conjunctiva, middle ear, stomach, small intestine, colon, nasopharynx, prostate	Surface goblet cell Duct of submucosal glands
MUC5AC	11p15	Lung, conjunctiva, middle ear, stomach, gallbladder, nasopharynx	Surface goblet cell
MUC5B	11p15	Lung, sublingual gland, laryngeal submucosal, esophageal glands, stomach, duodenum, gallbladder, nasopharynx	Surface goblet cells Submucosal glands
MUC19	12q12	Lung, salivary gland, kidney, liver, colon, placenta, prostate	Submucosal glands

organs; MUC5AC and MUC5B are the ones most commonly expressed in human airways.[3,4] Mucin genes comprise a single large central domain (approximately 10 kb) that encodes for serine-rich, threonine-rich, and proline-rich regions, which are the sites of *O*-linked glycosylation of mucins. Importantly, linked glycans present an extraordinary diversity[5] among species and even within species; this feature provides the highly efficient binding capability between mucus and almost any particle and/or pathogen deposited on the airways. The 5′ and 3′ genomic regions encode for the von Willebrand factor-like proteic regions, rich in cysteine,[6] which allow the disulfide bonds between mucin monomers to form the ultimate polymeric structure.

Airway Secretory Cells

The airways comprise ciliated and secretory cells, structured in a pseudostratified epithelium up to the main bronchi and as a simple cuboidal epithelium toward the peripheral airways. Mucus production in normal airways is low, approximately 10 to 100 mL/day; hence, airways are covered by a thin layer (approximately 5 µm) of mucus (Fig. 52-1B). In humans, MUC5AC is mainly produced by goblet cells[7] in the proximal airways, whereas goblet cells throughout the airways and submucosal glands mostly produce MUC5B.[8]

In healthy airways, epithelium goblet cells are outnumbered nearly fourfold by ciliated cells (Fig. 52-2A). Goblet cells contain cytoplasmic granules (see Fig. 52-1C), in which mucin polymers are firmly packed. When the polymers are secreted, the mucin polymers increase in size by 500 times their packed volume[9,10] secondary to hydration.

In airways with an internal lumen equal to or greater than 2 mm, mucus is largely produced by submucosal glands (see Fig. 52-2B and D). Mucus produced by the gland is drained through several tubules into the main duct, which finally narrows into a ciliated duct opening into the airways.[11] The submucosal gland is formed by mucus cells and serous cells. Gland serous cells secrete a low viscosity compounds with antiinflammatory and antimicrobial properties.

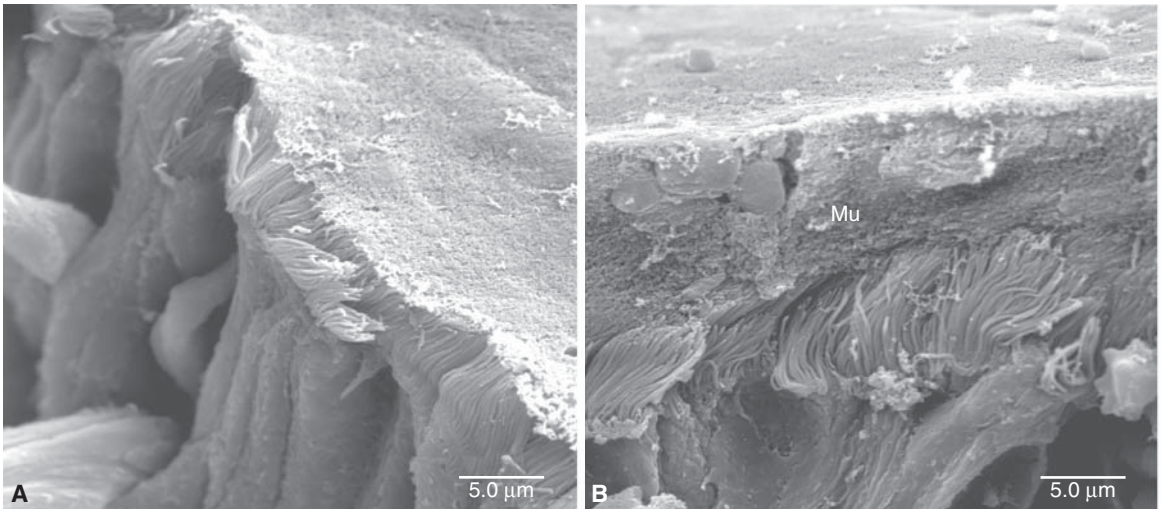


FIGURE 52-1 Microanatomy of the airway epithelium. The porcine airway epithelium was fixed with perfluorocarbon/osmium and imaged with a scanning electron microscope (A and B) and transmission electron microscope (C and D). **A.** The pseudostratified tracheal epithelium and the characteristic high density of cilia on the luminal surface are shown. Rare strings of mucus are evident above the cilia (magnification ×3000). **B.** A thin layer of mucus (approximately 5 µm) is demonstrated above the cilia (magnification ×3000).

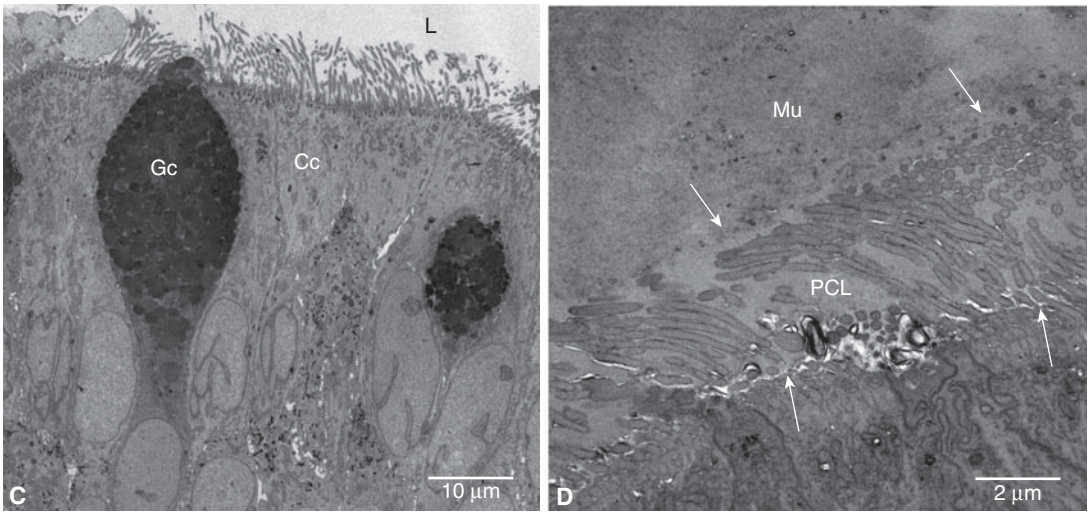


FIGURE 52-1 (*continued*) **C.** Higher magnification of the airway epithelium comprising goblet cells (*Gc*) and ciliated cells (*Cc*). Cilia are evident in the luminal (*L*) surface. Of note, electron-dense mucus granules of varying size are within the goblet cell (magnification ×3000). **D.** Microanatomy of the airway lining fluid. The *white arrows* delimitate the periciliary fluid. The electron-dense mucus layer (*Mu*) can be identified over the periciliary layer (magnification ×12,000). (Electron micrographs courtesy Dr. Nuria Cortadells, University of Barcelona, and Laia Fernandez-Barat, Hospital Clinic, Barcelona, Spain.)

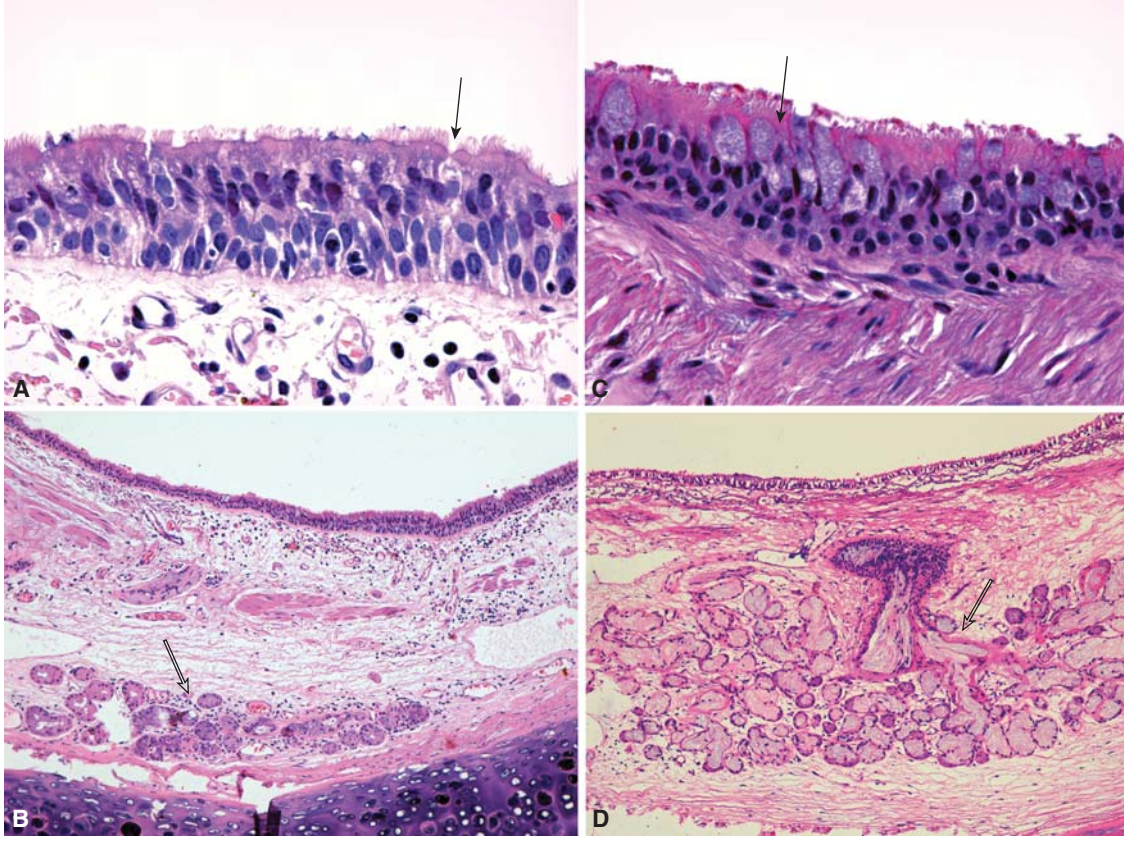


FIGURE 52-2 Representative sections of human epithelium from a healthy subject (A and B) and from a patient with chronic obstructive pulmonary disease (C and D). **A.** Magnification of the pseudostratified epithelium showing a goblet cell (*black arrow*) outnumbered by ciliated cells (magnification ×630). **B.** At lower magnification, a submucosal gland is identified with no signs of dilation (*empty arrow*) (magnification ×100). **C.** In patient with chronic obstructive pulmonary disease, goblet cell hyperplasia is evident. A representative goblet cell is indicated by the *black arrow* (magnification ×630). **D.** Hypertrophy of submucosal gland (*empty arrow*) is shown. Reid index approximately 0.7. Additionally, a disproportionate increase in retained mucus within the gland and collecting duct is evident with resulting dilation of the structure. Hematoxylin and eosin stain. (Pictures courtesy Prof. Jose Ramirez, Hospital Clinic, Barcelona, Spain.)

TABLE 52-2: MUC5AC EXPRESSION STIMULANTS

Inflammatory cytokines	TNF-α
	IL-1β
	IL-4
	IL-6
	IL-9
	IL-13
	IL-17
Bacterial products	LPS
	LTA
	Peptidoglycans
	Flagellin
Growth factors	EGF
	TGF-α
	Retinoic acids
	Thyroid hormones
Pollutants	Cigarette smoke
	Acrolein
Virus	Respiratory syncytial virus
	Rhinovirus

Abbreviations: EGF, epidermal growth factor; *IL*, interleukin; *LPS*, lipopolysaccharide; *LTA*, lipoteichoic acid; *TGF*, transforming growth factor; *TNF*, tumor necrosis factor.

See Thai et al[14] for a comprehensive review of regulation of mucins expression.

Several microbicidal products, that is, lysozyme, lactoferrin, collectins, defensins, and cathelicidins, have been identified in the airway lining fluid.[12,13]

Regulation of Mucus Production and Secretion

A small amount of mucus is continuously produced by goblet cells and submucosal glands so as to provide a barrier overlying the airway epithelium. Mucus production can be highly increased in response to stimuli. Several aspects of MUC5AC regulation have been elucidated in detail; conversely, regulation of MUC5B expression is still not entirely understood.[14] As depicted in Table 52-2, MUC5AC can be upregulated by several stimuli, among which interleukin-13 seems to play a primary role.[15,16]

Mucus secretion is regulated by three distinct neural pathways:[17,18] (a) the cholinergic, (b) the adrenergic, and (c) a nonadrenergic, noncholinergic (NANC) system. The cholinergic system is the most important motor control of secretion,[19] and cholinergic fibers can be identified in proximity to the submucosal glands. Parasympathetic nerve stimulation causes rapid mucus release through the muscarinic M3 receptors. Adrenergic stimulation of the airway epithelium causes only a small increase in mucus production. Finally, the NANC system is identified by the mucosecretory response following adrenoceptor and cholinoceptor blockade.[18,20] The main neurotransmitters of the NANC system are small-weight peptides, such as the vasoactive intestinal peptide, substance P, neurokinin A, and the gas nitric oxide.

Periciliary Liquid Layer and Mucociliary Clearance

The sol-phase, more properly termed *periciliary liquid layer*, is a thin low-viscosity fluid that extends to the height of the outstretched cilia[21] (see Fig. 52-1D). In humans, the periciliary liquid layer is approximately 7 μm thick and its volume is continuously regulated by the epithelial cells. Periciliary liquid layer water is driven by the luminal concentration of sodium chloride and resulting osmotic gradients. Hence, the epithelium controls the depth of the periciliary liquid layer through purinergic signaling[22,23] and activation of adenosine triphosphate $P2Y_2$ and adenosine A2b receptors. The purinergic signaling, in a paracrine–autocrine fashion, also regulates the cystic fibrosis transmembrane regulator chloride channel and the epithelial sodium channel.[24]

Each ciliated cell has approximately 200 cilia on its surface (see Fig. 52-1A), which move, within the periciliary liquid layer, at approximately 8 to 15 Hz.[25] Studies report mucociliary clearance rates between 4 and 20 mm/min, depending on the method of assessment.[26,27] Mucus clearance velocity decreases from central toward peripheral airways.[28,29] Interestingly, early studies have hypothesized that periciliary liquid layer is largely stationary.[30,31] More recent results[32,33] suggest that the outermost parts of the cilia (see Fig. 52-1B) initially move the mucus layer; as a result, because of the friction between mucus and the underlying fluid, the periciliary liquid layer is dragged along and travels at a similar rate.

Mucus Clearance via Two-Phase Gas–Liquid Transport

During breathing and cough, airflow interacts with the mucus lining the respiratory airways, which can be eventually propelled via a two-phase gas–liquid flow. Kim et al[34–36] first studied the critical conditions necessary to move mucus through such a mechanism. They demonstrated that the main factors consisted of (a) shear stress exerted by the airflow on the liquid layer; (b) the ratio between thickness of the mucus layer and the airway diameter; and (c) the rheologic properties of secretions. Importantly, during mechanical ventilation, inspiratory and expiratory airflows exert opposite shear forces on the mucus layer. Kim et al[36] assessed the in vitro effects of tidal airflow, tidal volume, and respiratory rate on movement of mucus simulants and found that mucus velocity can be predicted as follows:

$$Mucus\ Velocity \sim \rho v^{2*}(1\text{-}T_I/T_{TOT})^{*}\eta^{-1} \qquad (1)$$

where ρ is the gas density, v is the absolute value of the highest airflow velocity throughout the respiratory cycle, which is inversely related to the total cross-sectional area of the airways, T_I/T_{TOT} is the duty cycle, and η is the mucus

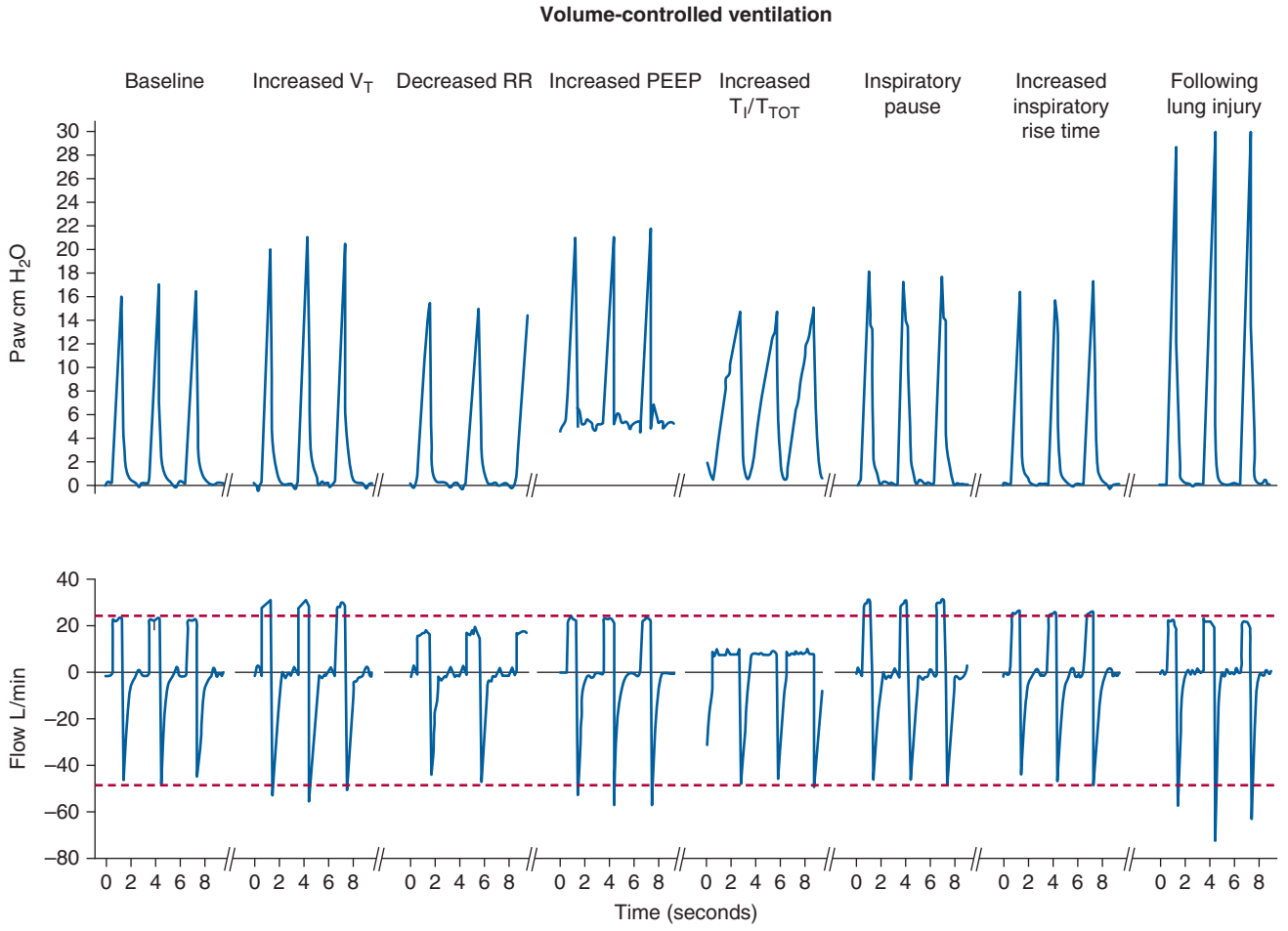


FIGURE 52-3 Pressure and flow waveforms during flow-controlled, volume-cycled ventilation in a healthy pig (36 kg) obtained with a SERVO-i mechanical ventilator (Maquet, Wayne, NJ). Inspiratory and expiratory flow rates generated with baseline ventilator settings (tidal volume [V_T] 290 mL, respiratory rate [*RR*] 20 breaths/min, duty cycle [T_I/T_{TOT}] 0.26) are compared against different adjustments of ventilator parameters. *Dotted red lines* indicate the highest inspiratory (21.6 L/min) and expiratory (–47.2 L/min) flow rates during baseline ventilation. An increase in tidal volume to 360 mL, an inspiratory pause of 6%, and an inspiratory rise time of 5% all increased inspiratory flow. Conversely, reducing the RR to 15 breaths/min and increasing T_I/T_{TOT} to 0.75, decreased the inspiratory flow. As expected, changes in lung volume, secondary to increased tidal volume or positive end-expiratory pressure (*PEEP*, 5 cm H_2O,) increased peak expiratory flow. Changes in elastic pulmonary conditions, induced by oleic-acid injury, caused an increase in peak expiratory flow. The effects of each individual ventilator setting on the net movement of mucus need to be thoroughly assessed by systematic in vivo studies.

viscosity. Tidal volume and respiratory rate were not associated with mucus movement; conversely, as reported in equation (1), the absolute value of the highest airflow influenced mucus movement. Indeed, the authors found that during volume-control mechanical ventilation mucus moved in waves, and the mucus speed was not influenced by the inspiratory flow until its rate reached 90% of the expiratory flow. A recent laboratory study by Volpe et al[37] confirmed previous results and also emphasized the role of lung impedance on mucus clearance. Intrinsic positive end-expiratory pressure (PEEP) caused by either elevated minute ventilation or expiratory resistance respectively improved and worsened mucus clearance.

Theoretically, during mechanical ventilation the difference between inspiratory and expiratory flow rate can be modulated by adjusting ventilator settings. As clearly described in Chapter 5, lung elastance, lung volume, and airway resistances are the major determinants of expiratory flow rate during passive expiration. In contrast, inspiratory flow can be easily modulated through the ventilator. For instance, Figures 52-3 and 52-4 imply that changes in (a) mode of ventilation, (b) tidal volume, (c) respiratory rate, (d) duty cycle (T_I /T_{TOT}), (e) inspiratory rise time, (f) inspiratory pause time, and (g) PEEP may all modify the inspiratory–expiratory flow rate difference. Despite consistent laboratory results, there is still great paucity of translational in vivo studies. To date, only one report in sheep has demonstrated the feasibility of mucus clearance via two-phase gas–liquid transport modulating the duty cycle.[38]

Mechanically ventilated patients are often positioned with the trachea oriented above the horizontal (i.e., the semirecumbent position). As a result, mucus transport via

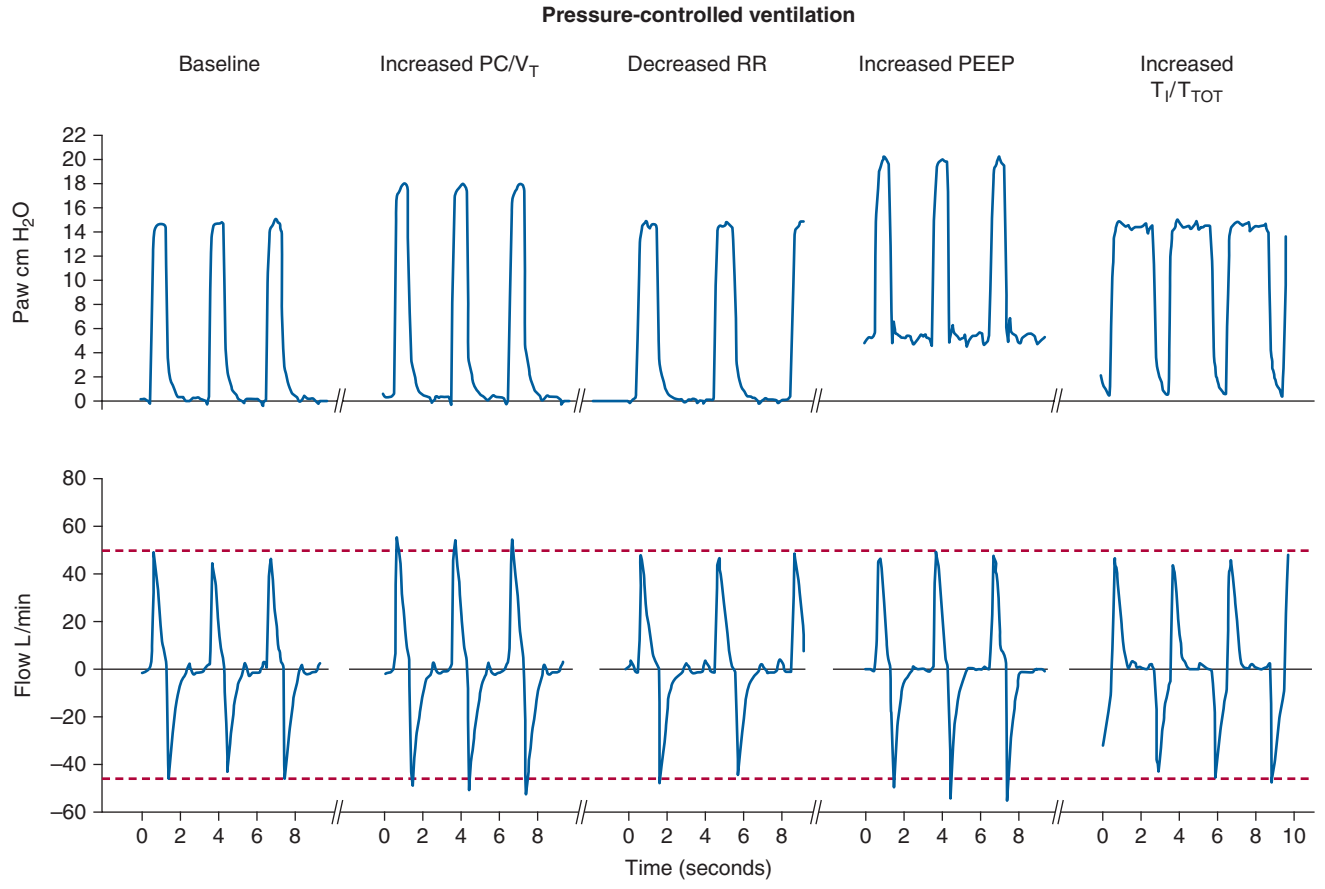


FIGURE 52-4 Pressure and flow waveforms during pressure-controlled ventilation in healthy pig (36 kg) obtained with a SERVO-i mechanical ventilator (Maquet, Wayne, NJ). The effects of pressure-limited modes of ventilation on airflow rates are more difficult to predict because inspiratory flow rate is partly related to the mechanical properties of the respiratory system. Inspiratory and expiratory flow rates generated through baseline ventilator settings (pressure control [*PC*] 14 cm H_2O, respiratory rate [*RR*] 20 breaths/min, duty cycle [T_I/T_{TOT}] 0.26) are compared to various adjustments of ventilator parameters. *Dotted red lines* indicate the highest inspiratory (47.2 L/min) and expiratory (−47.8 L/min) flow rates during baseline ventilation. Of note, only increases in pressure control from 14 to 17 cm H_2O produced an increase in inspiratory flow. Conversely, reducing respiratory rate to 15 breaths/min and increasing T_I/T_{TOT} to 0.75 decreased the inspiratory flow. Similarly to volume-controlled ventilation, changes in lung volume secondary to increased pressure control or positive end-expiratory pressure (*PEEP*; 5 cm H_2O) increased peak expiratory flow.

two-phase gas–liquid mechanism mainly depends on a balance between the airflow shear forces on the liquid layer and gravitational force. We have studied the effects of gravity in sheep,[39] positioned in a model of the semirecumbent position, and found that mucus, accumulated in the proximal trachea, moved in an abnormal backward direction toward and into the lungs (Fig. 52-5).

QUANTITATIVE ASSESSMENT OF SECRETION PRODUCTION AND REMOVAL

A quantitative assessment of mucus production and clearance in ventilated patients is essential to ascertain the benefits of novel therapeutic strategies; unfortunately, the methods for easy and reliable assessment at the bedside are still inadequate.

Mucus Production

The dynamics of mucin expression during mechanical ventilation are currently unknown and should be considered in future studies. Kirkham et al[4] first developed a Western blot analysis that allows quantitative measurement of different mucins from retrieved mucus. In clinical settings, mucus can be easily obtained during endotracheal suctioning and stored into a mucus trap. The volume of mucus should be quantified as soon as obtained so as to avoid quantification errors secondary to dehydration. Additionally, in daily clinical practice, it is also important to report qualitative characteristics of mucus, such as color and consistency, to promptly identify any acute or developing respiratory disease.[40]

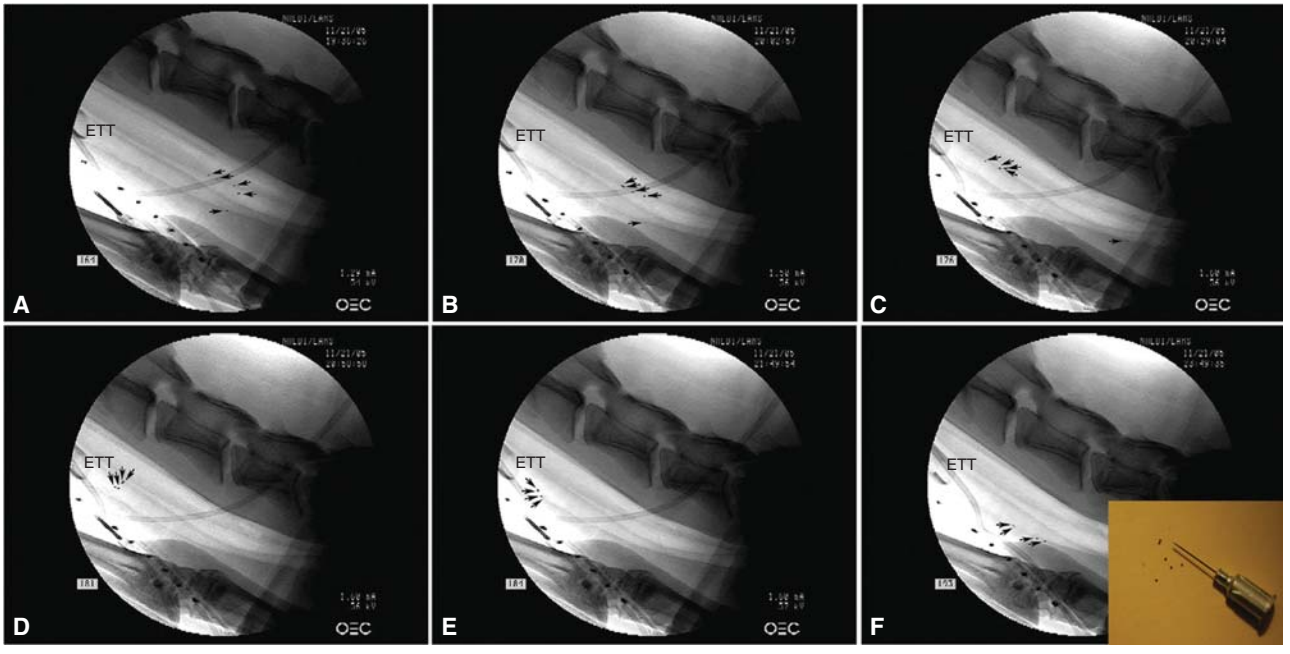


FIGURE 52-5 Tracheal mucus velocity studies in sheep after 12 hours of tracheal intubation and positioned with a tracheal orientation above horizontal. *Black/white arrows* indicate each tantalum disk, tracked to evaluate mucus transport. **A.** Following disk insufflation, five tantalum disks were deposited in the trachea; four disks were on the dorsal (nondependent) part of the trachea and one disk was on the ventral (dependent) part of the trachea (*black dots*). Fluoroscopic images taken (**B**) 24 minutes and (**C**) 59 minutes following insufflation show mucus transport toward the glottis on the nondependent part, while mucus on the dependent part of the trachea moves toward the lungs. **D** and **E.** After 80 minutes mucus almost reached the tip of the endotracheal tube, gravitated to the dependent part of the trachea, and (**F**) reversed flow back toward the lungs. The enclosed picture in F shows tantalum disks used for those experimental studies. Diameter, thickness, and weight of those disks are 0.60 mm, 0.10 mm, and 0.8 mg, respectively. (Adapted, with permission, from Li Bassi et al.[39])

Mucus Removal

The rate of mucus removal in vivo is assessed by measuring either (a) the velocity of traceable particles deposited within the trachea and/or bronchi or (b) the clearance rate of an inhaled radioactive tracer through a gamma camera. A brief description of the most common techniques are reported below and in Table 52-3, but it is important to note that most of these methods are difficult to apply in ventilated patients.

QUANTITATIVE ASSESSMENT VIA TRACEABLE PARTICLES

To measure the rate of mucus clearance, movement of a tracer needs to be followed over time and velocity appropriately computed. Normally, the tracer is deposited via the working channel of a bronchoscope. The anatomic location of the deposited tracer greatly influences the results, because an increased rate is reported from the peripheral toward the central airways.[28,29] In the cinebronchofiberscopic technique, as first described by Sackner et al,[27] ten to fifteen Teflon disks are insufflated into the trachea and their movement continuously monitored as they approach the bronchoscope. In clinical settings, movement of several other tracers has been evaluated through bronchoscopy. In the original studies of Keller et al[41] and in later reports,[42,43] 15 μL methylene blue dye was instilled into the airways of patients undergoing anesthesia, and movement of the front edge of the dye was then sequentially measured through the bronchoscope, and velocity calculated. Charcoal markers[44,45] have also been used. The main drawback of bronchoscopic techniques is the frequent invasive insertion of the bronchoscope, which may distort the results. The original technique was modified by Friedman et al,[46] who used fluoroscopic tracking of radiopaque disks of Teflon mixed with bismuth trioxide. In our laboratory, we use radiopaque disks made of tantalum.[39,47] Six to eight tantalum disks are insufflated into the trachea and their velocities averaged (see Fig. 52-5). Timed, serial, lateral fluoroscopic images are taken by means of a C-arm fluoroscopy system approximately every 5 minutes to compute tracheal mucus velocity through movement of the disks.

QUANTITATIVE ASSESSMENT VIA RADIOACTIVE TRACERS

Inhaled γ-emitting radioactive tracers have long been used to assess mucus clearance of the whole respiratory system; to quantify the rate of mucus transport, a radioactive bolus is typically deposited in the large airways (most commonly trachea) and its movement measured through external radioactivity counters. The technique was originally described by Yeates et al[26] and consisted of tracheal deposition of boluses

TABLE 52-3: TECHNIQUES FOR QUANTITATIVE ASSESSMENT OF MUCUS CLEARANCE

	Method of Assessment	Tracer	Technical Aspects	Settings	Comments
Traceable Particles	Cinebronchofiberscopy[27]	Teflon disks	Disk diameter: 0.67 mm Disk thickness: 0.13 mm Disk weight: 0.13 mg 10 to 15 disks are insufflated via bronchofiberscopy Velocity is computed via the relationship of the disk size to the distance from the distal lens of the bronchofiberscope	Clinical/laboratory	Deposition of particles and frequent assessment via bronchoscope may damage the airway epithelium altering mucus transport
	Bronchofiberscopy[41]	Methylene blue dye	15 µL of methylene blue dye are applied via an 18-gauge epidural catheter passed through the bronchoscope working channel The lens is positioned at the front edge of the dye and the distance from the endotracheal tube (ETT) exit measured. After a period of time, the bronchoscope is reintroduced, the leading edge of the spot relocated and the distance difference calculated to compute velocity	Clinical	Deposition of particles and frequent assessment via bronchoscope may damage the airway epithelium altering mucus transport
	Bronchofiberscopy[45]	Charcoal	5 to 15 µL of a suspension of carbon in saline The lens is positioned at the front edge of the dye and the distance from the ETT exit measured. After a period of time, the bronchoscope is reintroduced, the leading edge of the spot relocated and the distance difference calculated	Clinical	Deposition of particles and frequent assessment via bronchoscope may damage the airway epithelium altering mucus transport
	Fluoroscopy[46]	Teflon disks mixed with bismuth trioxide	Disk diameter: 0.64 mm Disk thickness: 0.08 mm Disk weight: 1.76 mg Timed serial lateral fluoroscopic images are taken through a C-arm fluoroscopy system to compute tracheal mucus velocity through movement of the disks A ruler with radiopaque markers is applied in close proximity of the animal's neck to help correct for magnification of fluoroscopic images	Clinical/laboratory	Fluoroscopic imaging avoids discomfort and potential bias associated with frequent bronchoscopy for assessment Potential risks linked to radiation exposure because of frequent assessments

	Fluoroscopy[47]	Tantalum Disk	Disk diameter: 0.60 mm Disk thickness: 0.10 mm Disk weight: 0.8 to 1 mg Timed serial lateral fluoroscopic images are taken through a C-arm fluoroscopy system to compute tracheal mucus velocity through movement of the disks A ruler with radiopaque markers is applied in close proximity of the animal's neck to help correct for magnification of fluoroscopic images	Laboratory	Fluoroscopic imaging avoids discomfort and potential bias associated with frequent bronchoscopy for assessment Potential risks linked to radiation exposure because of frequent assessments
Radioactive Tracers	Gamma camera[26]	Aerosolized human serum albumin microspheres with technetium-99 m	Albumin microspheres diameter: 0.5 µm Boli of radioactive microspheres are deposited on the large airways via breathing to near total lung capacity and at high airflow rate Studies may last up to 6 hours	Clinical/laboratory	The subject needs to drink water at frequent intervals to wash out any radioactivity in the esophagus Patient needs to be transferred to another department for gamma camera assessment
	Gamma camera[49]	10 to 80 µL bolus of albumin microspheres labeled with technetium-99 m	Microspheres albumin diameter: 5 to 40 µm The bolus is deposited on the tracheal mucosa through the working channel of the bronchoscope or a fine cannula	Clinical/laboratory	Patient needs to be transferred to another department for gamma camera assessment

of technetium 99m (^{99m}Tc) human serum albumin microspheres (0.5 μm) suspended in isotonic droplets, achieved by breathing close to total lung capacity and at high low rates. Movement rate of those radioactive boluses was then measured through timed-serial measurement of the radioactive activity for up to 6 hours. In later reports, the radioactive bolus was deposited inside the trachea through a catheter[48] or a bronchoscope.[49] Few reports have applied these methods in tracheally intubated patients,[50,51] mostly because the patient needs to be transferred for scintigraphic assessment, moreover, the analysis can be lengthy at times.

MUCUS DYSFUNCTIONS AND SOURCE OF SYMPTOMS IN DIFFERENT DISEASES

Patients with diseases associated with overproduction of mucus and impairment of its clearance, such as asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis, often require mechanical ventilation. Although mechanical ventilation is lifesaving during acute worsening of those diseases, the delicate balance between mucus hypersecretion and clearance can rapidly deteriorate.

Invasive Mechanical Ventilation

Mucus retention is highly prevalent in mechanically ventilated patients because of several factors. First, following tracheal intubation, mucociliary velocity is approximately 80% slower than normal.[50] Sackner et al.[52] demonstrated that inflation of endotracheal tube cuff lowers mucociliary velocity by 52% after only 4 hours. Second, when mucus reaches the proximal trachea outward clearance is not possible because of the inflated cuff; therefore, mucus accrues, unless it is aspirated through suctioning or enters the endotracheal tube. Third, continuous leakage[53] of bacteria-laden oropharyngeal secretions sustains airways infection and hypersecretion of mucus. Finally, critically ill patients are often incapable of effectively clearing retained mucus secondary to immobilization, weak cough, and muscle weakness.

Asthma

Asthma is a chronic inflammatory disease characterized by increased and inappropriate release of inflammatory mediators following antigen exposure and consequent airway smooth-muscle constriction.[54] Patients with asthma present with varying degrees of cough, shortness of breath, chest tightness, and wheezing. The role of mucus in asthma is often underestimated by clinicians[55] because mucus is typically stationary within small and medium airways and clearance is severely impaired, ultimately resulting in the inability to centralize secretions. Many mucus plugs within constricted airways may be identified in patients who die of status asthmaticus.[56,57] Mucus in asthma is highly viscous because of an abnormal concentration of plasma proteins,[58,59] DNA, cells, and proteoglycans. The abnormal presence of plasma proteins arises mainly from increased plasma exudation.[60]

Chronic Obstructive Pulmonary Disease

COPD is highly prevalent worldwide[61] and is the fourth leading cause of death according to the World Health Organization. The characteristic features of COPD are chronic bronchitis with obstruction or full closure of small airways impacted by mucus, enlargement of air spaces, and destruction of lung parenchyma resulting in loss of lung elasticity and emphysema.[62,63] In patients with COPD, the increased mucus production is strongly associated with goblet cell metaplasia and mucus gland hypertrophy (see Fig. 52-1C and D). MUC5B is overexpressed, particularly the low-charge glycoform. Hence, the rheologic properties of mucus are altered resulting in deficient mucociliary clearance.[64–66] Mucus hypersecretion is associated with progressive impairment of respiratory function[67] and death.[68]

Cystic Fibrosis

Cystic fibrosis is caused by a defective cystic fibrosis transmembrane regulator gene,[69] which results in impaired intraluminal chloride release and increase sodium absorption.[70] The electrolytes homeostasis of the periciliary fluid is compromised, hence, the volume of the periciliary liquid layer is depleted and cilia movement is severely perturbed. Indeed, the pathologic hallmarks of the disease are viscous secretions, which adhere tenaciously to the airways and often obstruct the lumen. Although MUC5B is increased relative to MUC5AC,[71] the overall concentration of those mucins is reduced,[72] but they rapidly increase during disease exacerbations.[73]

ROLE IN CAUSING ATELECTASIS, PNEUMONIA, AND OTHER DISORDERS

When mucus is retained, several complications occur as a consequence of (a) progressive reduction of the airways lumen, impacted by mucus, and/or (b) overgrowth of pathogens entrapped within the retained mucus. Excessive accumulation of secretions within the respiratory system and artificial airways makes it difficult to exhale, resulting in intrinsic PEEP and increased work of breathing. Shah et al[74] found a significant reduction in the internal volume of the endotracheal tube, which was proportional to the duration of mechanical ventilation. Indeed clinicians, upon extubation, often acknowledge the vast presence of secretion within the endotracheal tube. The mucus-related increase in airflow

resistance and work of breathing[75] causes breathing discomfort and may retard ventilator weaning.[76]

Mucus retained in the peripheral airways can ultimately cause atelectasis and gas-exchange impairment. In intubated patients, mucus can be suctioned only in the larger airways; hence, mucus within the small airways may produce complete and irreversible closure, because the pressures necessary to reopen small airways are extremely high and difficult to achieve safely in a ventilated patient. Patients at particular risk of developing mucus-related atelectasis are those with asthma, COPD, cystic fibrosis, infants, children, and those undergoing surgery. In surgical patients, mucociliary clearance becomes impaired in the operative room,[77] through the use of anesthetics and tracheal intubation; moreover, inefficient cough, associated with the underlying diseases or the anatomical site of the surgical procedure, increase the risk.

Retained mucus is also associated with lung infections. Patients with underlying respiratory diseases experience periodic exacerbations caused by pulmonary infections. The microbicidal products contained in mucus exert a time-limited effectiveness; Cole et al[78] elegantly demonstrated that bacteria added to nasal mucus rapidly acquired resistance to the antimicrobial factors within 24 hours. Those findings suggest that the antimicrobial properties of mucus and clearance work synergistically, and retained mucus eventually become colonized.

AIRWAY SUCTIONING

In intubated or tracheostomized patients, endotracheal suctioning consists of aspirating secretions retained within the artificial airway, trachea, and main bronchi via a suction catheter. Suctioning is one of the most common daily procedures. It should be performed only by qualified personnel, namely, physicians, respiratory therapists, or nurses, with appropriate skills and training to recognize the need for suctioning, perform it appropriately, and promptly respond to any potential complication.

Indications and Technical Procedure

INDICATIONS

The primary indication for endotracheal suctioning is to maintain patency of the airways, but it is also commonly performed to obtain secretions for diagnostic purposes. Current guidelines recommend that suctioning should not be performed routinely[79] to minimize the risk of unnecessary complications.

Several parameters have been suggested to detect the need for suctioning (Fig. 52-6). Researchers have focused especially on the typical sawtooth pattern of airflow in patients with secretions (Fig. 52-7). Jubran and Tobin[80] first proposed that retained mucus could be detected via the flow-volume loop, and reported that a sawtooth pattern had a good sensitivity and specificity. Guglielmotti et al[81] subsequently confirmed that the best predictors of the need of suctioning were (a) respiratory sounds heard via a stethoscope over the trachea, and (b) the sawtooth pattern on a real-time flow-volume loop (sensitivity 0.82, specificity 0.70).

ENDOTRACHEAL SUCTIONING PROCEDURE

Endotracheal suctioning begins with inserting a suction catheter into the artificial airway. Because there is no obvious advantage with deep suctioning versus shallow suctioning, the tip of the catheter should be placed in close proximity to the tip of the endotracheal tube before applying vacuum. As the catheter is pulled back, intermittent suction should be applied and the catheter continuously rotated. Shallow suctioning is particularly advisable in infants to minimize complications.[82,83] The only goal of suctioning is aspiration of secretions; hence, application of negative pressure, when the catheter is not close to secretions, or when all the mucus has already been aspirated (i.e., prolonged suctioning), only increases the risk of complications with no improvement in efficacy. Suctioning should last no more than 15 seconds[79] after inserting a catheter into an artificial airway.

Selection of Suction Methods and Catheters

OPEN VERSUS CLOSED SUCTIONING

Endotracheal suctioning can be performed either by disconnecting the patient from the ventilator (open suctioning) or through use of a suction catheter that does not require ventilator disconnection (closed suctioning), which is located inside a plastic contamination shield and in-line with the ventilator circuit.[84,85] Closed suctioning is beneficial in patients who require high levels of PEEP and inspired fractional concentrations of oxygen (FI_{O_2}). Several studies in adults with acute lung injury and acute respiratory distress syndrome (ARDS) have confirmed that, unlike open suctioning, closed suctioning prevents reduction of lung volume and desaturation.[86–88] These studies suggest that closed suctioning is especially appropriate in patients with most severe lung failure (partial pressure of arterial oxygen [$Pa_{O_2}/FI_{O_2} \leq 200$), who are intolerant of even brief disconnections from the ventilator. In studies by Cereda et al[86] and Maggiore et al,[88] open suctioning caused almost 1.5 L volume loss, half of which was secondary to the ventilator disconnection.[88] Results of studies assessing open and closed suctioning in newborns with respiratory distress syndrome[89–92] are consistent with data from adults.

Closed suctioning is also been introduced to reduce environmental contamination,[93,94] exogenous colonization of the airways via suction catheters[95] and potentially ventilator-associated pneumonia. Three meta-analyses[–98] have compared closed and open suctioning and found no

POTENTIAL INDICATORS FOR ENDOTRACHEAL SUCTIONING:

1) Visible secretions within the artificial airway
2) Dyspnea or apparent increased work of breathing
3) Pathological sounds (i.e., rhonchi, coarse and gurgling) heard *via* a stethoscope over the trachea
4) Progressive pulse oxymetry desaturation not otherwise explained
5) Increased peak inspiratory pressure in volume-controlled MV or decreased V_T in pressure-controlled MV
6) Sawtooth pattern identified at the real-time flow-volume loop

PREPARATION PRIOR ENDOTRACHEAL SUCTIONING:

EQUIPMENT

1) Consider closed suctioning system (or swivel connector) in patients with severe respiratory disease requiring high level of PEEP and FI_{O_2}
2) Ratio of catheter OD/artificial airway ID should be ≤ 0.7 in adults and ≤ 0.5 in children
   Suction catheter diameter (Fr) = Artificial airway internal diameter*3/2
3) Choose catheters with nonparallel lateral suction holes. In selected cases, a curved tipped catheter may be helpful to suction mucus within bronchi difficult to access
4) Prepare suction tubing
5) The level of vacuum should always be adjusted to the lowest level of vacuum that efficiently removes secretions. In general, vacuum ≤ 150 mm Hg in adults and 80–100 mm Hg in infants.

PATIENT PREPARATION

1) In patient on MV, heart rate, pulse oximetry, arterial pressure, and in particular cases, intracranial pressure, should be monitored throughout the procedure
2) If patient is conscious, explain the procedure
3) The use of saline to hydrate inspissated secretions and centralize secretions through cough lacks of clear evidence. If secretions appear dehydrated, check if humidification of inspired gases is appropriate
4) Hyperoxygenate for 120 sec using in adults FI_{O_2} of 100% and a 10% increase from baseline in infants. Of note, several ventilators now provide a single operational control for suction support

OPERATOR PREPARATION

1) Wash hands
2) Wear disposable apron and protector visor, particularly during open suctioning
3) Wear sterile glove on the hand manipulating the catheter, and nonsterile glove on the other hand
4) During open suctioning, retrieve the catheter from the sleeve and hold it. In particular, avoid manipulation of the distal catheter tip
5) Connect the catheter to suction tubing.
6) During closed or quasi-closed suctioning, the ventilator should be allowed to trigger to provide gas in response to negative pressure

PROCEDURE:

1) Insert the catheter into the artificial airway and advance its distal tip up to the proximal trachea
2) Intermittent suction should be applied through occlusion of the catheter suction control port
3) Withdraw suction catheter continuously rotating it
4) The procedure should last 15 sec or less from catheter insertion
5) Check and appropriately treat any potential cardiovascular, pulmonary, and neurologic complication throughout the procedure

FOLLOW-UP:

1) Assess respiratory cardiovascular and neurologic parameters
2) Consider hyperoxygenation
2) Consider recruitment maneuver in selected patients with ARDS and ALI
3) Rinse suction tubing and, in case of closed suctioning system, suction catheter
4) Dispose of the suction catheter apron and gloves into the proper containers

FIGURE 52-6 Suggested operative protocol for endotracheal suctioning. *ARDS*, acute respiratory distress syndrome; *ALI*, acute lung injury; FI_{O_2}, inspiratory fraction of oxygen; *ID*, internal diameter; *MV*, mechanical ventilation; *OD*, outer diameter; *PEEP*, positive end-expiratory pressure; V_T, tidal volume.

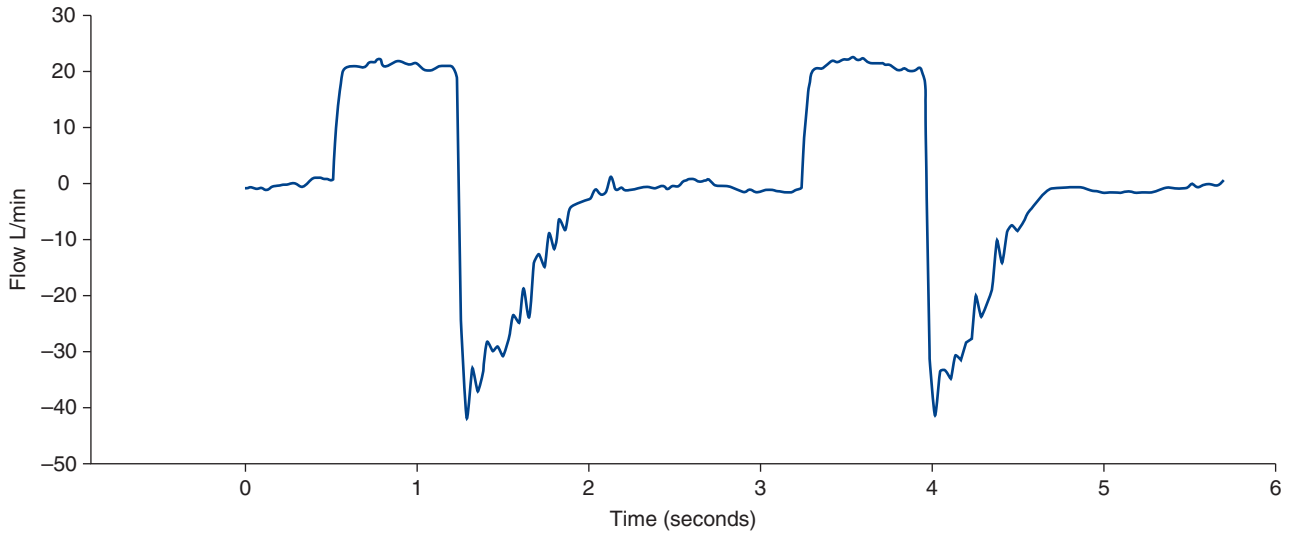


FIGURE 52-7 Flow waveform during volume-controlled mechanical ventilation. The typical expiratory sawtooth pattern used as an indicator for endotracheal suctioning can be recognized. Of note, the presence of water condensation within the circuit should be excluded before proceeding with suction.

benefits in preventing ventilator-associated pneumonia. Siempos et al[97] analyzed data from nine randomized trials, comprising of 1292 patients; data pooled from four showed a higher incidence of respiratory tract colonization using closed suctioning.

During closed suctioning it is important to note that triggered ventilator autocycling partially compensates for the loss of pressure, and investigators[99,100] have shown that the distal dispersion of secretions by ventilator airflow may reduce the effectiveness of closed versus open suctioning.

CATHETER CHARACTERISTICS

The main features that should be considered when choosing the most appropriate suction catheter are (a) the ratio between catheter outer diameter of the catheter and the internal diameter of the artificial airway; and (b) the size, number, and location of the suction holes. The outer diameter of the suction catheter greatly influences the loss of lung volume during the procedure. A larger catheter increases endotracheal tube resistance and facilitates loss of lung volume, because aspirated gas is not rapidly replaced by gas flowing through the endotracheal tube. These theories were clearly elucidated in early reports by Rosen et al[101,102] and confirmed in laboratory studies assessing pediatric[103,104] and adult[105] catheters. Evidence from those studies strongly suggests that the ratio of suction catheter outer diameter to artificial airway internal diameter should be 0.7 or less in adults and approximately 0.5 in children.

Several investigators have evaluated intrinsic characteristics of the suction catheter to identify factors associated with efficacy and safety.[106–109] Sackner et al[110] first demonstrated that invagination of the tracheal mucosa into the side holes frequently occurred with all the different catheter designs. In a more recent report, Shah et al[109] assessed six suction catheters (Fig. 52-8) with different designs and found that all performed equally with low viscosity mucus simulant; when viscosity resembled airway secretions, larger and nonparallel side holes were more efficient. In certain instances, a curved tipped catheter[111–113] may help when suctioning mucus within bronchi difficult to access with a straight catheter.

Additional Equipment

In ventilated patients, strict monitoring during endotracheal suctioning is strongly advised.[79] It is especially important to monitor heart rate, oxygen saturation, arterial pressure, and, in particular cases, intracranial pressure, throughout the procedure.

VACUUM ADJUSTABLE REGULATOR

The level of vacuum should always be adjusted before suctioning, so as to improve efficacy and minimize complications. Few studies have evaluated the efficacy and safety of suctioning at increasing vacuum levels. The latest guidelines[79] recommend a vacuum no higher than 150 mm Hg in adults and 80 to 100 mm Hg in neonates, although the lowest level of negative pressure that efficiently removes secretions should always be favored.

ADDITIONAL EQUIPMENT FOR STERILE SUCTIONING

Theoretically, during open suctioning there is a risk for environmental contamination from the patient and exogenous colonization of the patient. First and foremost, hand hygiene before and after the procedure is mandatory. Endotracheal suctioning is an invasive procedure and the use of sterile

Catheter	Side-Hole Diameter	Size	Whistle Design	Side-Hole Design
Cardinal Tri-Flo	3 mm	14 Fr		
Kendall Regu-vac	4 mm, 6.35 mm apart	14 Fr		
Kendall Sensi-vac	5 mm, 9.52 mm apart	14 Fr		
Medline Delee	4 mm, 9.52 mm apart	14 Fr		
Medline Whistle Tip	4 mm	14 Fr		
Portex suction tray	4 mm	14 Fr		

FIGURE 52-8 14 Fr suction catheters studied in vitro by Shah et al employing a mucus simulant with viscoelastic properties similar to human mucus. Nonparallel position and larger diameter of the suction holes were the major determinants of catheter's efficacy. (Used, with permission, from Shah et al.[109])

gloves is advisable, although there are no clinical studies specifically investigating the association between the use of unsterile gloves and respiratory infections. Blackwood et al[114] reported that gloves are important even during closed suctioning because of potential contamination of staff hands from the flush port.

SWIVEL CONNECTOR

A quasiclosed suctioning system, via a swivel adapter[115] positioned at the proximal tip of the endotracheal tube, is an alternative approach to minimize the loss of lung volume and desaturation during suctioning.[88,116] Investigators[87,88] found that suctioning through either a swivel adapter or a closed suctioning system similarly limited the decrease in lung volume as compared with open suctioning. Importantly, as during closed suctioning,[117] the ventilator should be allowed to autocycle to compensate for the loss of gas.

STERILE WATER

The use of 2 to 5 mL boluses of saline, instilled into the endotracheal tube before suctioning to induce cough and hydrate inspissated secretions remains controversial and lacks clear evidence. The first concern is that saline instillation, particularly in the semirecumbent position, may drip into the lungs and cause serious adverse effects, such as oxygen desaturation,[118,119] tachycardia,[119,120] dyspnea, and anxiety.[121] Second, several studies[122,123] have consistently demonstrated the presence of bacterial biofilm within the endotracheal tube, hence, instillation of saline may dislodge pathogens.[124] Caruso et al[125] published a report on 262 patients randomized to receive either isotonic saline instillation before suctioning or no treatment. The authors found a lower incidence of ventilator-associated pneumonia, and no significant differences in secondary outcomes. Because of limited evidence and the potential for adverse effects, routine saline instillation cannot be recommended; moreover, when mucus progressively becomes thicker, the humidifier's performance should be checked.

Complications of Endotracheal Suctioning and Preventive Measures

After discharge from an intensive care unit, patients remember endotracheal suctioning as one of the most unpleasant and painful procedures;[126–128] such memories may affect later quality of life.[129]

Once inside the trachea, the suction catheter frequently adheres to the tracheal mucosa, and may lead to the impairment of mucociliary transport[130] and severe mucosal injury.[110,131] Sackner et al[110] first addressed this problem by devising a novel suction catheter with a modified tip to prevent contact against the tracheal mucosa. In a later report[106] the new catheter was compared against standard catheters in dogs, and the investigators demonstrated that the risk of mucosal injury was specifically associated with deep suctioning rather than catheter design or vacuum level. Intermittent suctioning is recommended to prevent mucosal invagination into the suction holes.

Endotracheal suctioning is associated with several cardiovascular, pulmonary, and neurologic complications. Bradycardia and hypertension are the most frequent cardiovascular complications, mostly as a result of a vagal reflex and resulting in increases in parasympathetic and sympathetic activities.[132–135]

Hypoxemia during suctioning is extremely common, particularly in adults with severe lung disease[86,88] or infants.[92] As described above, closed or quasiclosed systems have been

used to prevent those complications. Hyperoxygenation before the procedure is also used to prevent hypoxia,[136,137] and several ventilators now provide a control for automatic preoxygenation and postoxygenation. A meta-analysis,[138] based on pooled data from fifteen studies in adults, demonstrated a 49% reduction of suction-related hypoxia when pre-hyperoxygenation and post-hyperoxygenation was applied. There is no clear evidence as to the level of FI_{O_2} that should be used to hyperoxigenate. In adults, FI_{O_2} of 100% is widely used. Hyperoxia, however, may be deleterious,[139] particularly in neonates; hence, in these instances, a 10% increase[79,140] from baseline is recommended. A recruitment maneuver applied after suctioning in selected patients with ARDS or acute lung injury is associated with more rapid return of baseline lung volume and reversal of hypoxia.[88,141,142] Finally, severe bronchoconstriction has been demonstrated during suctioning in animals[143,144] and humans.[145]

In patients with intracranial hypertension, an abrupt burst of coughing provoked by tracheal stimulation could increase the intracranial pressure; if there is not a concomitant increase in cerebral blood flow, brain ischemia may ultimately result.[146–148] Several drugs have been tested, mainly in adults, to blunt the responses to suctioning, including barbiturates,[149] narcotics,[150,151] anesthetic agents,[152–155] and neuromuscular blocking agents.[149,156,157] These drugs should be indicated on a case-by-case basis and the potential adverse hemodynamic effects of such agents[151,158] should be balanced against the perceived benefits.

Lastly, suctioning may increases endogenous and exogenous colonization of the lower airways. Manipulation of the suction catheter before insertion,[159] passage of the catheter within the colonized artificial airway,[160] and mucosal injury caused by negative pressure[110] are possible culprits involved in suctioning-related colonization of the airways. In ventilated newborns, transient bacteremia has been associated with endotracheal suctioning.[161] Finally, a number of studies found that closed suctioning catheters were easily colonized and associated with higher incidence of airways colonization;[161–165] nevertheless, the evidence is still controversial and, as described above, no increase in incidence of ventilator-associated pneumonia was found, even when the catheter was not changed daily.[166]

MANUAL VENTILATION TECHNIQUES

Exhaled Ventilation Techniques

In ventilated patients, who have excessive mucus production but are unable to produce an efficient cough, physiotherapists often apply manual and mechanical procedures with a goal of increasing expiratory flow and facilitating outward drainage of secretions[167] via annular two-phase gas–liquid flow.[36]

Manual hyperinflation to promote mucus clearance was originally described by Clement and Hubsch in 1968.[168] Manual hyperinflation is performed by disconnecting the patient from the ventilator and providing, via a resuscitator bag, a slow inspiration of a larger tidal volume, an inspiratory hold, and a quick release of circuitry pressure to assure a high expiratory flow rate. Extreme heterogeneity exists for the procedure and equipment.[169] A recent Dutch survey[170] substantiates this and relates how even the most important features of the procedure are frequently overlooked. Manual hyperinflation is commonly applied for mobilization of retained secretions, to recruit atelectatic lung regions, and to improve gas exchanges. During the procedure, the lack of respiratory monitoring and the potential to reach very high airway pressure[171] are of great concern. Significant hemodynamic fluctuations during the procedure have been reported.[172] The procedure should be performed by caregivers trained in the maneuver[173] and is usually contraindicated in patients with hemodynamic instability, undrained pneumothorax, intracranial hypertension, severe bronchospasm, and ARDS requiring a high level of PEEP or FI_{O_2}.[174] Among studies that specifically looked at mucus transport during manual hyperinflation, Jones et al[175] assessed transport of simulated mucus of three different viscosities and found that outward movement of mucus was consistently increased, particularly low viscosity artificial mucus. In eighteen intensive care unit patients positioned on their side, Hodgson et al[176] found increased retrieval of mucus following manual hyperinflation. One report[177] demonstrated even greater efficacy when the procedure was combined with the lateral Trendelenburg position.

It is commonly advocated that tidal volume be increased to 50% above baseline during manual hyperinflation, or an inspiratory pressure lower than 40 cm H_2O be achieved. Singer et al,[172] however, found that manual hyperinflation generated heterogeneous ranges of peak inspiratory pressure and tidal volume; therefore, inline manometers, spirometers, or both should be used both in research and clinical setting.

Three studies[178–180] compared the effects of manual hyperinflation against hyperinflation delivered by the ventilator; amounts of aspirated secretions were similar.[178,179]

Ventilatory Circuits for Manual Hyperinflation

The type of circuit used during manual hyperinflation strongly influences the resulting airflow rates, airway pressures, and mucus clearance. Circuits can be classified on the basis of the characteristics of the inflation bag, location of the fresh gas inlet, and expiratory valve.

FLOW-INFLATING BAG CIRCUITS

The most common rebreathing circuits used for manual hyperinflation are the Mapleson-A/Magill, Mapleson-C, and Mapleson-F (Fig. 52-9). The circuits consist of a highly compliant 2 L rubber or neoprene bag (with an open expiratory port in the Mapleson-F circuit) and an adjustable pressure-limiting valve (Magill and Mapleson-C circuits).

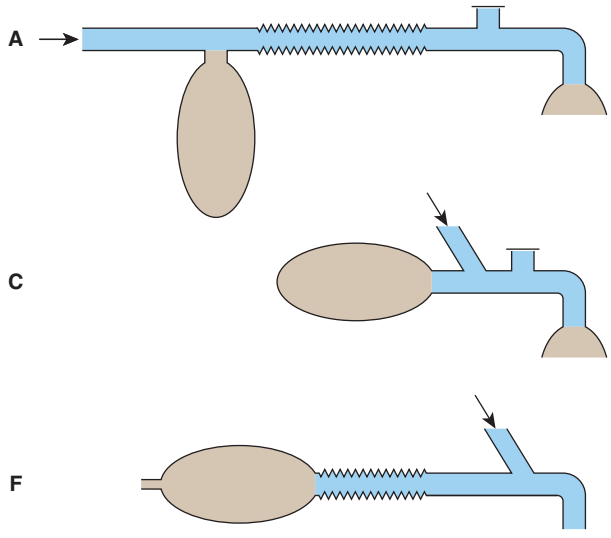


FIGURE 52-9 Most common semiclosed ventilatory circuits for manual hyperinflation delivered with a flow-inflating bag. The Mapleson A/Magill, Mapleson-C, and Mapleson-F are shown. Circuits differ in terms of location of fresh-gas inlet and presence of expiratory port (F) or valve (A and C). *Black arrows* indicate the fresh gas inlet.

The compliant bag allows the operator to better assess the patient's respiratory compliance during the procedure. The gas inlet is close to the patient in the Magill and Mapleson-C circuits and it is commonly connected to 100% oxygen at a flow rate of 15 L/min. During inspiration, an appropriate adjustment of the adjustable pressure limiting valve is required to inflate the bag and to provide ventilation at the necesary respiratory rate and volume. Differently, to ensure a rapid exhalation, the bag is fully and promptly released and the adjustable pressure limiting valve can be adjusted to the fully open position, and manually held closed during inspiration.

SELF-INFLATING BAG CIRCUITS

The self-inflating bag circuits comprise a silicone bag that is connected to the patient's artificial airway via a non–rebreathing valve assembly. At the other side of the bag are located the fresh-gas inlet and the oxygen-reservoir bag. Several studies in the recent decades have assessed performance of the Laerdal 1.6 L adult bag (Laerdal Medical Corp, New York, NY) and the Air Viva bag (now discontinued).

The ratio between the inspiratory and expiratory flow rates is the most important factor during manual hyperinflation. As expected, a longer inspiratory time is associated with a slower inspiratory flow rate.[181] In contrast, expiratory flow depends on (a) nonmodifiable factors, such as airways or endotracheal tube resistances and respiratory compliance, and (b) modifiable factors, that is, end-inspiratory lung volume and breathing circuits. In vitro studies[181,182] have compared performance of different breathing circuits for manual hyperinflation and have shown that the Mapleson-C and Mapleson-F circuits generate faster expiratory flow than do circuits with self-inflating bags. Moreover a clinical study by Hodgson et al[183] of patients receiving manual hyperinflation with a Laerdal and Mapleson-C circuit, found more secretions retrieved with the latter. In a more recent in vitro study,[184] the Mapleson-C circuit generated greater peak expiratory flows when compared to the Mapleson-A circuit, probably because of intrinsic characteristics of the exhalation valve.

ROLE OF PHARMACOLOGIC AGENTS

Numerous drugs commonly used in ventilated patients profoundly affect mucociliary clearance and increase mucus retention. Oxygen,[185] inhaled anesthetics,[42,43,186] and narcotics[187] have shown dose-dependent and time-dependent inhibitory effects on mucociliary clearance. Because mucus is composed mostly of water, administration of fluids and diuretics may affect hydration and rheologic properties of airway mucus.[188] Furosemide has a direct inhibitory effect on the $NaK(Cl)_2$ cotransporter located in the basolateral membrane of the airways epithelium and may influence the volume of the periciliary liquid layer. A study in mechanically ventilated patients[189] revealed some deleterious effects of furosemide on mucus transportability; further research is needed particularly because of conflicting laboratory results.[190,191]

Mucoactive Agents

Remarkably little data exist on the use of mucoactive agents in ventilated patients, and most of the knowledge in the field is provided by clinical trials assessing long-term effects of such agents in patients with underlying chronic respiratory diseases. Mucoactive drugs used in intensive care unit settings can be divided in mucolytics and mucoregulators.

Mucolytics alter viscoelastic properties of mucus by either dissociating the mucus polymers or the cellular residuals within mucus. *N*-acetylcysteine dissociates the disulfide bonds that generate the final mucin polymeric structure, hence, enhances fluidity of mucus to facilitate its clearance.[192] *N*-acetylcysteine can be administered intravenously, orally, and aerosolized, although it can cause airway irritation when inhaled.[193] Only one randomized, controlled study[194] has been conducted in ventilated patients. *N*-acetylcysteine had no significant benefit on viscosity of secretions or the risk of mucus plugs. Likewise, sodium 2-mercaptoethane sulphonate (MESNA) is a mucolytics agent[195] that reduces mucus disulfide bonds. The agent can be administered via a nebulizer[196] or instilled directly into the airways.[197] MESNA may induce severe bronchospasm and coadministration of a bronchodilator is advisable in intubated critically ill patients. Increased mucus concentration of highly polymerized DNA, caused by degenerated polymorphonuclear leukocytes, greatly alters the viscoelastic properties of mucus. The

resulting thick and tenacious mucus narrows the airways and may cause atelectasis. Recombinant human deoxyribonuclease hydrolyses DNA and has been largely used in patients with cystic fibrosis.[198] Scattered work has been published in ventilated pediatric patients, on the use of recombinant human deoxyribonuclease, inhaled or administered via bronchoscopy, to resolve established atelectasis secondary to mucus plugs.[199–205]

Mucoregulators affect mucus production and secretion. Among these drugs, anticholinergics, glucocorticoids, and β_2-adrenergic agonists are routinely prescribed in critical care, mainly to reduce bronchospasm and airway inflammation, often overlooking the important effects on airways secretions. Inhaled anticholinergics agents, such as atropine, ipratropium, and tiotropium, thwart mucus hypersecretion of submucosal glands. Glucocorticoids indirectly influence production of mucus by reducing airways inflammation. Similarly, macrolide antibiotics exert an immunomodulatory effect that can result in decreased mucus production. β_2-adrenergic agonists enhance mucociliary clearance.[206–209] The bronchodilator action may also favorably influence the peripheral interaction between airflow and retained mucus.

IMPORTANT UNKNOWNS

As already discussed, most of the quantitative techniques to assess mucus clearance were developed approximately 40 years ago, and currently they are applied in laboratory settings. Thus, surrogate end points have been used in research, that is, changes in oxygenation, pulmonary mechanics, and amount of aspirated secretions—all of which increase the odds for negative studies[210] and produce controversy in the field.

First and foremost, in daily clinical practice, indications for endotracheal suctioning remain uncertain. Studies have demonstrated that respiratory waveforms can predict the presence of retained secretions,[80,81] yet we do not know whether it is safe to allow mucus to accumulate in the proximal trachea until it is detected by such monitoring. The proximal trachea is often colonized by seepage of bacteria-laden oropharyngeal fluids; hence, mucus may provide a perfect media for exponential growth of pathogens that eventually flow[39] backward into the lungs driven by gravity. Second, several laboratory[36,37] and animal studies[38,39] suggest that the net movement of retained mucus is governed by gravity and tidal airflow forces. Those theories have been extrapolated to the pathogenesis of ARDS because mucus and noxious fluids, from an initially contained locus of infection, may propagate through the airways and ultimately cause ARDS.[211,212] Finally, although hypersecretion of mucus is universally found during prolonged ventilation, even in patients without underlying respiratory disease, the pathophysiologic basis of such hypersecretion is still unknown and there are no studies assessing the effects of mechanical ventilation on expression of mucins.

THE FUTURE

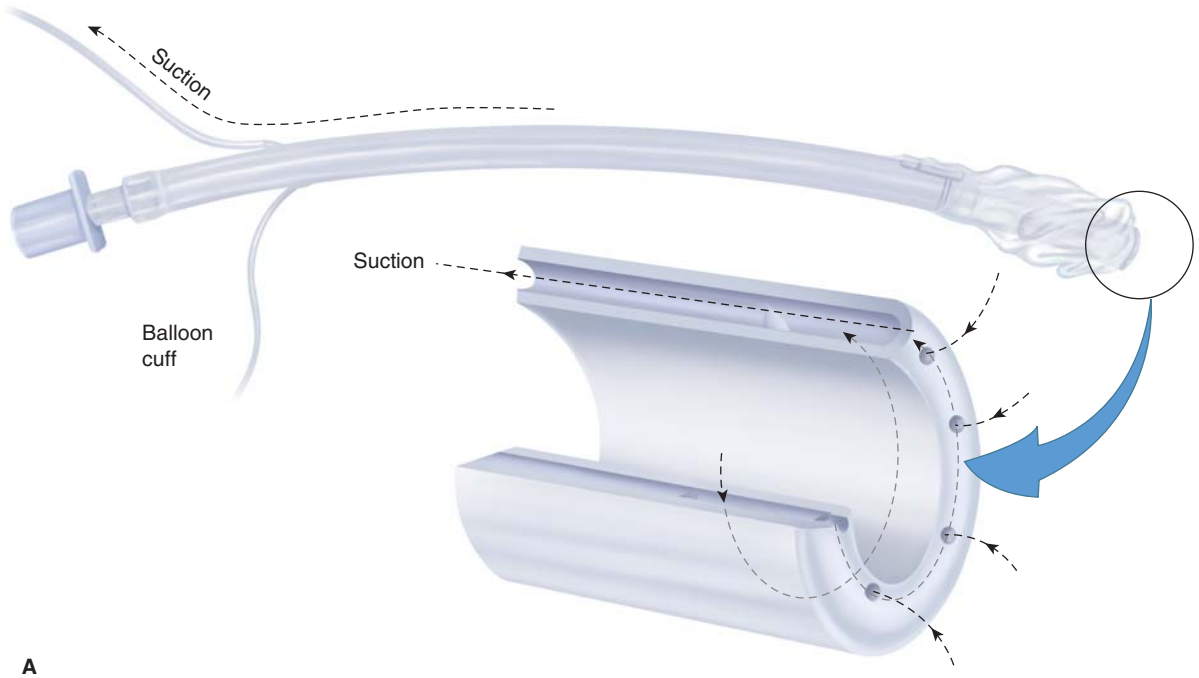
Several promising areas exist for future laboratory and clinical research. Development of new reliable techniques to quantitatively assess movement of airway secretions within the proximal and lower airways is the first priority. Graf et al[213] have employed sequential computed tomography to trace a radiopaque mucus simulant in preserved ex vivo porcine lungs. Although the technique was designed to track lung biofluids, the experimental approach provides an attractive option for future studies.

Given the adverse effects and the frequent use of endotracheal suctioning, efforts should be made to devise new strategies to clear mucus from the airways more efficiently and safely. Two prototypes have been described. The Mucus Slurper[214] (Fig. 52-10) consists of a novel endotracheal tube that provides intermittent and automatic suction at its tip. Using the Mucus Slurper, we were able to avoid endotracheal suctioning over 72 hours of mechanical ventilation, and we prevented any accumulation of mucus within the endotracheal tube and proximal trachea.[215] The Mucus Shaver[216] (Fig. 52-11) is an inflatable device that removes all accumulated mucus and biofilm within the endotracheal tube. Those prototypes, although currently not commercialized, offer novel insights into future designs and provide research directions to improve removal of secretions.

Another novel device that detects airway secretions through the analysis of airway sounds was recently described.[217] Although further experimental and clinical evaluation of the device is needed, analysis of airway sounds to detect retained secretions is intriguing and could be a valuable option to signal the need for suctioning.

SUMMARY AND CONCLUSION

The airway lining fluid, composed of mucus and periciliary fluid, overlies the airway epithelium and constitutes a first-line of defense. Mucus is continuously cleared from the airways by cilia and by a two-phase gas–liquid mechanism. Ventilated patients often retain secretions because of mucus hypersecretion and impaired clearance. The effects of gravitational force and ventilator settings on mucus transport are seldom considered, but may be major mechanisms of mucus retention in ventilated patients; these theories require comprehensive evaluation in future studies. Endotracheal suctioning is an essential procedure to remove accumulated mucus within large airways, but can cause discomfort and several complications. Further research is needed to identify the proper indications for suctioning and to improve the technology and safety of the procedure. Manual hyperinflation is based on the principles of mucus transport by means of a two-phase gas–liquid mechanism and, in selected patients, can be useful to centralize retained secretions. Unfortunately, most of the quantitative techniques used to assess mucus clearance are difficult to apply in ventilated patients, and



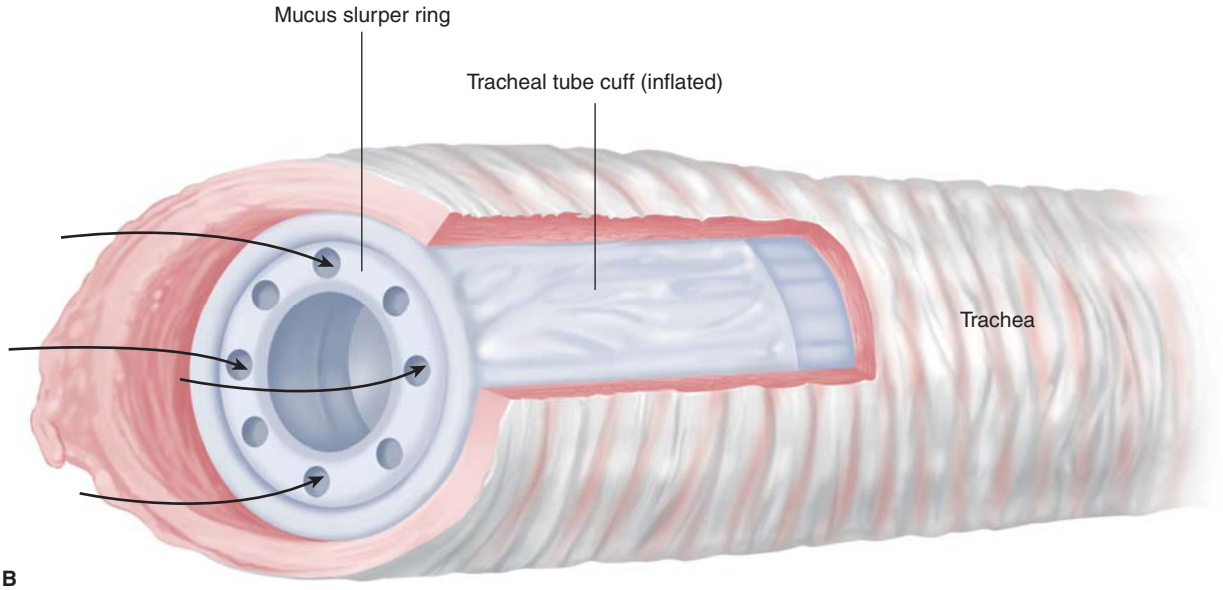
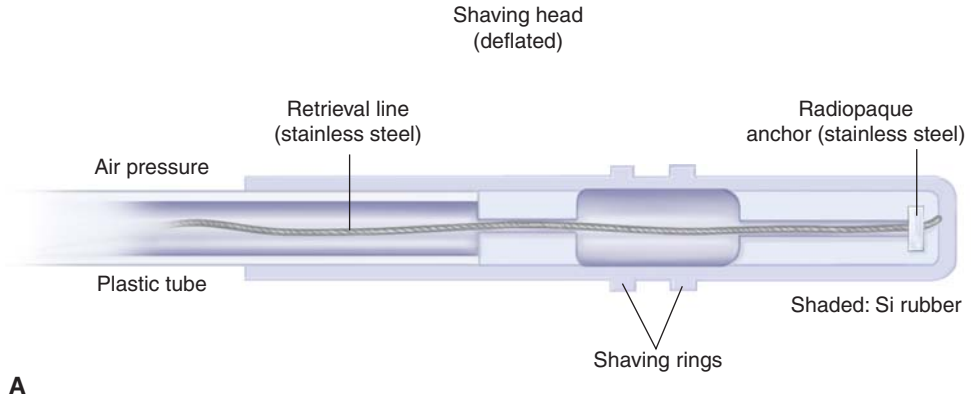
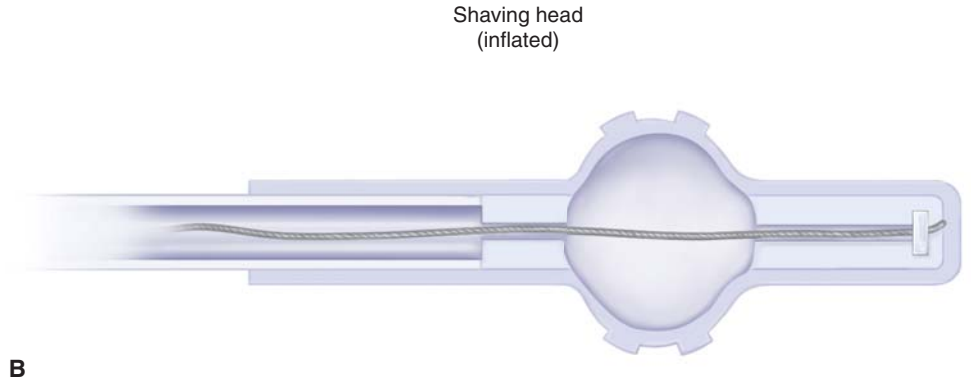


FIGURE 52-10 The Mucus Slurper. **A.** The Mucus Slurper is a modified Hi-Lo EVAC tracheal tube (Mallinckrodt Medical, Athlone, Ireland) in which the built-in evacuation lumen is extended beyond the cuff and connected to a vinyl hollow ring with eight holes. Suction at the distal tracheal tube tip is intermittent and automatic. **B.** The cuff of the Mucus Slurper is positioned at the very tip to reduce accumulation of mucus between the cuff and the tip of the Mucus Slurper. When the cuff is inflated, the eight suction holes has no contact with the tracheal mucosa. (Used, with permission, from Kolobow et al[214] and Li Bassi et al.[215])





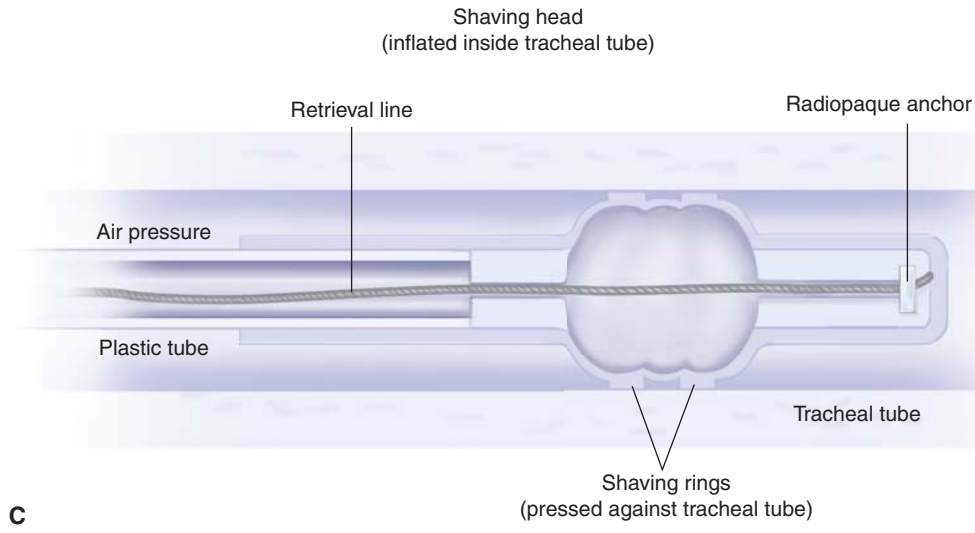


FIGURE 52-11 The Mucus Shaver. The Mucus Shaver is a 28-cm-long plastic tube with a 2-cm-long silicone inflatable balloon at its tip, with two or more 1.0-mm-wide, 0.5-mm-thick silicone rubber "shaving rings" (**A** and **B**). The device is inserted into the artificial airway up to its tip; then the balloon is inflated sufficiently to force the two shaving rings firmly against the internal wall (**C**). Finally, while inflated, the Mucus Shaver is gently retrieved to remove all accumulated mucus and biofilm. (Used, with permission, from Kolobow et al.[216])

consequently surrogate end points are commonly used to measure the response to interventions, increasing the potential for negative studies and hampering progress in the field.

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53 FIGHTING THE VENTILATOR

Martin J. Tobin
Amal Jubran
Franco Laghi

A patient is connected to the ventilator. His eyes are closed and he appears calm. The ventilator is making soft rhythmic noises, and the patient's chest is expanding and receding in unison with the ventilator. A sweep of signals is gently traversing the monitor screen.

This peaceful scene erupts suddenly. The patient bolts upright. His eyelids retract. His nostrils flare. Sweat drips from his brow. His skin turns blue. His sternocleidomastoids contract vigorously. His rib spaces retract. One or more alarms sound loudly.

A patient fighting (or bucking) the ventilator is frightening not only to the patient but to staff. If the physician cannot find the source of the problem and fix it, the patient may die in minutes. The physician must immediately diagnose and manage the problem, and do both concurrently. The physician quickly scans the monitors for clues. Sometimes the problem is immediately spotted and solved, such as disconnected ventilator tubing.

If the cause is not immediately obvious, the physician's primary responsibility is to ensure adequate ventilation. This requirement takes precedence over diagnosis. After disconnecting the patient from the ventilator, the physician (or staff) starts to ventilate the patient manually with a self-inflating bag containing 100% oxygen. This step is both therapeutic and diagnostic (Fig. 53-1).[1,2] If the distress resolves, it indicates that the problem originated in the ventilator. If the distress continues, it indicates the problem is within the patient.

INITIAL ASSESSMENT

Where a physician begins the assessment varies with the particulars of the patient's presentation. The following sequence is not appropriate for all patients.

Because hypoxia can be rapidly lethal, the pulse oximeter reading is noted. Although several factors can give rise to erroneous readings, the displayed saturation generally bears a close relationship to the oxygen saturation on an arterial blood-gas test.[3]

If the high-airway-pressure alarm is sounding, the physician should, if possible, perform an end-inspiratory occlusion

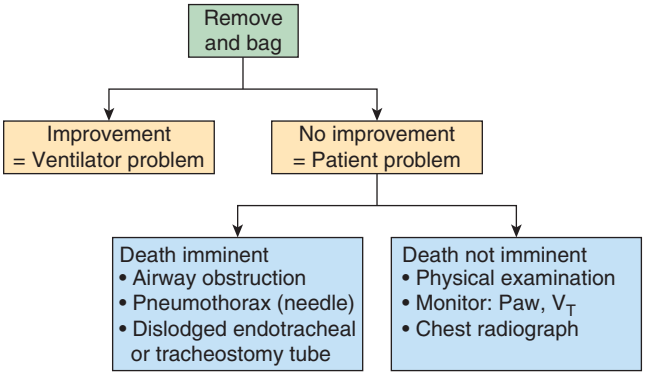

FIGURE 53-1 Removing the patient from the ventilator and providing manual ventilation with a bag (100% oxygen) is both therapeutic and diagnostic. Patient improvement indicates that the ventilator is the cause of the distress. Lack of improvement indicates that the problem is within the patient. If death appears imminent, the physician rapidly checks for airway obstruction (by passing a suction catheter), a dislodged endotracheal or tracheostomy tube, and a pneumothorax (if deemed likely, a small-gauge needle is inserted); depending on the clinical picture, other life-threading problems, such as aortic dissection, should be considered. If death is not imminent, the physician undertakes a more detailed physical examination and assessment of monitored variables. A chest radiograph may also be obtained. *Paw*, airway pressure; V_T, tidal volume.

maneuver to measure the plateau pressure (Fig. 53-2). An increase in peak airway pressure without a proportional increase in plateau pressure indicates narrowing of the airway.[4] Narrowing may arise from bronchoconstriction, an increase in secretions, a collection of fluid in the inspiratory limb of the ventilator circuit, kinking of the tubing, a foreign body, or herniation of the cuff of the endotracheal tube over its distal tip.

An increase in peak airway pressure accompanied by a proportional increase in plateau pressure indicates a decrease in thoracic compliance, which may arise within the lung or from extrinsic compression. A decrease in lung compliance may arise from pulmonary edema, early stages of the acute respiratory distress syndrome, dynamic hyperinflation associated with intrinsic positive end-expiratory pressure (PEEPi), and atelectasis. Extrinsic compression may be caused by rapid collection of pleural fluid (hemothorax, parapneumonic effusion, or transudative effusion) or a pneumothorax. If a tension pneumothorax is suspected and death appears imminent, the physician should insert a 14- to 16-gauge needle into the second intercostal space. If a gush of air is heard, a thoracostomy tube is inserted. Gastric distension, ileus, ascites, or extensive eschar formation can also cause a decrease in thoracic compliance.

A major obstruction of the airway will commonly cause oxygen desaturation and an increase in peak airway pressure. If obstruction is suspected, the clinician should pass a suction catheter through the airway to determine if the airway is patent and to remove secretions or other material that is causing a blockage.

The alarm may signal a low exhaled tidal volume (V_T). This can arise because of movement of the endotracheal tube into the hypopharynx or esophagus. It can also arise because of a disconnection in the ventilator circuit or a leak in the system. Many conditions can cause an increase in respiratory rate. Accordingly, a high rate is a very sensitive marker of an important change in a patient's condition. Because it is influenced by so many factors, it is not helpful in directing the clinician to the cause of the new change.

The patient's pattern of breathing may signal a marked increase in work of breathing. Important signs include tracheal tug (how much the larynx descends with each inspiration); palpable activity of the sternocleidomastoid muscles; recession in the suprasternal notch, supraclavicular space, and intercostal spaces; and paradoxical movement of the rib cage and abdomen (Fig. 53-3).

Auscultation of the chest may suggest a pneumothorax or movement of the endotracheal tube into the right main-stem bronchus. Cardiac auscultation may reveal the Hamman crunch, signaling the presence of pneumomediastinum. A new murmur may signal the development of a ventricular septal defect or other cardiac source of acute distress.

The pressure and flow tracings on the ventilator screen may provide clues to the sudden change in patient status. The contour of the airway pressure tracing may exhibit excessive scooping, indicating increased inspiratory effort; this pattern is seen when the delivered inspiratory flow no longer meets patient demand (Fig. 53-4).[5,6] The flow tracing

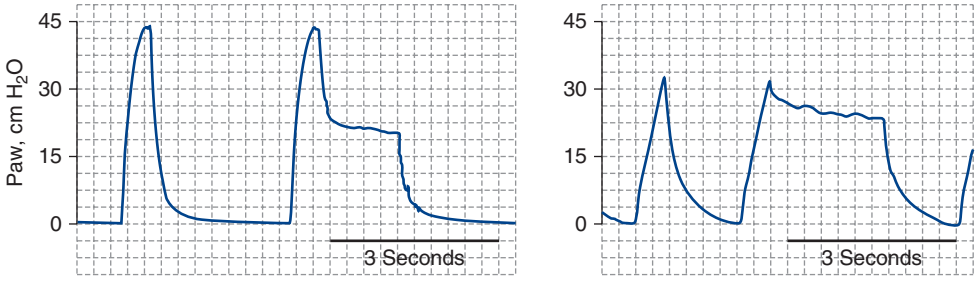

FIGURE 53-2 End-inspiratory occlusion maneuver during passive ventilation in two patients. In each patient, the second displayed breath was occluded for 2 seconds or less—a period that was not sufficient to achieve a complete plateau in either patient. *Left panel.* Airway pressure (*Paw*) drops by 24 cm H_2O during the end-inspiratory occlusion maneuver, indicating the presence of increased airflow resistance. *Right panel.* Paw drops by 5 cm H_2O during the end-inspiratory occlusion maneuver, indicating decreased respiratory compliance consequent to noncardiogenic pulmonary edema secondary to sepsis.

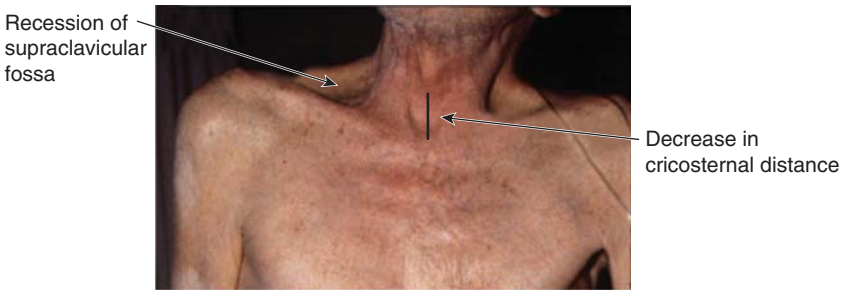

FIGURE 53-3 Examination of the neck in a patient with acute respiratory distress. Inspection reveals recession of the supraclavicular fossa, recession of the suprasternal notch, increased tracheal tug (not visible on the photograph), and prominent sternocleidomastoid muscles. Palpation confirms phasic activity of the sternocleidomastoid muscles, tracheal tug, and decreased cricosternal distance, indicative of hyperinflation.

may not return to the zero-flow line in the period immediately before the next inspiration, indicating PEEPi.[4] The flow tracing may exhibit a sawtooth pattern, indicating excessive secretions.[7]

A decrease in end-tidal carbon dioxide tension (P_{CO_2}) can be helpful. A sudden decrease in end-tidal P_{CO_2} may arise with pulmonary embolism or air embolism. Esophageal intubation also causes end-tidal P_{CO_2} to fall to zero. Unfortunately, end-tidal CO_2 readings do not reliably reflect arterial CO_2 tension (P_{CO_2}) in patients with underlying lung disease.

The blood pressure reading may signal a hypertensive crisis. The differential diagnosis of a fall in arterial pressure is wide, and influenced by clinical context. In a patient with a myocardial infarction, a fall in arterial pressure may signal the onset of cardiogenic shock. A pulmonary artery catheter can provide important clues. A new onset of large V (ventricular) waves in the pulmonary artery wedge tracing suggests the development of acute mitral regurgitation secondary to ruptured chordae tendineae cordis (Fig. 53-5).[8] The electrocardiogram (ECG) may reveal arrhythmias or ST-segment elevation. In contrast to the average patient, communication with an intubated patient is very difficult. A nonintubated patient who develops acute distress consequent to an acute myocardial infarction is able to relay the onset of crushing chest pain to staff. The presence of a tracheal tube prohibits speech. Nevertheless, clinicians can obtain a considerable amount of information about the nature of symptoms. Nurses are frequently more patient and skilled than physicians in achieving an ongoing dialogue with a patient.

The sequence of the above steps will vary with the clinical context. The approach is also incomplete. For example, sudden distress may have no cardiopulmonary cause. Instead, it may originate in a blocked Foley catheter leading to an overdistended bladder.

Based on the initial assessment, a physician diagnoses the most likely cause of a change in a patient's condition. Table 53-1 lists the most common causes of sudden respiratory distress in a ventilated patient.

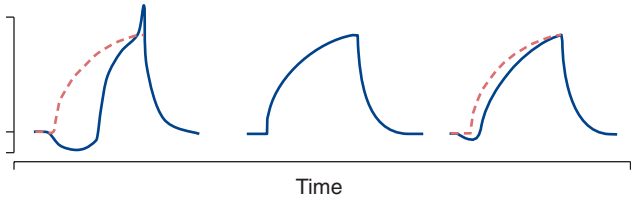

FIGURE 53-4 Airway pressure waveforms recorded in a patient shortly after the initiation of mechanical ventilation (*left*), in a patient making no respiratory effort (controlled mechanical ventilation, *middle*), and in a patient receiving an appropriate level of assist-control mechanical ventilation (*right*). The *dashed lines* on the left and right panels reproduce the tracing achieved by passive, controlled mechanical ventilation as occurs in a patient receiving neuromuscular blocking agents. The *left waveform* depicts a patient in respiratory distress who has excessive work of breathing; this can be inferred from the initial concavity, which results from vigorous inspiratory effort, and the spike at the end of ventilator assistance, which is the result of expiratory muscle recruitment. The *middle waveform* depicts a patient making no respiratory effort. The *right waveform* depicts a patient performing an appropriate amount of respiratory work: The small downward dip at the start of the breath indicates the small inspiratory effort required to trigger the ventilator, and the distance between the *solid line* (actual airway pressure) and *dashed line* (expected tracing during controlled ventilation, as in the middle panel) is proportional to the amount of work performed by the patient's inspiratory muscles while the ventilator is providing assistance. The patient in the right panel is performing much more respiratory work than the patient in the middle panel and much less work than the patient in the left panel. (Used, with permission, from Tobin et al.[6])

ARTIFICIAL AIRWAY PROBLEMS

Several different problems with artificial airways can produce acute respiratory distress in the ventilated patient.

Movement of the Endotracheal Tube

An endotracheal or tracheostomy tube that is initially properly positioned may subsequently move up or down in a patient's airway. Downward movement into a main-stem bronchus (endobronchial intubation) is estimated to occur in approximately 10% of ventilated patients.[9–11] It is usually caused by inadequate external fixation of the endotracheal tube, excessive neck movement, or both.[12]

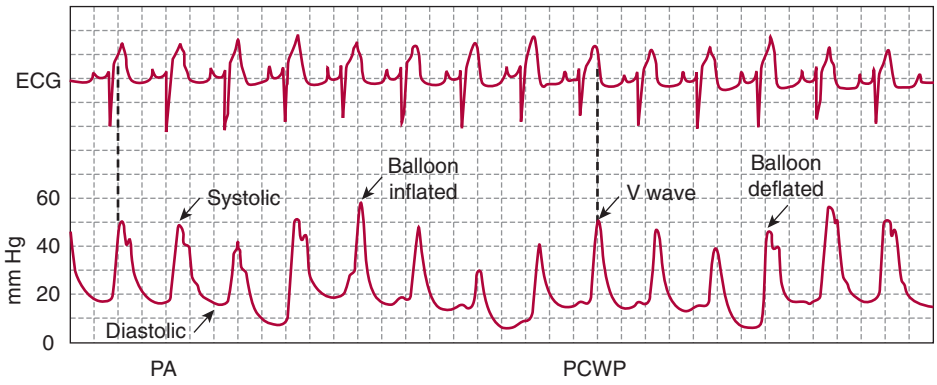

FIGURE 53-5 Simultaneous recordings of electrocardiogram (ECG, *top*) and pulmonary artery (*PA*) pressure (*bottom*) in a patient with acute mitral insufficiency. Following inflation of the balloon, giant *V* waves are seen in the pulmonary capillary wedge pressure (*PCWP*) tracing. Before balloon inflation and after balloon deflation, the PA tracing has a characteristic bifid appearance secondary to both a PA systolic wave and a V wave. Note that the V wave occurs later in the cardiac cycle than does the PA systolic wave, which is synchronous with the T wave on the electrocardiogram.

Main-stem intubation occurs more often on the right side, because the right main-stem bronchus forms a less-acute angle with the trachea than does the left main-stem bronchus[11] and because the bevel of most endotracheal tubes is directed rightward (Fig. 53-6). The lack of ventilation to the contralateral lung produces atelectasis, which, in turn, causes shunting of blood and hypoxemia. The delivery of a high volume to the intubated lung predisposes to the development of a pneumothorax.[4]

Clues to the development of endobronchial intubation include an increase in peak airway pressure accompanied by a proportional increase in plateau pressure, asymmetric expansion of each hemithorax, and a decrease in breath sounds over the contralateral lung. In a prospective study, however, Brunel et al[10] found that clinicians considered breath sounds equal over both lung fields in 60% of patients with an endobronchial intubation.

If endobronchial intubation is suspected, the endotracheal tube should be pulled back a few centimeters, the chest auscultated again, and the position of the tube confirmed by radiography. The problem can be prevented by securing the tip of the tube at least 3 to 4 cm above the carina, and obtaining a radiograph at the time of intubation.[12] In addition, centimeter markings on an endotracheal tube are helpful as a reference, although not completely reliable.[10] In general, an endotracheal tube should be secured at reference markings

TABLE 53-1: CAUSES OF SUDDEN RESPIRATORY DISTRESS IN A PATIENT RECEIVING MECHANICAL VENTILATION

Patient-related causes
- Artificial airway problems
  - Movement of the endotracheal tube
  - Cuff herniation external
  - Compression of the endotracheal tube by the cuff
  - Cuff leak
  - Endotracheal tube kinking
  - Foreign body
  - Tracheoesophageal fistula
  - Innominate artery rupture
  - Malpositioning of the nasogastric tube
  - Build-up of secretions
- Bronchospasm
- Pneumothorax
- Pulmonary edema
- Pulmonary embolism
- Acute hypoxemia
- Blood in the endotracheal tube
- Dynamic hyperinflation
- Abnormal respiratory drive
- Alteration in body posture
- Drug-induced problems
- Abdominal distension
- Agitation

Ventilator-related causes
- Ventilator malfunction
- External ventilator circuit
  - Leaks or disconnects
  - Condensate
  - Inline nebulizers
- Inadequate ventilator support
- Patient–ventilator dyssynchrony

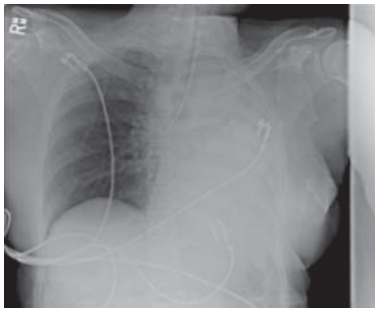

FIGURE 53-6 Right main-stem intubation. The endotracheal tube was inserted too far down, resulting in intubation of the right main-stem bronchus and atelectasis of the left lung with resultant mediastinal shift toward to the left.

of 23 cm in men and 21 cm in women.[10] On the chest radiograph, the tip of the endotracheal tube should be located at a level corresponding to the top of the aortic knob when the head is in a neutral position.[13]

An endotracheal tube may also migrate above the vocal cords, or get dislodged into the esophagus.[11] Esophageal intubation may arise as a result of attempts to blindly reposition an endotracheal tube. Malpositioning causes sudden distress accompanied by phonation, audible escape of air through the nose and mouth, absence of tube condensation, decrease in tidal volume (V_T), decrease (or increase) in peak airway pressure, and abdominal distension. Chest radiography can be misleading because the trachea overlays the esophagus, making it difficult to tell whether the tube is located in the esophagus or trachea. A reading of zero on an end-tidal CO_2 monitor helps in detecting esophageal intubation (Fig. 53-7). Upward movement of an endotracheal tube usually results from excessive neck movement and/or inadequate tube fixation. Conrardy et al[12] found that neck extension caused an endotracheal tube to move an average of 1.9 cm away from the carina, but movement was as much as 5.2 cm in some patients. This observation may explain why patients who are carefully restrained can still self-extubate.

Cuff Herniation

Herniation of the cuff of an endotracheal tube over its distal tip can cause complete airway obstruction.[11] This problem most commonly occurs after changes in position of the tube or changes in the posture of the head and neck. Clues to cuff herniation include an increase in peak airway pressure, resistance during manual ventilation, a decrease in V_T, difficulty in passing a suction catheter, and an abnormal musical sound during inspiration.[2] Deflation of the cuff produces immediate relief. In a stable patient with an unclear source of airway obstruction, the diagnosis may not be made without bronchoscopy.

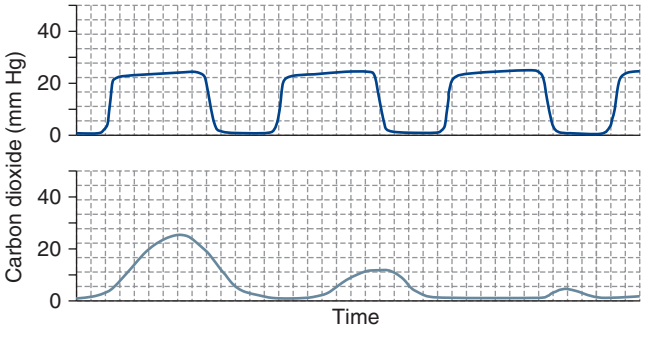

FIGURE 53-7 End-tidal CO_2 tracing and esophageal intubation. *Upper panel.* End-tidal CO_2 tracing in a patient in whom an endotracheal tube was inserted correctly in the trachea. During inhalation, end-tidal CO_2 is 0 mm Hg. During exhalation, the CO_2 tracing rises steeply, attains a near plateau, and then quickly returns to the baseline. The end tidal CO_2 in this patient, 25 mm Hg, is below the normal range of 35 to 45 mm Hg. *Lower panel.* End-tidal CO_2 tracing in a patient in whom an endotracheal tube was erroneously inserted in the esophagus. The expected shape of the CO_2 tracing has been replaced by small transient rises in the CO_2 tracing, which progressively decrease with each squeeze of the Ambu bag.

External Compression of the Endotracheal Tube by the Cuff

External compression of an endotracheal tube as a result of an inflated cuff is a rare cause of airway obstruction (Fig. 53-8).[14]

Cuff Leak

The failure of the cuff on an endotracheal tube to form a seal with the wall of the trachea leads to gas leakage, which may or may not be of clinical consequence.[11] A large leak may cause the ventilator alarms to sound, signaling a low peak airway pressure and low exhaled V_T, and cause alveolar hypoventilation. Other clues include ability to phonate, frothy secretions in the patient's mouth, hearing a gurgle over the trachea or larynx on auscultation, a discrepancy between expired and inspired V_T, and failure to maintain a set level of PEEP.[11]

The most common cause of cuff leak is malposition of the endotracheal tube. Consequently, the development of a cuff leak should cause the physician to reevaluate tube position.

The cuff may be deflated not only because of a leak in the cuff itself, but also because of a leak in the pilot balloon or in the external valve assembly.[13] A clamp placed on the cuff inflation tubing proximal to the valve and pilot balloon can temporarily correct this problem (without having to immediately replace the endotracheal tube).

Complete rupture of a cuff can lead to aspiration of saliva, vomit, or food; the entire endotracheal tube needs to be replaced.

Endotracheal Tube Kinking

The endotracheal tube can become kinked as a result of changes in the position of the head and neck.[10] Some authors have recommended immersing an endotracheal tube in warm saline as a means of decreasing the incidence of mucosal trauma and epistaxis following nasal intubation,[15] but this practice has been reported to give rise to subsequent kinking.[16] Kinking may also occur if the tube softens through being warmed by heated humidified gas,[13] or when the patient bites the tube. Figure 53-9 shows an instance of endotracheal-tube kinking that was attributed to earlier movement of the tube from one angle of the mouth to the other.[17] We speculate that this shift in position of the tube might have led to a force acting in a direction perpendicular to the torque of the natural curve of an endotracheal tube, and thus induced kinking. Kinking leads to an increase in peak airway pressure and difficulty in passing a suction

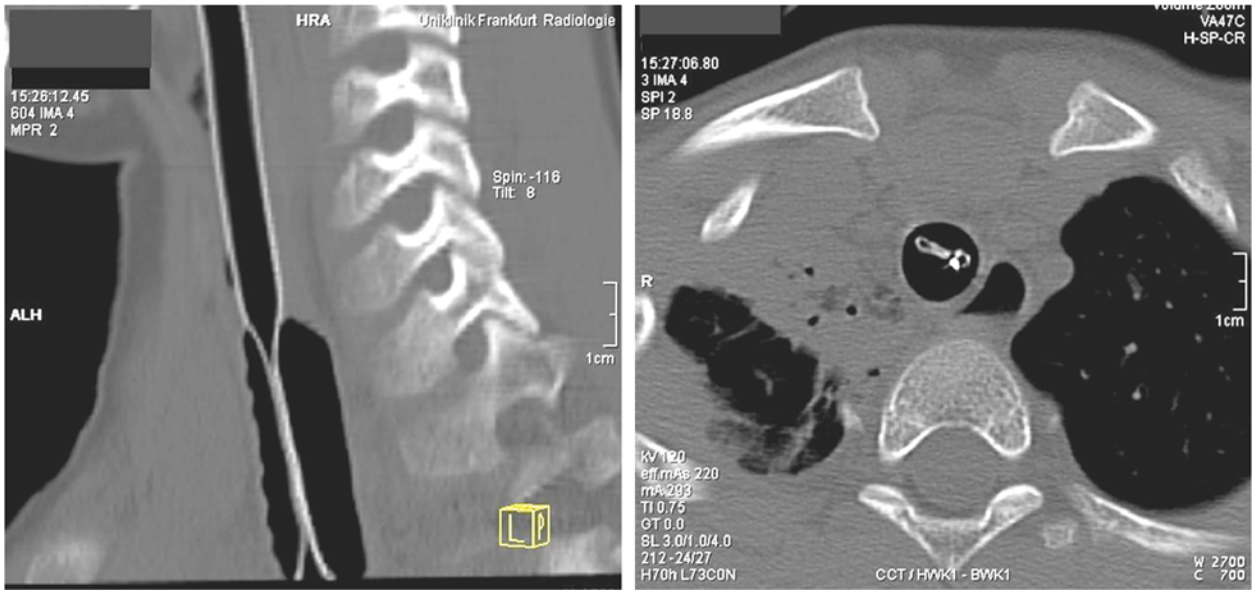

FIGURE 53-8 External compression of endotracheal tube. Computed tomography images of the sagittal plane of the cervical spine and trachea (*left panel*) and transversal plane at the level of the first thoracic vertebra (*right panel*) in an 8-year-old boy who required endotracheal intubation as a result of multiple injuries received in a traffic accident. The inflated cuff produced critical obstruction of the endotracheal tube. The *white dot* on the scan in the right panel indicates the obstructed lumen of the tracheal tube. (Used, with permission, from Hofstetter et al.[14])

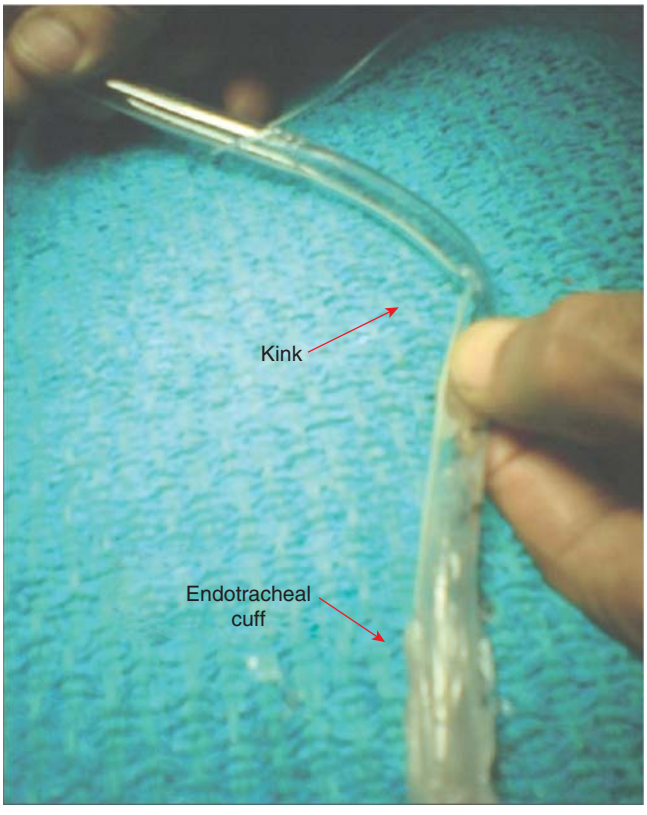

FIGURE 53-9 A kink found approximately 10 cm above the cuff of an endotracheal tube in a direction opposite to the natural curvature of the tube (toward the convex side) that resulted approximately an hour after the tube had been moved from the right angle of mouth and fixed on the left angle. (Used, with permission, from Hariharan et al.[17])

catheter. When this occurs, the endotracheal tube should be withdrawn and replaced.

Foreign Body

The endotracheal tube can become occluded with a variety of foreign bodies, including dried lubricant,[18] surgical tape,[18] a broken stylet sheath,[19] plastic debris retained from the time of manufacturing the Murphy eye in the tube,[20] and nasal turbinates avulsed during nasotracheal intubation.[21]

Tracheoesophageal Fistula

Tracheoesophageal fistula is a rare complication that is primarily caused by ischemia of the tracheal wall secondary to pressure from an overinflated cuff or by movement of a tracheal tube or its tip.[22] Patients with this complication typically have had both a tracheal tube and a nasogastric tube in place for a long time.[11,23]

Clues to the presence of a tracheoesophageal fistula include the inability to deliver a preset V_T despite a functional cuff, gastric distension, audible leak of air through the mouth, copious airway secretions, the suctioning of gastric contents from the lower respiratory tract, and clinical deterioration and coughing on deflation of the cuff.[13] Diagnosis needs to be verified by bronchoscopy with direct visualization of the esophagus or by cine-esophagography or cine-tracheography.[13] Most experts believe that closure of the fistula demands operative repair; opinions vary as to optimal timing.[13]

Innominate Artery Rupture

Erosion of the innominate artery has been reported to occur in 0.4% to 4.5% of tracheostomies.[24] Most ruptures occur at some point during the first three weeks after a tracheotomy,[24] with peak incidence 7 to 14 days after the procedure.[25] The underside of the tracheal tube, the tracheal cuff, or the tip of the tube erode through the anterolateral tracheal wall, at the point where the innominate artery crosses the trachea. Risk factors include excessive movement of the tube, excessive movement of the neck, overinflation of the cuff, or radiotherapy. Several authors emphasize that making a tracheotomy incision below the third tracheal ring increases the risk of fistula formation, but the complication can occur even when the incision is placed between the second and third tracheal rings, as recommended.[25]

Any peristomal bleeding or hemoptysis in a patient with a recent tracheotomy should lead to detailed assessment to ascertain the underlying cause. Bleeding within 48 hours is usually associated with local factors such as traumatic puncture of anterior jugular or inferior thyroid veins, mucosal abrasion from a suction catheter, or systemic coagulopathy. Bleeding occurring 3 days to 6 weeks after a tracheotomy should be judged to be the result of innominate artery rupture until proven otherwise.[25] The clinical presentation may be quite dramatic, with blood gushing from the tracheal tube. It may be heralded by pulsation of the tracheal cannula or a "sentinel bleed," which is reported to occur in more than 50% of patients.[25]

Adequate oxygenation is the mainstay of immediate management with simultaneous identification and termination of bleeding.[25] The tracheostomy cuff should be overinflated in an attempt to achieve tamponade, and the cuffed tube advanced so that the balloon lies distal to the tracheostomy stoma. An attempt should be made to digitally compress the artery by inserting an index finger into the stoma and compress the artery against the posterior surface of the manubrium.[24] If this is successful, a blood transfusion should be administered while the patient is being transported to the operating room for sternotomy and ligation of the vessel. Time should not be wasted in performing imaging studies. Mortality is extremely high: greater than 85% in a review of the world literature.[24]

OTHER PROBLEMS

Malposition of the Nasogastric Tube

A stiff nasogastric tube can easily bypass the cuff of an endotracheal tube and enter the airway. If the nasogastric tube is connected to suction, the continuous negative pressure will create a constant flow of gas out of the airways.[26] Consequently, the low V_T alarm will sound. The negative pressure can also cause triggering of the ventilator. In particular, ventilator triggering in a patient who is receiving a paralytic agent suggests that a nasogastric tube is misplaced in the airway. Other complications of nasogastric tubes include passage of the tube through the tracheobronchial tree into the pleural space, causing the formation of a bronchopleural fistula; infusion of nutritional solutions through the misplaced nasogastric tube can cause an empyema. A nasogastric tube can also cause esophageal perforation leading to pneumomediastinum, pneumothorax, and tracheoesophageal fistula.

Secretions

Airway secretions can cause problems by being too copious or too dry. Excessive secretions can lead to mucus plugging and atelectasis. To avoid this problem, careful bronchial toilet and frequent suctioning are necessary in patients with copious secretions. If atelectasis occurs and fails to resolve with conservative measures, bronchoscopy should be undertaken.

A helpful clue to the presence of excessive secretions is the presence of a sawtooth pattern on the flow tracing.[7] In a study of fifty intubated patients, Jubran and Tobin[7] found that the presence of a sawtooth pattern was approximately six to eight times more likely in patients who had secretions than in patients without secretions. Conversely, a smooth flow-volume curve was about one-quarter as likely to be found in patients with secretions as in patients without secretions. Clinical examination had much higher false-positive and false-negative rates (42% and 43%, respectively) than the flow-volume curves (12% and 14%, respectively). The usefulness of a sawtooth pattern for detecting secretions was confirmed by Guglielminotti et al[27] in a study of sixty-two patients who were receiving pressure-support or assist-control ventilation.

A tracheal tube bypasses the upper airway, which normally heats and humidifies inspired gas. Consequently, secretions may become excessively dry and encrusted. Inspissated secretions can cause significant blockage of the tracheal tube over a relatively short period.[23] Clues to this problem include an increase in peak airway pressure without an associated increase in plateau pressure, and difficulty in passing a suction catheter. Obstruction appears to be a greater problem when heat and moisture exchangers are employed, as opposed to hot water humidifiers (see Chapter 51).

When secretions dry and accumulate, they can cause complete obstruction or ball-valve obstruction of the endotracheal tube. When this occurs at the distal tip of the tube, positive pressure during inspiration will cause the mass to move away from the tip, permitting the flow of gas. During expiration, expiratory pressure will push the mass of dried secretions into the distal port producing occlusion and cessation of airflow. The ball-valve obstruction causes pulmonary hyperinflation and may produce a tension pneumothorax.[28]

Bronchospasm

Bronchoconstriction is a common cause of sudden respiratory distress. Clues to its development include an increase in peak airway pressure with little or no change in plateau pressure. Clinical manifestations include wheezes, pulsus paradoxus, and evidence of increased work of breathing (recession of the suprasternal space, supraclavicular fossae, and intercostal spaces; heightened activity of the accessory muscles; tracheal tug; and paradoxic motion of the rib cage and abdomen). Management includes bronchodilator therapy.

Pneumothorax

Sudden respiratory distress in a ventilator-supported patient should always arouse suspicion of a pneumothorax, because 60% to 90% of such pneumothoraces are reported to be under tension (Fig. 53-10).[29] Chapter 44 provides a full discussion of barotrauma and its pathogenesis.

A pneumothorax is typically associated with an increase in peak airway pressure and a proportional increase in plateau pressure. Other manifestations include hyperresonance, tracheal deviation to the contralateral side, decreased breath sounds, and cardiovascular collapse. If a pneumothorax is suspected and death is imminent, a 14- to 16-gauge needle should be inserted into a second intercostal space. If a gush of air is heard, a thoracostomy tube is inserted. If the patient is stable, however, a chest radiograph should first be performed to verify the diagnosis before inserting a chest tube.

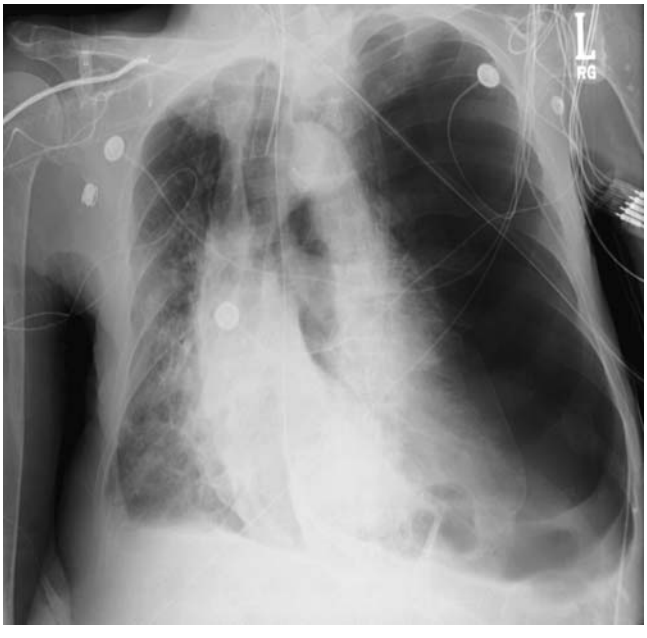

FIGURE 53-10 Development of a large left pneumothorax in a mechanically ventilated patient. Portable anteroposterior chest radiograph showing large (tensionlike) pneumothorax with significant displacement of heart and mediastinum to the opposite side. Vascular congestion of the right lung also noted.

Pulmonary Edema

Pulmonary edema can cause sudden distress associated with an increase in plateau pressure and a smaller increase in the gradient between the peak and plateau pressures. When present, pink, frothy secretions and an increase in pulmonary artery wedge pressure are particularly helpful.

Pulmonary Embolism

Acute pulmonary embolism is an uncommon cause of sudden respiratory distress in a ventilated patient. Typical manifestations include dyspnea, tachypnea, chest pain, fever, hemoptysis, pleural rub, and features of deep vein thrombosis. An important clue, when it occurs, is sudden hypoxemia with no change in peak airway pressure—a unique combination. The risks associated with transporting a critically ill patient alter the approach to diagnosis. Bedside duplex ultrasonography of the leg veins is a reasonable initial test.[30] Although ventilation–perfusion scans are difficult to perform in a ventilated patient, they have reasonable diagnostic reliability.[31] Helical computed tomographic scanning is worthwhile, although doubts have been raised about its accuracy in this setting.[32]

Acute Hypoxemia

Some ventilated patients present with acute hypoxemia, which may or may not be accompanied by acute distress. The differential diagnosis for new onset of hypoxemia can be considered in terms of ventilator-related problems, progression of the underlying disease, onset of a new medical problem, effects of interventions and procedures, and medications.[33] Table 53-2 lists the causes of worsening oxygenation in the ventilated patient.

Blood from the Endotracheal Tube

The return of bright red blood from a tracheal tube is alarming.[34] It is most commonly caused by trauma from a suction catheter, especially in patients with inflamed airways. Trauma secondary to the cuff also causes bleeding: The most dramatic form is innominate artery fistula. Airway bleeding may arise with infection, such as necrotizing pneumonia or tracheobronchitis. Pulmonary hemorrhage may be part of the underlying disease, such as Goodpasture syndrome, Wegener granulomatosis, neoplasm, or disseminated intravascular coagulation. Blood mixed with pink, frothy secretions suggests pulmonary edema. Pulmonary embolism accounts for a small proportion of patients with hemoptysis.

Pulmonary artery rupture can arise as a complication of pulmonary artery catheterization.[35] Rupture usually results from inflating the balloon when the catheter is too far distal. Risk factors include advancing the catheter with the balloon deflated, failure to observe the pulmonary artery

TABLE 53-2: CAUSES OF WORSENING OXYGENATION IN THE VENTILATED PATIENT

Ventilator-related problems
- Airway malfunction
- External circuit malfunction
- Ventilator malfunction
- Inappropriate ventilator settings

Progression of an underlying disease process
- Acute respiratory distress syndrome
- Cardiogenic pulmonary edema
- Pneumonia
- Sepsis
- Acute exacerbation of asthma or chronic obstructive pulmonary disease

Onset of a new problem
- Pneumothorax
- Atelectasis
- Aspiration (gastric or oropharyngeal)
- Ventilator-associated pneumonia
- Sepsis
- Pulmonary thromboembolism
- Fluid overload
- Bronchospasm
- Retained secretions
- Shock
- Seizure

Effects of interventions and procedures
- Endotracheal suctioning
- Changes in body position
- Chest physiotherapy
- Bronchoscopy
- Thoracentesis
- Peritoneal dialysis
- Hemodialysis

Medications
- Bronchodilators
- Vasodilators
- β–blockers

pressure while the balloon is being inflated (inflation should cease immediately when a wedged tracing is obtained), hand flushing of the catheter while it is wedged, and pulmonary hypertension. If pulmonary artery rupture is suspected, the patient should be placed in a lateral decubitus position with the affected lung down, a double-lumen endotracheal tube inserted (to protect the contralateral lung), and arrangements made for surgical intervention.

Dynamic Hyperinflation

Ventilator-supported patients commonly display tachypnea and an increased time constant (secondary to increased respiratory resistance and/or low pulmonary compliance), which predisposes to the development of dynamic hyperinflation.[36] This hyperinflation is associated with the presence of a positive recoil pressure at the end of expiration, termed *intrinsic PEEP (PEEPi)* or *auto-PEEP*.[37,38]

Hyperinflation may cause significant patient discomfort for at least two reasons. One, it decreases the efficiency of force generation by the respiratory muscles. Two, it increases work of breathing because inspiration occurs at the upper, less compliant portion of the pressure–volume curve of the lung, where inwardly directed elastic recoil of the chest wall poses an additional elastic load.[39,40] To initiate inspiratory gas flow, a patient has to generate a negative pressure equal in magnitude to the opposing elastic recoil pressure (level of PEEPi) (Fig. 53-11). Likewise, if a patient with PEEPi is triggering a ventilator, the patient has to generate a negative-pressure equal in magnitude to the level of PEEPi in addition to the set minimum circuit pressure drop before a ventilator-assisted breath is initiated. This is one factor that accounts for the common occurrence of failure to trigger despite obvious respiratory effort (Fig. 53-12).[41,42]

Therapeutic measures to decrease PEEPi include bronchodilator agents, employment of a large-bore endotracheal tube; decreasing the minute ventilation by controlling fever or pain; and minimizing the ratio of inspiratory time to expiratory time by increasing inspiratory flow rate, or using non-distensible tubing in the ventilator circuit.

Addition of external PEEP can also decrease work secondary to the inspiratory threshold load effect of PEEPi.[38,43] To initiate inspiratory flow, alveolar pressure must be decreased below ambient pressure. During normal spontaneous breathing, this is accomplished by only a small decrease in pleural pressure. For alveolar pressure to fall below ambient pressure in the presence of hyperinflation, however, a much greater decrease in pleural pressure is required. If ambient pressure is elevated by the application of external PEEP, inspiration is more easily accomplished because alveolar pressure needs to be decreased only below the level of external PEEP (rather than below zero). This may seem paradoxical: External PEEP, which is commonly used to induce hyperinflation in patients with microatelectasis, is being used to decrease the work of breathing induced by hyperinflation.

This paradox can be understood by considering the analogy of a waterfall over a dam.[40] The height of the waterfall represents the critical closing pressure of airways in patients with PEEPi and chronic obstructive pulmonary disease (COPD) (Fig. 53-13). Thus, elevating downstream pressure, as with external PEEP, has no influence on either expiratory airflow or the pressure upstream (PEEPi) from the site of critical closure (Fig. 53-13, *upper panel*). This situation exists until downstream pressure is elevated to a value equal to the critical closing pressure (Fig. 53-13, *middle panel*). Once downstream pressure is elevated above the critical closing pressure (the height of the waterfall), however, the pressure upstream increases immediately, and hyperinflation is exacerbated (Fig. 53-13, *lower panel*).

The counteracting effect of external PEEP operates only in the setting of airflow limitation. In the absence of airflow limitation, or when PEEPi results from expiratory muscle activity, the addition of external PEEP is a hindrance and adds to work of expiration. It is important to keep in mind that while external PEEP can help decrease inspiratory work,

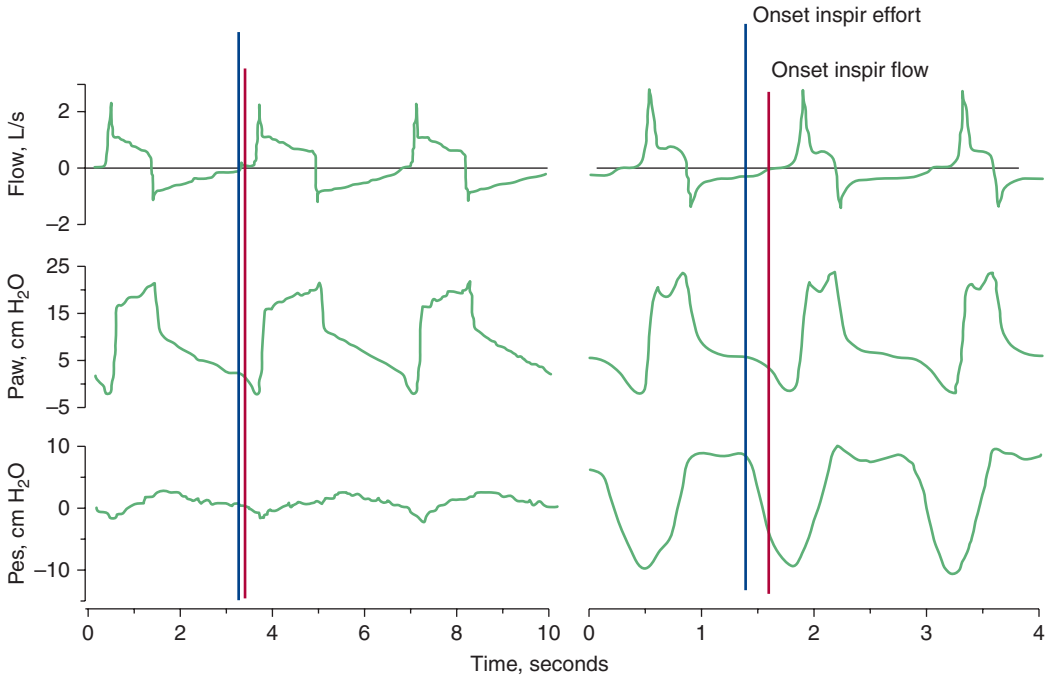

FIGURE 53-11 Differing degrees of intrinsic positive end-expiratory pressure (PEEPi) in patients with chronic obstructive pulmonary disease. Tracings are flow, airway pressure (*Paw*), and esophageal pressure (*Pes*) in two patients with chronic obstructive pulmonary disease receiving assisted ventilation with pressure support set at 20 cm H_2O (no external PEEP is applied). The patient on the left had a myocardial infarction complicated by congestive heart failure, and the patient on the right had sepsis. PEEPi, estimated as the difference in esophageal pressure between the onset of inspiratory (*Inspir*) effort (*vertical blue line*) and the onset of inspiratory flow (*vertical red line*), was 0.5 cm H_2O in the patient on the left and 10.6 cm H_2O in the patient on the right. This method of estimating PEEPi is based on the assumption that the change in esophageal pressure reflects the inspiratory muscle pressure required to counterbalance the end-expiratory elastic recoil of the respiratory system.

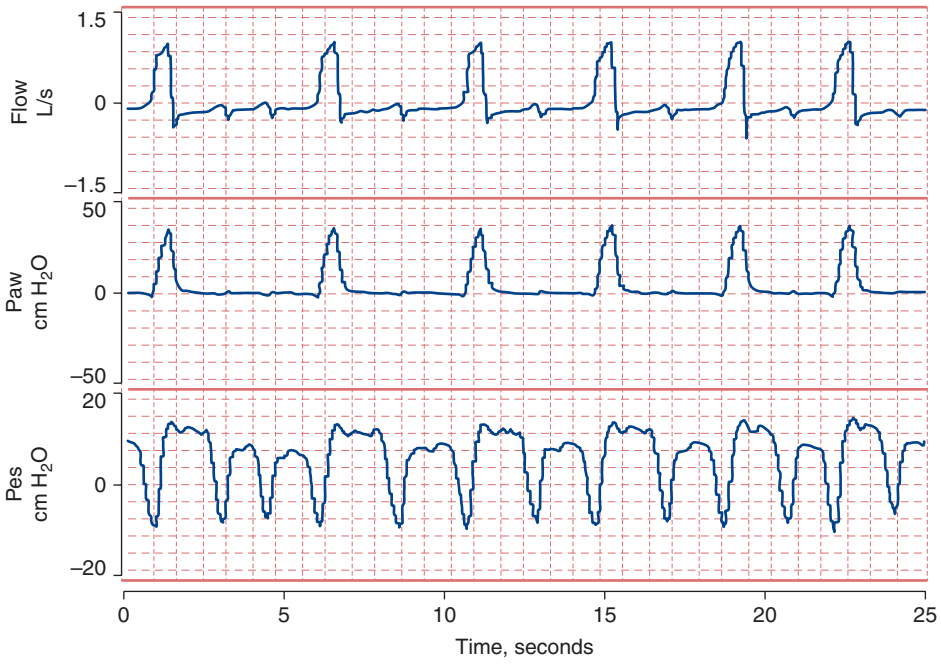

FIGURE 53-12 Failure to trigger the ventilator. Flow, airway pressure (*Paw*), and esophageal pressure (*Pes*), in a patient with chronic obstructive pulmonary disease who is receiving assist-control ventilation at the following settings: tidal volume 600 mL, inspiratory flow 60 L/min, trigger sensitivity –2 cm H_2O, and positive end-expiratory pressure 0 cm H_2O. The patient's intrinsic respiratory rate is 28 breaths/min, whereas the number of breaths delivered by the ventilator is 16 breaths/min. That is, 43% of the patient's inspiratory efforts fail to trigger ventilator assistance. Contractions of the inspiratory muscles during the failed triggering attempts cause a temporary deceleration of expiratory flow and much less obvious decreases in airway pressure. The temporary decelerations in expiratory flow are followed by temporary accelerations of expiratory flow that coincide with the termination of the unsuccessful inspiratory effort.

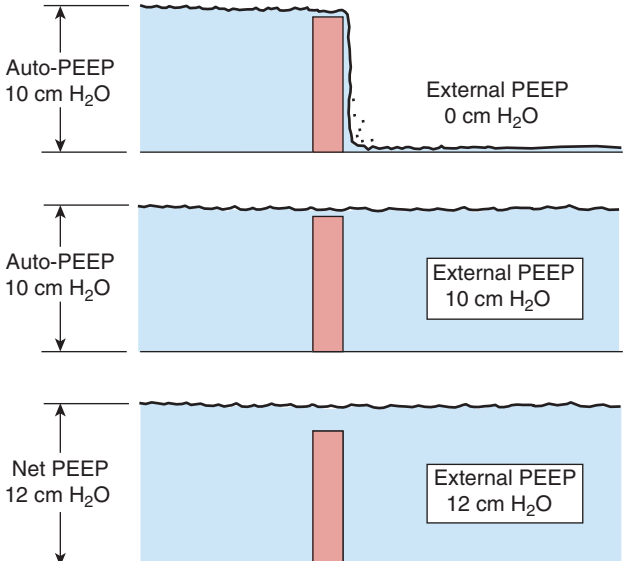

FIGURE 53-13 The analogy of a waterfall over a dam (indicated by the *solid block*) is used to explain the effect of external PEEP (downstream pressure) on PEEPi (upstream pressure) during expiration. Elevation of downstream pressure with external PEEP has no influence on either expiratory flow or upstream pressure (PEEPi) until it is equal to the critical closing pressure. When downstream pressure exceeds the critical closing pressure, the pressure upstream increases and hyperinflation is exacerbated. (Used, with permission, from Tobin and Lodato.[40])

it does nothing to relieve the accompanying hyperinflation, which has other detrimental effects.[39] Another caveat is the heterogenous distribution of lung units in patients with airflow limitation, each with its own critical closing pressure.[44] Given the regional inhomogeneities among lung units, the average level of PEEPi must exceed the lowest regional alveolar pressure. Thus, external PEEP equal to PEEPi could cause hyperinflation in the faster-emptying lung units.[45–47] To minimize this risk, it is prudent to limit the level of external PEEP to approximately 70% of the level of PEEPi.

The importance of PEEPi as a cause of electromechanical dissociation during cardiopulmonary resuscitation is now well recognized.[48,49] Rosengarten et al[48] reported a dramatic example. A young woman with acute severe asthma was intubated 25 minutes after initial presentation. Ventilation was commenced with a V_T of 8 to 10 mL/kg and a respiratory rate of 10 to 14 breaths/min. Oxygen saturation increased momentarily. Five minutes after intubation, blood pressure could not be recorded. External cardiac massage was instituted, but the patient remained in electromechanical dissociation. Twenty-five minutes after intubation, the situation was considered irretrievable. All resuscitation was stopped. Three minutes later, the patient returned to sinus rhythm, and the pulses became palpable. Ventilation was recommenced at 15 breaths/min. Within 15 seconds, the pulse disappeared. Ventilation was reduced to 6 to 8 breaths/min, and the pulse returned. Ventilation was transiently increased on three more occasions, and blood pressure disappeared each time. Seventy-five minutes after commencing resuscitation, the patient's blood pressure was 165/80 mm Hg. The patient suffered initial ischemic brain damage, but eventually made a close to complete recovery. In retrospect, it is clear that this patient suffered repeated episodes of circulatory arrest as a result of unrecognized ventilator-induced hyperinflation.

If faced with persistent hypotension in a patient with airflow limitation who is undergoing cardiopulmonary resuscitation, elevated PEEPi should be suspected. In such instances, the patient should be subjected to an apnea trial (after first ventilating the patient with 100% oxygen).[13] Ventilation is stopped for 1 minute, and blood pressure measured. If blood pressure improves, ventilation is resumed, but aiming to achieve a lower minute ventilation.

Inadequate Respiratory Motor Output

Decreased respiratory neuromuscular output may cause sudden deterioration in a patient's respiratory status. Decreased respiratory motor output, however, is not typically accompanied by respiratory distress. Respiratory motor output may be decreased as a result of acute neurologic disorders, heavy sedation, or neuromuscular blocking agents.[50] A normal, or even elevated, motor output may be insufficient to maintain alveolar ventilation if ventilatory demands or the mechanical load suddenly increase.

Elevated Respiratory Motor Output

Excessive respiratory motor output may cause severe respiratory alkalosis, which, in turn, may cause arrhythmias, hypotension, cerebral vasoconstriction, and seizures.[51,52] Ventilation can be stimulated by many physiologic, psychologic, and pathologic factors.[50] Extreme anxiety and panic cause dyspnea, fear, tachycardia, and palpitations, and when a patient misinterprets the basis of these symptoms, hyperventilation commonly develops.[53,54] A patient's likelihood of hyperventilating in response to stress probably depends on biologic vulnerability, personality, and cognitive variables.[54]

Several respiratory and nonrespiratory organic disorders stimulate breathing. The best known example is asthma, and even mild or moderate airway obstruction may be accompanied by a fall in partial pressure of arterial carbon dioxide (Pa_{CO_2}) to below 25 mm Hg.[55] The mechanism of the hyperventilation is uncertain: It is probably related to hyperinflation[56] and stimulation of vagal afferents,[57] and it is not reversed by bronchodilation.[58] The reduction in Pa_{CO_2} is quantitatively consistent with hypoxic stimulation of the peripheral chemoreceptors, although supplemental oxygen does not restore ventilation to normal.[59] Respiratory stimulation also occurs in patients with COPD,[60] pulmonary fibrosis,[60,61] pneumonia,[62] pulmonary embolism,[63] pulmonary hypertension,[60,64] and heart failure.[65] In asthma, the most profound hyperventilation occurs with relatively mild disease,[55,66] and the same may apply with the other causes of respiratory stimulation. Pain stimulates breathing,[67] whereas hyperventilation increases the pain threshold.[68] Hyperventilation can be severe with certain drug overdoses,

such as aspirin,[69] and it is a striking feature of sepsis[70] and major organ system failure,[71] although it does not occur in thyrotoxicosis. Acute diabetic ketoacidosis stimulates the peripheral chemoreceptors to produce deep rapid breathing and hypocapnia.[72]

Plum et al[73] coined the term *central neurogenic hyperventilation* to describe nine patients with tachypnea, of metronomic regularity, which persisted for hours or days at a time. Plum et al[74] subsequently revised their opinion, and attributed the heightened ventilation to stimulation of afferent peripheral reflexes arising in the lung and chest wall. It has not been possible to reproduce central neurogenic hyperventilation in animals. In their own clinical practice, Plum et al[74] are convinced of having seen only three patients with the condition, although brain histology was obtained in none of these cases. A few patients have been reported who displayed profound respiratory alkalosis, persisting during sleep or after administration of morphine, with normal oxygenation, normal chest radiography, and who had histologic evidence of pathology in the pons or some other area of the brain.[75–80] The rarity of this disorder is supported by the data of North et al.[81] Of 227 patients admitted to a neurosurgical unit, fifty-seven had a respiratory rate greater than 25 breaths/min and nine of these had a Pa_{CO_2} less than 30 mm Hg. In all but one patient, however, the tachypnea and hypocapnia could be explained by hypoxemia associated with a pulmonary abnormality or metabolic acidosis. While hyperventilation in critically ill patients with an acute neurologic disorder is rarely neurogenic in nature, it nevertheless carries a poor prognosis.[81–84]

Body Posture

An alteration in body posture can cause a fall in partial pressure of arterial oxygen (Pa_{O_2}) of as much as 30%,[33,85] especially in patients with unilateral lung disease. The hypoxemia is secondary to the effect of gravity on blood flow, as blood is shunted through the diseased dependent lung.

Drug-Induced Deterioration

Hypoxemia may result from worsening of ventilation–perfusion relationships secondary to bronchodilators or vasodilators (e.g., nitroglycerin or nitroprusside). Administration of intravenous lipid compounds can also produce hypoxemia.[33] Aminoglycoside antibiotics can provoke or aggravate neuromuscular blockade and produce respiratory embarrassment.[86] High levels of theophylline may produce agitation and/or seizures.

Abdominal Distension

Abdominal distension can cause elevation of the diaphragm, basilar atelectasis, and deterioration in ventilation–perfusion relationships. Abdominal distension may result from gastric distension, ascites, peritoneal dialysis, or bowel perforation. Gastric distension may result from a prolonged or difficult attempt at intubation; elevation of mouth pressure above the lower esophageal sphincter pressure during the delivery of manual ventilation; or tracheal pressure exceeding the cuff pressure and lower esophageal sphincter pressure and the mouth remaining closed during mechanical ventilation.[87,88] Massive distension, "meteorism," can produce gastric rupture. Insertion of a small-bore nasogastric tube helps prevent or alleviate this complication.

Massive colonic distension without small intestinal dilation or distal obstruction (Ogilvie syndrome) has been described in patients receiving mechanical ventilation (Fig. 53-14).[89,90] The mechanism is not known, but exaggerated aerophagia may be an important factor. Perforation of an overdistended cecum is often the first evidence of this complication. Accordingly, abdominal radiographs should be obtained in patients with abdominal distension, and cecostomy should be considered when the cecal diameter exceeds 9 cm. Massive colonic distension with or without massive ascites can also complicate *Clostridium difficile* colitis.[91]

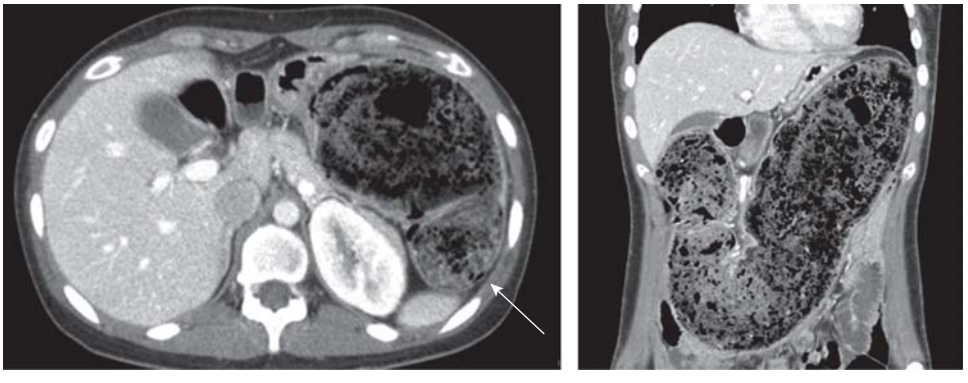

FIGURE 53-14 Ogilvie syndrome in a 31-year-old woman. Axial (*left panel*) and coronal (*right panel*) contrast-enhanced computed tomography images demonstrate a markedly distended transverse colon with large amount of fecal material. The *arrow* in the left panel points at the transitional zone (splenic flexure) that is devoid of any obstructive lesions. (Used, with permission, from Choi et al.[89])

Agitation

Ventilated patients develop agitation as a result of four major factors: pain, anxiety, delirium, and dyspnea. Innumerable factors can cause pain in a critically ill patient, ranging from simple factors such as poorly applied adhesive tape to the pain of a major surgical procedure. Feelings of anxiety, insecurity, fear, and panic are very common in ventilator-dependent patients,[92,93] including a fear of impending death. Untreated pain and anxiety can lead to insomnia and delirium. These problems are aggravated by the discomfort of dyspnea, which may result from injudicious ventilator settings (see *Patient–Ventilator Dyssynchrony* below). It is important to follow a systematic approach when evaluating a patient for the source of pain or anxiety, because simple problems, such as an overdistended bladder, may be overlooked while a search is conducted for a more esoteric source of distress.

VENTILATOR MALFUNCTION

Resolution of a patient's distress with the onset of bagging indicates that the problem lies within the ventilator or its external circuit (see Fig. 53-1). Malfunction of the ventilator may arise from tubing connected to a wrong outlet; a poor fit of connections; uncoupling of connections; defective material; obstruction of the circuit secondary to kinks, intraluminal fluids, or a malfunctioning valve; or malfunction of microprocessor controls. If malfunction is suspected, the ventilator should be replaced while each component is checked against the schematic circuit diagram. When a patient's delivered V_T is adequate and distress is relieved by manual ventilation, a fault in the setting of the fractional inspired oxygen concentration should be suspected. This problem can be verified by obtaining an independent direct measurement of inspired oxygen concentration.

External Ventilator Circuit

The ventilator circuit primarily consists of the tubing and connectors that form inspiratory and exhalation limbs; the humidifier; the exhalation valve assembly and flow measuring devices; adaptors placed within the circuit for monitoring or delivering medications; and inline filters.[13] Problems within this circuit that can cause patient distress include leaks, disconnects, accumulation of condensate, and inline nebulizers.

LEAKS OR DISCONNECTS

A leak may arise in parts of the circuit assembly that screw together. Leaks or uncoupling of connections will cause sounding of the low pressure and low V_T alarms. The Y-connection to the tracheal tube is the most common site of a disconnection. Other locations of disconnections and leaks include the humidifier system, an incompetent exhalation valve assembly, disconnection of the proximal line that connects the pressure tap at the Y-piece to the ventilator manometer, or small ruptures in the tubing.

In patients ventilated with pressure support, a leak at any location in the circuit, including at the cuff of the endotracheal tube, predisposes to a unique problem.[94] During pressure support, the ventilator strives to maintain a preset level of pressure throughout inspiration. A leak, however, will tend to cause the airway pressure to fall. To prevent the fall in airway pressure, the ventilator increases inspiratory flow. The algorithm employed by many ventilators for terminating the time of lung inflation is a fall in inspiratory flow to an absolute value of 5 L/min (or a fall in flow of 75% from the peak value). The increase in flow being delivered by the ventilator means that inspiratory flow never falls to the threshold required for termination of inflation. This phenomenon results in the unremitting application of positive pressure, which is relieved by correcting the leak.

CONDENSATE

Gas supplied to the inspiratory limb is typically warmed to 32°C (89.6°F) to 34°C (93.2°F) and fully saturated with water vapor. The gas cools as it passes through the inspiratory tubing, causing condensate to form. The condensate accumulates in a U-loop of the circuit. If enough condensate accumulates, movement of the water can cause the ventilator to trigger. During assist-control ventilation, excessive triggering can lead to barotrauma or hemodynamic compromise. During pressure-support or pressure-controlled ventilation, the resistance caused by the condensate may cause a decrease in achieved V_T for a set airway pressure.

INLINE NEBULIZERS

The insertion of a continuous-flow nebulizer between the patient and the pressure sensor within the ventilator can lead to hypoventilation during pressure support or intermittent mandatory ventilation (IMV).[95] When a patient's mean inspiratory flow rate is less than the flow of gas used to power the nebulizer (6 to 10 L/min), airway pressure will not fall sufficiently to trigger the ventilator. Moreover, the continuous flow from the nebulizer creates a bias flow, which the ventilator interprets as forming part of the patient's minute ventilation. Consequently, the low minute volume alarm will not sound.

Patient–Ventilator Dyssynchrony

Patient–ventilator dyssynchrony can lead to considerable patient distress, and it also impedes the effectiveness of the ventilator in decreasing respiratory work. For the most effective unloading of the inspiratory muscles, the ventilator should cycle in synchrony with the patient's central respiratory rhythm. For perfect synchronization, the period

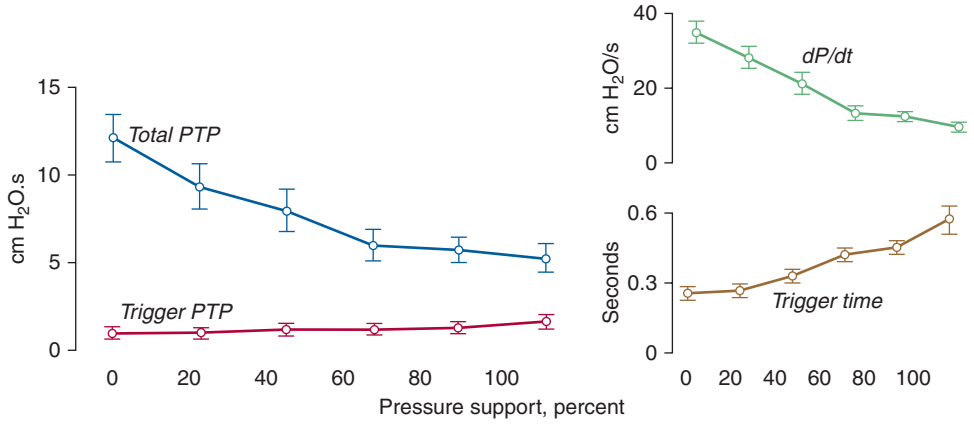

FIGURE 53-15 Graded increases in pressure support produced a decrease in total pressure-time product (*PTP*) per breath (*blue symbols*), although PTP during the trigger phase (*red symbols*) did not change (*left panel*). The constancy of PTP during triggering probably resulted from different factors becoming operational at different levels of assistance (*right panel*). At low levels of pressure support, respiratory motor output (dP/dt *green symbols*) and intrinsic positive end-expiratory pressure (PEEPi) were high but triggering time was short (*brown symbols*), resulting in a large change in pleural pressure over a brief interval. At high levels of pressure support, dP/dt and PEEPi were low but triggering time was long, resulting in a smaller change in pleural pressure over a longer time. (Based on data from Leung et al.[91])

of mechanical inflation must match the period of neural inspiratory time (the duration of inspiratory effort), and the period of mechanical inactivity must match the neural expiratory time.[96,97] The interplay between the ventilator and the respiratory neuromuscular apparatus is complex, and problems can arise at several points in the respiratory cycle: the onset of ventilator triggering, the remainder of inspiration after triggering, the switch from inspiration to expiration, and the end of expiration.[42]

TRIGGERING OF THE VENTILATOR

Patients reach the set sensitivity by activating their inspiratory muscles. For a given set sensitivity, the delay between onset of patient inspiratory effort and onset of ventilator assistance is a function of a patient's respiratory motor output. When a patient's respiratory drive is low, assistance may not begin until well into the patient's inspiratory time, thereby causing the ventilator to cycle almost completely out of phase with the patient's respiratory cycle. When the threshold to open the demand valve is reached and the ventilator starts to provide positive-pressure assistance, the inspiratory neurons do not simply switch off, and a patient may expend considerable inspiratory effort throughout the machine-cycled inflation.[98] The level of patient effort during this post-trigger phase is closely related to a patient's respiratory motor output at the point of triggering.[99] As such, measures that decrease respiratory drive may enhance respiratory muscle rest during mechanical ventilation.

If respiratory motor output at the point of triggering is important, one might expect that effort during the time of triggering would determine patient effort during the remainder of inspiration.[100] To investigate this issue, Leung et al[99] applied graded levels of pressure support in eleven critically ill patients. They achieved a fourfold reduction in overall patient effort. Yet patient effort during the time of triggering did not change. The constancy of effort during the trigger phase was probably secondary to different factors becoming operational as the level of ventilator assistance was varied (Fig. 53-15). Thus, increases in the level of ventilator assistance do not substantially decrease patient effort during the time of triggering.

INEFFECTIVE TRIGGERING

At high levels of mechanical assistance, up to one-third of a patient's inspiratory efforts may fail to trigger the machine (see Fig. 53-12).[99,101,102] The number of ineffective triggering attempts increases in direct proportion to the level of ventilator assistance.[99] Surprisingly, unsuccessful triggering is not the result of poor inspiratory effort. In a study of factors contributing to ineffective triggering, a decrease in the magnitude of inspiratory effort at a given level of assistance was not the cause; indeed, effort was 38% higher during nontriggering attempts than during the triggering phase of attempts that successfully opened the ventilator valve.[99] Significant differences, however, were noted in the characteristics of the breaths before the triggering and nontriggering attempts. Breaths before nontriggering attempts had a higher V_T than did the breaths before triggering attempts, 486 ± 19 and 444 ± 16 mL, respectively, and a shorter expiratory time, 1.02 ± 0.04 and 1.24 ± 0.03 seconds, respectively. An abbreviated expiratory time does not allow the lung to return to its relaxation volume, leading to an increase in elastic recoil pressure. Indeed, PEEPi was higher at the onset of nontriggering attempts than at the onset of triggering attempts: 4.22 ± 0.26 versus 3.25 ± 0.23 cm H_2O. Thus, nontriggering results from premature inspiratory efforts that are not sufficient to overcome the increased elastic recoil associated with dynamic hyperinflation.[99]

When triggering fails as a result of dynamic hyperinflation, the nontriggering on that breath allows the lungs to more completely empty in preparation for the next breath. Occasionally, two or three failed triggering attempts take place before triggering becomes successful. Because there is no lung inflation during a failed triggering attempt, mechanical exhalation continues for a longer time and end-expiratory volume continues to fall until triggering becomes successful. This pattern may occur repeatedly such that it resembles the Wenckebach pattern of atrioventricular block on an ECG.[103]

In addition to an increase in elastic recoil pressure,[99] an elevated PEEPi can also result from an increase in expiratory muscle activity. Parthasarathy et al[97] investigated the relative contributions of these two factors to ineffective triggering in healthy subjects receiving pressure support and in whom they induced airflow limitation with a Starling resistor. Nontriggering was linked to the fraction of PEEPi caused by elastic recoil but not to the fraction caused by expiratory effort. This observation suggests that external PEEP might be clinically useful in reducing ineffective triggering.

Although the magnitude of expiratory effort does not appear to influence the success of triggering attempts, the time that expiratory efforts commence in relation to the cycling of the ventilator is an important factor. Parthasarathy et al[97] quantified the relationship between the onset of expiratory muscle activity, measured with a wire electrode in the subject's transversus abdominis, and the termination of mechanical inflation by the ventilator. At pressure support of 20 cm H_2O, mechanical inflation was found to continue for a longer time into neural expiration in the breaths preceding nontriggering attempts. Continuation of mechanical inflation into neural expiration counters expiratory flow, and also decreases the time available for unopposed exhalation. Consequently, elastic recoil increases. In turn, a greater inspiratory effort will be needed to achieve effective triggering. In this way, the time that a patient commences an expiratory effort (in relation to cycling-off of mechanical inflation) partly determines the success of the ensuing inspiratory effort in triggering the ventilator.

DOUBLE TRIGGERING

Some patients exhibit two mechanical inflations within a single neural inspiration, a phenomenon known as *double triggering* (Fig. 53-16). With assist-control ventilation, double triggering is likely when the set mechanical inspiratory time is substantially less than a patient's neural inspiratory time. In this situation, mechanical inflation terminates while the patient is still making an inspiratory effort. After a brief period, the ventilator may trigger again, resulting in a second inflation within the same neural inspiration and, thus, greater alveolar distension than with the delivery of a single tidal volume.[103]

With pressure-support ventilation, double triggering is likely when the time constant is short (low resistance, high elastance) and patient neural inspiratory time is relatively long (a slow, spontaneous respiratory rate).[104] Following the loss of ventilator pressure after a first triggering attempt, volume decreases because the pressure exerted by the inspiratory muscles (Pmus) alone is not sufficient to sustain elastic recoil. During this phase, the persistence of neural inhalation will cause a progressive increase in Pmus, while elastic recoil continues to decrease. If the patient's neural inspiratory time is sufficiently long, a point is reached where Pmus will exceed elastic recoil and flow will become inspiratory and double triggering will occur.[105]

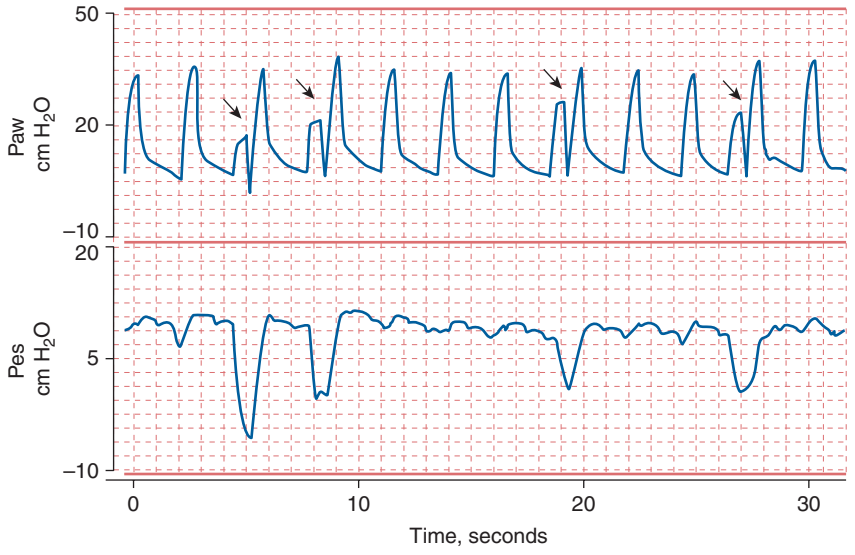

FIGURE 53-16 Four incidents of double triggering, each indicated by an *arrowhead*. Airway pressure (*Paw*) and esophageal pressure (*Pes*) in a patient with COPD and pneumonia who was receiving assist-control ventilation at the following settings: tidal volume 600 mL, inspiratory flow 60 L/min, trigger sensitivity −2 cm H_2O, and positive end-expiratory pressure 5 cm H_2O. The duration of neural inhalation of the double-triggered breaths, roughly equivalent to the width of the associated swings in esophageal pressure, was substantially longer than the neural inhalation of the normally triggered breaths.

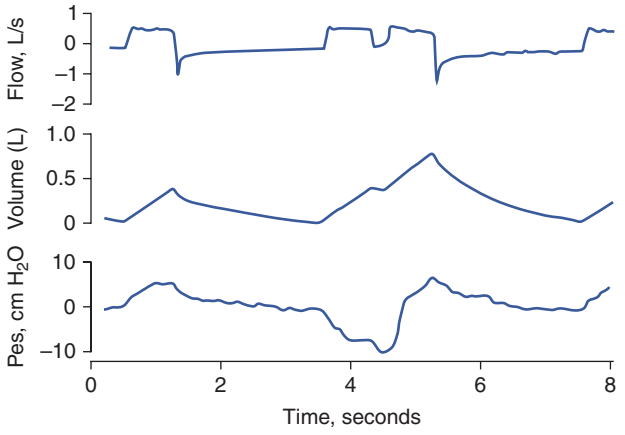

FIGURE 53-17 Volume stacking caused by double triggering. Flow (*top panel*), volume (*middle panel*), and esophageal pressure (*Pes*; *lower panel*) in a patient with COPD receiving assist-control ventilation. During first breath, esophageal pressure remains positive indicating that the patient did not trigger the inflation. During the second breath, esophageal pressure becomes negative indicating active inspiratory effort, which lasts more than 1 second; the duration of mechanical inflation is 0.6 second. The longer duration of neural inspiration as compared with mechanical inflation causes the ventilator to deliver a second breath before there is time for exhalation. As a result, end-inspiratory lung volume increases (breath stacking) with a consequent increase in elastic recoil. The increase in elastic recoil is responsible for the higher peak expiratory flow on the second breath as compared with the first breath.

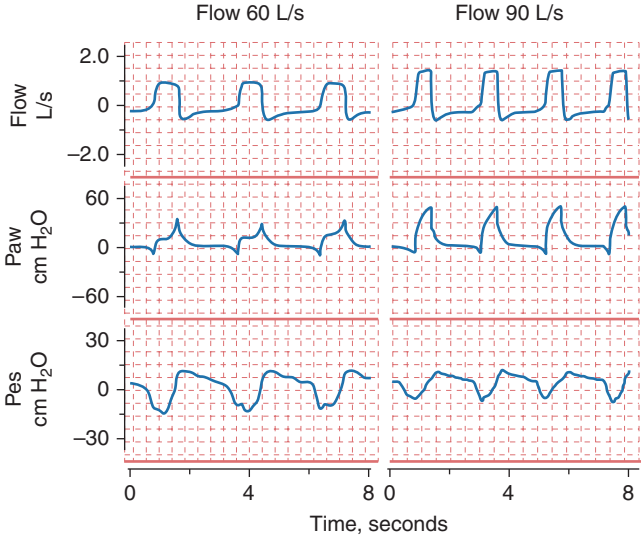

FIGURE 53-18 Influence of ventilator flow setting on patient effort. Flow (inspiration directed upward), airway pressure (*Paw*), and esophageal pressure (*Pes*) in a patient with respiratory failure who is receiving assist-control ventilation; inspiratory flow is set at 60 L/min in the *left panel* and at 90 L/min in the *right panel*. At an inspiratory flow of 60 L/min (*left panel*), the pronounced negative deflection in airway pressure (patient effort to trigger the ventilator) together with subsequent extensive scalloping signifies that the inspiratory flow delivered by the ventilator is insufficient to meet the high demand. At an inspiratory flow of 90 L/min (*right panel*), the small negative deflection in airway pressure together with the subsequent smooth convex contour signifies that the delivered flow satisfies the patient's respiratory drive. Accordingly, the flow of 90 L/min achieved greater unloading of the respiratory muscles, as signaled by the shorter duration of inspiratory effort and the smaller swings in esophageal pressure.

Randomized clinical trials have revealed that use of a high tidal volume (12 mL/kg) is associated with an increased mortality in patients with the acute respiratory distress syndrome.[106] Consequently, it has become standard practice to lower the delivered tidal volume in order to minimize alveolar overdistension; for example, to keep the inspiratory pressure during a pause at the end of inspiration (plateau pressure) to 32 cm H_2O or lower.[106] A low tidal volume is typically accompanied by a short mechanical inspiratory time and thus these patients are especially susceptible to double triggering. Accordingly, conscious attempts to lower tidal volume can paradoxically result in greater alveolar distension than occurs with conventional tidal volume settings (Fig. 53-17). An additional (and often unrecognized) factor that may produce alveolar distension is the tachypnea-associated increase in intrinsic PEEP that accompanies lowering of tidal volume.[107]

SETTING OF INSPIRATORY FLOW

When a patient is first connected to a ventilator, inspiratory flow is set at some default value, such as 60 L/min. Many critically ill patients, however, have an elevated respiratory motor output and the initial flow setting may be insufficient to meet flow demands. As a result, patients will struggle against their own respiratory impedance and that of the ventilator (Fig. 53-18). Consequently, the work of breathing increases. Clinicians sometimes increase flow so as to shorten the inspiratory time and increase the expiratory time. But an increase in flow causes immediate and persistent tachypnea; as a result, expiratory time may be shortened.[108] In healthy subjects, Laghi et al[109] found that increases in inspiratory flow from 30 L/min to 60 and 90 L/min caused increases in the respiratory rate of 20% and 41%, respectively.

A main reason that clinicians increase inspiratory flow is to decrease inspiratory time, in the hope of allowing more time for expiration and thus decrease PEEPi, especially in patients with COPD. Because increased flow usually leads to an increase in rate, the expected shortening of expiratory time might actually increase PEEPi. Laghi et al[110] studied this phenomenon in ten patients with COPD (Fig. 53-19). As with healthy subjects, an increase in flow from 30 to 90 L/min caused the respiratory rate to increase from 16.1 ± 1.0 to 20.8 ± 1.5 breaths/min. Despite the increase in rate, PEEPi fell from 7.0 ± 1.3 to 6.4 ± 1.1 cm H_2O. The decrease in PEEPi arose because of an increase in expiratory time, 2.1 ± 0.2 to 2.3 ± 0.2 seconds, which allowed more time for lung deflation. Why did expiratory time increase? An increase in inspiratory flow is usually achieved by shortening mechanical inspiratory time. The shortened inspiratory time combined with time-constant in homogeneity of COPD will cause overinflation of some lung units to persist into neural

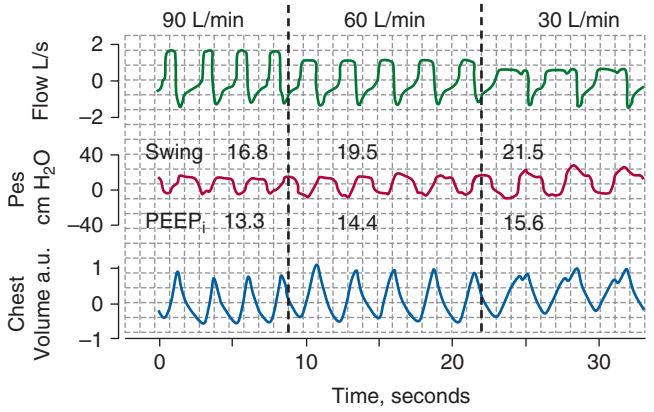

FIGURE 53-19 Continuous recordings of flow, esophageal pressure (*Pes*), and the sum of rib cage and abdominal motion in a patient with COPD receiving assist-control ventilation at a constant tidal volume. As flow increased from 30 to 60 and 90 L/min (from right to left; i.e., the opposite of the usual presentation), frequency increased (from 18 to 23 and 26 breaths/min, respectively), PEEPi decreased (from 15.6 to 14.4 and 13.3 cm H_2O, respectively), and end-expiratory lung volume also fell. Increases in flow from 30 L/min to 60 and 90 L/min also led to decreases in the swings in Pes from 21.5 to 19.5 and 16.8 cm H_2O, respectively. (Used, with permission, from Laghi et al.[110])

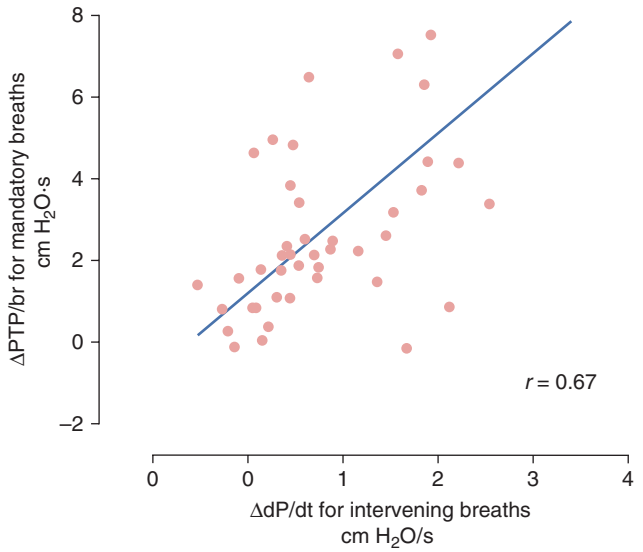

FIGURE 53-20 The change in pressure-time product per breath (*PTP/br*) during mandatory breaths (of IMV) consequent to the addition of pressure support of 10 cm H_2O to a given level of IMV was related to the change in respiratory motor output (dP/dt) effected by pressure support during the intervening breaths ($r = 0.67$; $p < 0.0001$). The more that pressure support decreased respiratory motor output during the intervening breaths, the greater was the reduction in patient work during the mandatory ventilator breaths delivered during IMV. (Used, with permission, from Leung et al.[99])

expiration. Continued inflation during neural expiration causes stimulation of the vagus nerve, which prolongs expiratory time.[111,112]

Mode-Specific Effects of Inspiratory Unloading

Pressure support and IMV are sometimes combined in a given patient. In an international survey of mechanical ventilation,[113] this combination tied with assist-control ventilation as the most commonly used mode of ventilation in North America (34% for each). The rationale for combining the two modes is unclear. Presumably, clinicians use pressure support to overcome the work imposed by the endotracheal tube and demand valve during the non-mandatory breaths.

Examining the response of the respiratory centers to this combination of modes provides useful insight into patient–ventilator interaction. A decrease in the number of mandatory breaths produces a decrease in the average V_T,[99] with inevitable increase in the ratio of dead space to V_T. To avoid a decrease in alveolar ventilation, the patients increased respiratory motor output, inspiratory effort, and rate. Adding pressure support of 10 cm H_2O caused a decrease in effort at any given IMV rate. The decrease in effort during the mandatory ventilator breaths was related to the decrease in respiratory motor output during the intervening breaths ($r = 0.67$) (Fig. 53-20).[99] In other words, the reduction in motor output during the intervening breaths achieved by adding pressure support was carried over to the mandatory breaths, facilitating greater unloading. Combining IMV and pressure support provides a sometimes useful means of achieving a high level of assistance; the combination has a clinical advantage when it is difficult to achieve a high inspiratory flow in the assist-control mode, as with the Siemens 900C ventilator (Siemens Corporation, New York, NY), although few of these machines are likely to be in current use.

Inspiration–Expiration Switching

In studies of interactions between patient effort and mechanical ventilation, remarkably little attention has been paid to the switch between inspiration and expiration. The most common mode of ventilation is some form of volume assistance,[113] such as assist control or IMV. "Cycling-off" of mechanical inflation, however, may be based only indirectly on volume. Instead, inspiratory flow is commonly preset and the ventilator adjusts inspiratory time to achieve a given V_T. This system is more precisely termed *time-cycled ventilation*. Inflation time is constant with a time-cycled machine, but patients invariably display considerable breath-to-breath variability in inspiratory time.[114] Accordingly, a patient's neural inspiratory time may be shorter or longer than the inflation time of the machine. If the machine delivers the set V_T before the end of a patient's neural inspiratory time, ventilator assistance will cease while the patient continues to make an inspiratory effort—with double triggering (two ventilator breaths for a single effort) a likely consequence.[104]

During assist-control ventilation, when a patient's neural inspiratory time is short, ventilator inflation may continue into neural expiration and thus decrease the time available

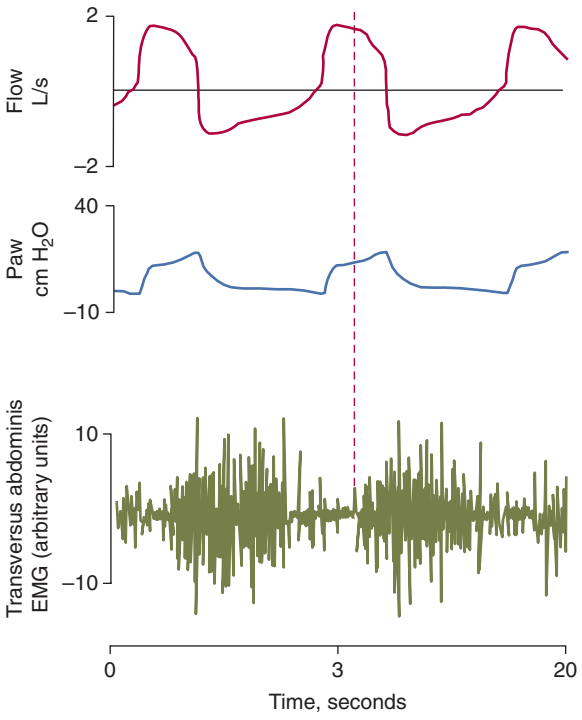

FIGURE 53-21 Recordings of flow, airway pressure (*Paw*), and transversus abdominis electromyography (*EMG*) in a critically ill patient with COPD receiving pressure support of 20 cm H_2O. The onset of expiratory muscle activity (*vertical dotted line*) occurred when mechanical inflation was only partly completed. (Used, with permission, from Parthasarathy et al.[97])

for lung emptying. The sense of being unable to empty the lungs may cause patients to activate the expiratory muscles with the result that the patient appears to fight or buck the ventilator (Fig. 53-21). The decrease in time for emptying also increases the likelihood for dynamic hyperinflation and thus inspiratory efforts that fail to trigger the ventilator.

With pressure support, the algorithm used for "cycling-off" of mechanical inflation varies among brands (see Chapter 8). On most ventilators, the termination of inspiratory assistance during pressure support is set at a default threshold, such as 25% of the peak inspiratory flow or inspiratory flow of 5 L/min. That is, when inspiratory flow falls to 25% of the peak value or below 5 L/min, inspiratory pressurization switches off. Such algorithms can be problematic in patients with COPD because increases in resistance and compliance produce a slow time-constant of the respiratory system. The longer time needed for flow to fall to the threshold value can cause mechanical inflation to persist into neural expiration. In twelve patients with COPD receiving pressure support of 20 cm H_2O, five recruited their expiratory muscles while the machine was still inflating the thorax.[115] The patients who recruited their expiratory muscles during mechanical inflation had an average time constant of 0.54 seconds, compared with an average of 0.38 seconds in the patients who did not exhibit expiratory muscle activity. The persistence of mechanical inflation into neural expiration is very uncomfortable, as is well recognized with use of inverse-ratio ventilation. Algorithms that achieve better coordination between the end of mechanical inflation and the onset of a patient's expiration may lessen this form of patient–ventilator asynchrony.[116,117]

Sleep–Wake State

The transition between sleep and wakefulness can lead to respiratory distress in the ventilated patient. More surprisingly, the transition between wakefulness and sleep can also cause distress. Specifically, the selection of ventilator mode and settings can provoke sleep disruption. Ventilated patients experience considerable sleep disruption, with as many as seventy-nine arousals and awakenings per hour.[118,119] Sleep disruption can adversely affect patient outcome.[120]

In eleven critically ill patients, Parthasarathy and Tobin[121] studied the interaction between ventilator mode and sleep. Sleep fragmentation was greater during pressure support than during assist-control ventilation: 79 versus 54 arousals and awakenings per hour (see Fig. 53-9). Six of the eleven patients developed central apneas during pressure support, but not during assist-control ventilation. V_T was 8 mL/kg during assist-control; pressure support was titrated to achieve the same V_T. The level of pressure support was 16.8 ± 1.5 cm H_2O in patients with apneas and 19.6 ± 2.6 cm H_2O in patients without apneas; thus, apneas did not result simply from a higher level of pressure support.

Sleep fragmentation, measured as the sum of arousals and awakenings, was greater during pressure support than during assist-control: 79 ± 7 versus 54 ± 7 events per hour. Disturbed sleep during pressure support was related to the development of central apneas ($r = 0.57$), which, in turn, was significantly related to the difference between P_{CO_2} during resting breathing and the patient's apnea threshold (end-tidal CO_2[$\Delta P_{ET}CO_2$]) ($r = -0.83$) (Fig. 53-22). $\Delta P_{ET}CO_2$ was the most important determinant for the development of apneas: As $\Delta P_{ET}CO_2$ grew wider, the number of central apneas increased. The addition of 100 mL of dead space to the ventilator circuit in the six patients who developed apneas produced a 4.3 mm Hg increase in end-tidal CO_2, decreased the frequency of central apneas, from fifty-three to four apneas per hour, and the frequency of arousals and awakenings, from eighty-three to fourty-four events per hour. This study shows that while critically ill patients have a background level of sleep disturbance, secondary to factors such as pain, medications, staff interruptions, noise, and light, the mode of mechanical ventilation can further aggravate sleep disruption.

The observation that ventilator mode can aggravate sleep disruption was confirmed by Bosma et al.[122] In thirteen patients undergoing polysomnography, these investigators adjusted the levels of pressure support ventilation and proportional-assist ventilation to achieve a similar degree of inspiratory muscle unloading. The number of arousals and awakenings were significantly greater with pressure support

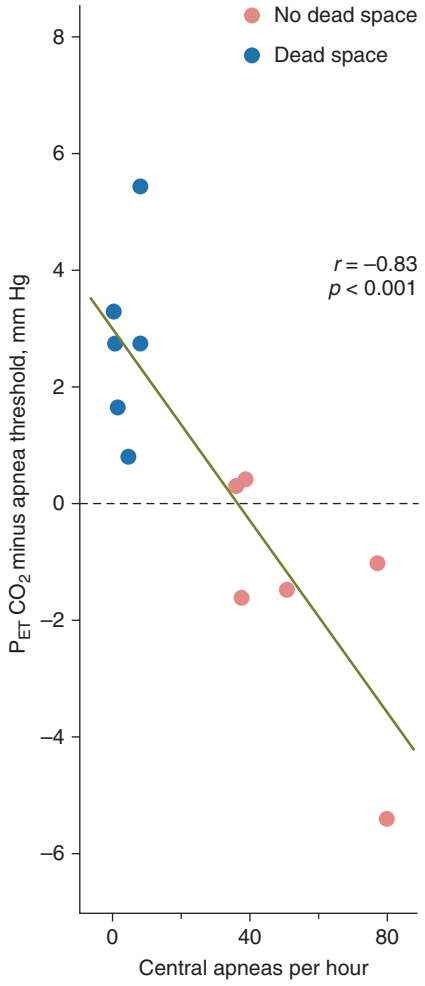

FIGURE 53-22 The difference between the average end-tidal CO_2 ($P_{ET}CO_2$) and the apnea threshold plotted against the number of central apneas per hour of pressure support alone (*red symbols*) and pressure support with added dead space (*blue symbols*) in six patients. The average end-tidal CO_2 was measured during both sleep and wakefulness. The mean number of central apneas per hour was strongly correlated with the end-tidal CO_2 during a mixture of both sleep and wakefulness (including the transitions between sleep and wakefulness) ($r = -0.83$, $p < 0.001$). (Used, with permission, from Parthasarathy et al.[121])

than with proportional-assist ventilation. Moreover, the number of patient–ventilator asynchronies per hour correlated significantly with the number of arousals per hour ($r^2 = 0.71$).

Cabello et al[123] compared sleep quality while patients were randomized between assist-control ventilation, pressure support set by the patient's attending physician, and pressure support continuously adjusted by a closed-loop knowledge-based system. In contrast to the report by Parthasarathy and Tobin,[121] sleep architecture, sleep quantity, and sleep fragmentation were equivalent with the three ventilator modes.

The different results in the two studies can be explained by the method of selecting tidal volume in the study of Cabello et al.[123] A tidal volume of 8 mL/kg was employed during assist-control ventilation, whereas a tidal volume between 6 and 8 mL/kg was targeted during pressure support.[123] The median (twenty-fifth to seventy-fifth percentile) tidal volumes were 500 mL (380 to 500 mL) during assist-control ventilation, 450 mL (357 to 521 mL) during clinician-adjusted pressure support, and 390 mL (330 to 492 mL) when a closed-loop knowledge-based system was used to continuously adjust pressure support. The findings of these three studies of mechanical ventilation during sleep in critically ill patients indicate that pressure support, when carefully adjusted to avoid hyperventilation, does not increase the amount of sleep fragmentation over that experienced with assist-control ventilation. If, however, pressure support is set in the manner of everyday clinical practice, it is likely to lead to sleep fragmentation.[121,122]

The alterations in breathing pattern and gas exchange induced by sleep have important implications for the selection of ventilator settings. During pressure support, sleep induced a 23% increase in inspiratory time and a 126% increase in expiratory time, as compared with wakefulness.[121] Sleep caused the respiratory rate to decrease by 33% during pressure support and by 15% during assist-control ventilation (Fig. 53-23). The level of pressure support is commonly titrated to respiratory rate, which provides a reasonable guide to patient effort.[115,124] Pressure support is commonly titrated during the daytime without the clinician being sure whether the patient is asleep or awake. If the patient is asleep

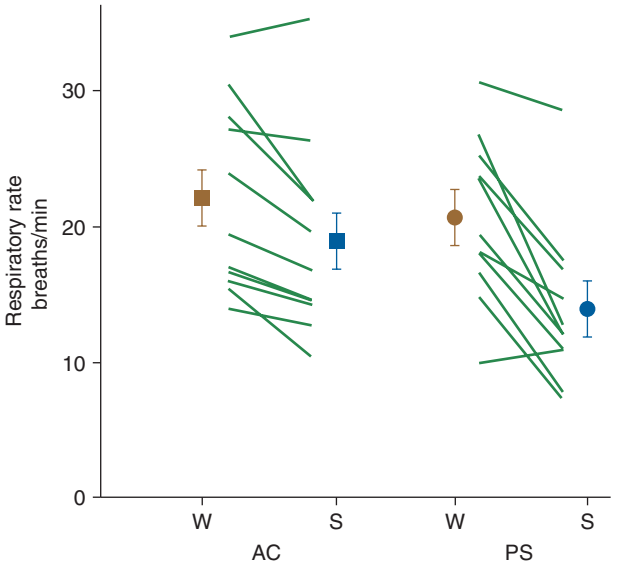

FIGURE 53-23 Respiratory rate during assist-control ventilation (*AC*) and pressure support (*PS*) in eleven critically ill patients. For each mode, the lines connect the mean value for each patient during wakefulness (*W, left*) and sleep (*S, right*). Compared with wakefulness, group mean respiratory rate was lower during sleep (*blue symbols*) than during wakefulness (*red symbols*). The difference between sleep and wakefulness was greater for pressure support than for assist-control ventilation. (Modified, with permission, from Parthasarathy and Tobin.[121])

at the time of the adjustment, a point at which respiratory rate will be relatively low, then, on awakening, the increase in a patient's rate may cause a considerable increase in effort.

PHARMACOTHERAPY

If a specific cause of acute distress cannot be detected and corrected (see Table 53-1) and reassurance provides no relief, pharmacologic agents are commonly employed. The agents most often used are derived from the following primary classes: opiate analgesics, benzodiazepines, selective α_2 agonist,[125] and neuromuscular blocking agents. Chapter 50 provides a complete discussion of these agents.

In managing the patient who is fighting the ventilator, neuromuscular blocking agents have several disadvantages: They mask a patient's complaints and physical findings; unrecognized disconnection of the ventilator circuit can produce apnea with catastrophic hypoxemia; elimination of cough predisposes to the development of atelectasis; and prolonged paralysis or weakness may persist after their use.

SUMMARY

Sudden distress in a ventilator-supported patient is a medical emergency. The first rule is to ensure adequate ventilation. The patient should be disconnected from the ventilator and manually ventilated with 100% oxygen. While this is being performed, a systematic effort should be made to try to determine the cause of distress and correct it. If the distress is the result of poor coordination of a patient's respiratory efforts with the rhythm of the ventilator, this can usually be resolved by careful adjustment of the ventilator settings and the administration of analgesic or sedative agents, or both.

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54

PSYCHOLOGICAL PROBLEMS IN THE VENTILATED PATIENT

Yoanna Skrobik

Psychological and psychiatric disturbances occur frequently in mechanically ventilated patients, and cause patients, their loved ones, and their caregivers considerable distress. This chapter familiarizes the reader with commonly observed psychological and psychiatric symptoms in ventilated critically ill patients; briefly discusses the challenge of making a psychiatric diagnosis in the context of the ventilated patient; and describes what is known of the three disorders most commonly described in this patient population: delirium, depression, and posttraumatic stress disorder.

Traditional psychological and psychiatric assessments in the adult patient rely on the patient's ability to engage in conversation. Baseline psychological health and personality, a patient's relationship with his or her acute or chronic illness, a patient's emotional response to it, and the clinical context in which the patient is placed are typically considered in this evaluation. Assessment of the psychological and psychiatric state of a mechanically ventilated patient is hindered by the presence of an endotracheal tube, which makes verbal communication impossible. A tracheotomy with a talking valve, and a face mask, also limits speech. Beyond problems of verbal communication, the sudden and dramatic onset of a ventilated patient's illness, the use of pharmacologic sedation, the layout of an intensive care unit (ICU), and a critical care physician's unfamiliarity with psychological assessments have hampered descriptions of psychiatric and psychological issues.

Psychiatric diagnoses are made on the basis of clinical criteria. These criteria were, for many decades, highly variable depending on a school of thought and geographical provenance. Lobotomies, incremental electroshock therapy to re-create neuropsychiatric normalcy, and insulin-coma treatments exposed psychiatric professionals to scientific and public criticism. Over the last 40 years, psychiatric diagnoses have been structured more rigorously by experienced psychiatrists based on symptom and disease classifications through the use of systems such as the *International Classification of Diseases* (ICD) from the World Health Organization, and the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) from the American Psychiatric Association. The tenth revision of the *International Statistical Classification of Diseases and Related Health Problems* (ICD-10) was published in 1991; the fourth revision of the *Diagnostic and Statistical Manual of Mental Disorders,* DSM-IV-TR, was published in 2000. The ICD-11 is expected in 2011 and the DSM-V update is anticipated in 2013.

The ICD-10 and the DSM-IV-TR rely on diagnostic criteria compiled by expert psychiatrists and, in the case of the DSM-IV, on the basis of described and published patient symptoms. Two problems become apparent when applying these diagnostic criteria to critically ill patients. The first is the challenge of applying diagnostic criteria to a mechanically ventilated patient if the symptom constellations have been gathered in a different—usually ambulatory—population. Apathy, for instance, a feature of depression, may be expected in a septic ventilated patient receiving propofol, making its value as a diagnostic criterion of depression in this context uncertain. The second is that these DSM or ICD criteria have not been investigated in terms of validity in ventilated patients, whether acutely or chronically ill, nor are the criteria correlated with outcomes in such patients.

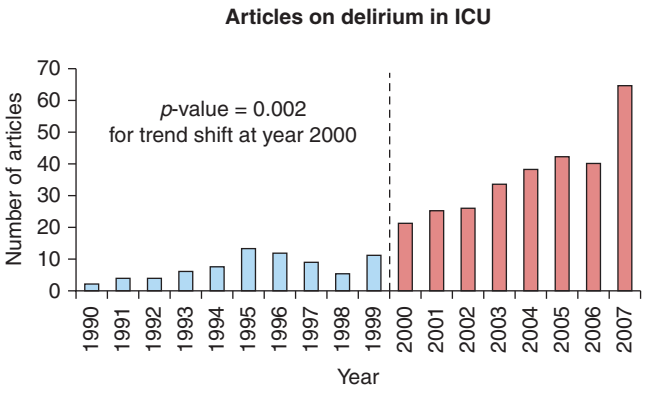

FIGURE 54-1 The number of publications on delirium in the critical care setting (in mechanically ventilated and nonmechanically ventilated patients) over 17 years. (Modified, with permission, from Morandi A, Pandharipande P, Trabucchi M, et al. Understanding international differences in terminology for delirium and other types of acute brain dysfunction in critically ill patients. *Intensive Care Med.* 2008;34:1907–1915.)

Psychiatric or psychological disturbances in the ventilated critically ill patients have been given many names, such as ICU psychosis, septic encephalopathy, and apathy. Semantic descriptions for disorders such as delirium[1] vary by geographic region. Over the last decade, publications on psychiatric topics such as delirium in ventilated patients have increased significantly (Fig. 54-1). Two factors may have influenced this change. Two intensivist-led publications in 2001[2,3] sensitized clinicians to the notion of screening ventilated patients for delirium through the use of simple screening tool, applicable at the bedside. More delirium-related publications followed, with subsequent interest in other psychiatric and psychological disorders, such as depression and posttraumatic stress disorder. Almost simultaneously, researchers with an interest in ICU outcomes in adult respiratory distress syndrome (ARDS), whose focus was initially on respiratory physiology, realized the main impediments to recovery for these patients were myopathy and psychological distress.[4,5] Three psychiatric syndromes—delirium, depression, and posttraumatic stress disorder—have since been identified with increasing frequency[6] in ventilated critically ill patients and ICU survivors.[7] The associations between these diagnoses and poor outcomes, including length of stay, quality of life, and cognitive impairment, have led to a cry for pharmacologic intervention for delirium by interventionists, and for further longitudinal studies[8,9] by those interested in the sequelae of what had traditionally believed to be rapidly reversible (and almost irrelevant) disorders.

What is understood of these three psychiatric syndromes is limited by the dearth and relative novelty of literature on the topic.[10] Current knowledge should be considered in light of the methodological limitations in establishing a diagnosis as described above.

Most publications reviewed for this chapter are focused exclusively or largely on mechanically ventilated patients, a group that some authors argue is particularly susceptible to psychiatric complications, such as delirium.[11] Information from nonventilated patients is discussed if it is consistent with what has been published on ventilated patients, but only if it provides insight not available from the literature on mechanically ventilated patients per se. Reviewed studies are limited to critical care and stepdown units; studies in patients receiving home ventilation or chronic ventilation on a hospital ward or a specialized institution were not considered. The disproportion between the delirium literature in critical care and that describing other syndromes, which is more modest, explains the discrepancy in content herein.

DIAGNOSTIC AND CONTEXTUAL CHALLENGES

Unsurprisingly, publications on the subject of psychological and psychiatric disorders in ICU patients have been driven by the medical perspective of the psychiatric diagnosis. Most physicians attempt to classify psychological or psychiatric symptoms as diseases, with attributable biologic alterations and reproducible symptoms. Medical culture[12] drives a rigid medical approach, and a rationalization of "disease"; the narrow view of biologic alterations and their diagnostic criteria is the focus of what we publish and read. Dimensions such as illness (the patients' perception of the self) and sickness (the social dimension and impact of the diagnosis, particularly a psychiatric one) are seldom addressed. In settings outside critical care, caregivers understand that a patient's well-being depends on psychological integrity. Such well-being, and perhaps even the will to survive, are hindered if the patient is unable to recognize his or her own self during disease, or if that very self is compromised, a common occurrence in the foreign, disturbing, and overwhelmingly technological setting of the ICU. This wretchedness is complicated by a complete dependence on machines and personnel. What little autonomy a patient retains is seldom fostered or encouraged. The relationship with the caregiver, or a significant person in the patient's life, also contributes to healing, or to a more serene journey toward death. The social impact of a psychological or psychiatric disease may interfere with this patient–caregiver or patient–significant person relationship, and constitute a dimension of "sickness." Establishing a diagnosis of depression and delirium requires descriptors; the dimensions of illness and sickness, however, may be what cause the greatest distress. Patient recovery and postdischarge outcomes may be related to these dimensions of illness and sickness; however, our limited understanding of these facets as experienced by patients, their caregivers, and loved ones limits a global understanding of the psychological and psychiatric issues and precludes a holistic approach to care.

Furthermore, context is important in establishing whether endogenous or exogenous factors trigger psychiatric or psychological disturbances. Some psychiatric diagnoses can be made with clarity. For instance, mania in an ambulatory outpatient has in many cases a recognizable pattern, associated biochemical abnormalities, and a predictable response to

medication. Syndromes such as depression can come from within, or be considered a normal response (in grieving, for example). Other mood states such as anxiety range from normal to pathologic, and have not been defined in the critically ill. Several symptoms (sadness, paranoid delusions, or harrowing flashbacks) could, arguably, be considered contingent, temporary, and normal responses to painful, traumatic, or near-death experiences. Overlapping syndromes of delirium and depression have been described.[13,14] The administration of psychotropic drugs in high doses over prolonged periods of time adds an important confounder, as do personality traits and the amount of cognitive reserve. This issue of context makes the attribution of a psychiatric diagnosis to a set of symptoms particularly challenging in the critical care setting. Dialog is a key element in differentiating these factors as potential contributors, in establishing the diagnoses, and in proffering expression as a form of early therapeutic intervention. Verbal dialog is challenging in the context of mechanical ventilation. Weakness, which precludes movement, facial expression, or both, further challenges (or is perceived as challenging) the examiner and contributes to the real or perceived barriers to communication.

The three most commonly described psychiatric syndromes in ICU patients and survivors are delirium, depression, and posttraumatic stress disorder. Each is discussed in turn.

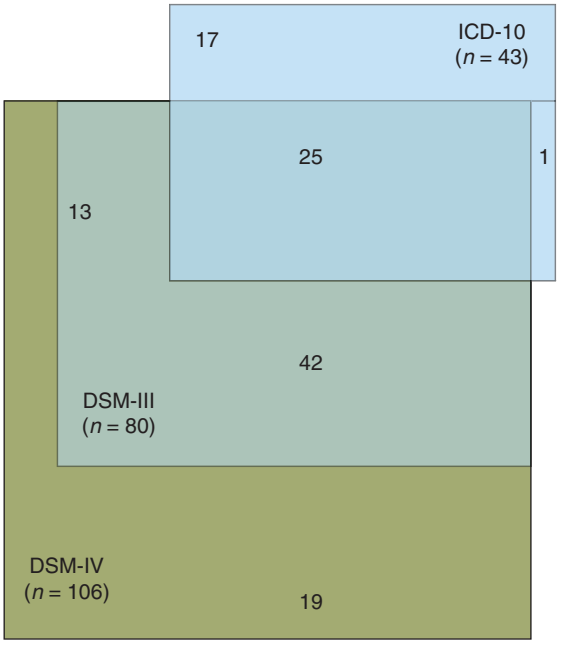

FIGURE 54-2 Comparison of different screening tools in the same population of 425 nonmechanically ventilated elderly medical or nursing home patients using DSM-IV criteria and earlier DSM criteria (DSM-III) as well as ICD-10 criteria. More ($n = 106$) patients were identified as having delirium with the DSM-IV than with any other set of diagnostic criteria. (Adapted, with permission, from Laurila JV, Pitkala KH, Strandberg TE, Tilvis RS. Impact of different diagnostic criteria on prognosis of delirium: a prospective study. *Dement Geriatr Cogn Disord*. 2004;18:240–244.)

DELIRIUM

The patient you spoke to and communicated with yesterday on ICU rounds is a little more difficult to rouse this morning. When you approach him, he initially looks surprised and frightened; as you introduce yourself and remind him of yesterday's conversation, he appears uncertain of who you are and of his surroundings. As you continue speaking, he looks away and appears to stare at something on the ceiling. The nurse reports that a few hours earlier he was grasping at what appeared to be imaginary objects in front of him. He did not sleep last night.

Delirium, with its traditional symptoms described here, frightens patients. The delusions and hallucinations they experience transiently and usually for the first time in their lives are upsetting; paranoid thoughts are common. When cognitive function normalizes in the fluctuating course that characterizes delirium, patients wonder if they are losing their minds and if they will ever return to the way they were before. Because 40% of patients present symptoms only between midnight and 8 AM, careful attention to the nurse's report of a patient's behavior is helpful in recognizing the problem.

Diagnosis

A diagnosis of delirium is based on the reference standard of symptoms described in nonventilated patients deemed clinically delirious, mostly among geriatric patients where the syndrome is prevalent. The DSM-IV criteria require a fluctuating disturbance in cognition and in consciousness in the context of an acute medical illness. Conversely the World Health Organization's ICD-10[15] includes different criteria for clinical and research use, both of which include a broad range of features that capture the phenomenologic complexity of the syndrome. Comparison of these two sets of criteria in a group of 425 nonventilated elderly medical or nursing home patients showed that applying the DSM-IV criteria identified more ($n = 106$) patients as having delirium than did the ICD-10 criteria, with twenty-five patients considered delirious by both sets of diagnostic criteria (Fig. 54-2).[16] Surprisingly, this study reported similar outcomes, in terms of mortality or length of stay, regardless of the criteria applied to diagnose delirium (Table 54-1).

Thorough descriptions of the natural history of delirium in ventilated patients are lacking, as is a good understanding of its basic scientific and biologic mechanisms. In 2001, two groups reported independently validated delirium screening scales for use in ventilated critically ill patients.[3,4] The first, the Intensive Care Delirium Screening Checklist (ICDSC), is an eight-point item scale, where four points or more correspond to a clinical diagnosis of delirium. The scale was validated against the clinical bedside opinion of a psychiatrist. The advantage of using this eight-item scale with a four-point cutoff is its ability to detect subsyndromal delirium in patients with scores of more than 0 but less

TABLE 54-1: OUTCOMES (MORTALITY OR LENGTH OF STAY) IN RELATIONSHIP TO THE CRITERIA (DSM IV, DSM III, AND ICD-10) USED TO DIAGNOSE DELIRIUM IN 425 NONMECHANICALLY VENTILATED ELDERLY MEDICAL OR NURSING HOME PATIENTS (OUTCOMES WERE SIMILAR)

Prognostic Variable	DSM-IV ($n = 106$)	DSM-III ($n = 80$)	ICD-10 ($n = 43$)	p-value[a]
Mortality/1 year, %	34.9	36.3	41.9	n.s.
Mortality/2 year, %	58.5	62.5	65.1	n.s.
Mean days in institutions/1 year[b]	220(150)	230(148)	211(157)	n.s.
New admissions to permanent institutional care/2 year, %	55.0[33/60]	60.0[24/40]	64.3[9/14]	n.s.
In permanent institutional care or deceased/2 year, %	90.6	93.8	97.7	n.s.

n.s. = Not significant. Figures in parentheses indicate standard deviations, those in brackets actual number institutionalized/total number from community care, *y* care.

[a]Proportions and their differences were tested by the χ^2 test, d.f. = 3.

[b]Means and their differences were tested by analysis of variance.

Source: Adapted, with permission, from Laurila JV, Pitkala KH, Strandberg TE, Tilvis RS. Impact of different diagnostic criteria on prognosis of delirium: a prospective study. *Dement Geriatr Cogn Disord.* 2004;18:240–244.

than 4 items. Subsyndromal delirium is considered clinically significant by psychiatrists[17,18] and, in ventilated and nonventilated ICU patients, predicts an intermediate risk of prolonged length of stay and mortality when compared with asymptomatic patients,[19] who did better, or delirious patients, whose prognosis was the worst. The second delirium scale was originally adapted as a simplification of the DSM-IV–based Confusion Assessment Method (CAM) scale, so as to make it applicable to ventilated patients; it was validated against the clinical opinion of a geriatrician. This modified scale, the Confusion Assessment Method in Intensive Care Units (CAM-ICU),[2] is binary. Other scales, such as the Delirium Detection Scale (DDS) and the Nursing Delirium Screening Scale (NuDESC), have also been assessed in critically ill patients; only the ICDSC and the CAM-ICU are presented here because of their broad application to and validation in ventilated patients, and because of their psychometric quality.

Clinicians are reported to underrecognize delirium.[20,21] This has led some critical care professional societies to promote routine critical care delirium screening.[22] Canadian governing bodies mandate it for hospital accreditation. Perusal of the literature on screening tools, however, shows that these validated screening tools yield a broad distribution of incidences of this condition. Studies describing the binary CAM-ICU in similar populations reveal delirium incidences that range from 10%[23] to over 80%. Sedation may confound the scale measurements.[24] In contrast, the range in reported delirium rates using the ICDSC is somewhat narrower: 32%[25] to 45%.[21] In addition to grading cognitive normalcy, subsyndromal delirium and delirium the ICDSC describes specific symptoms,[26] and with them, the prognosis conferred by each one. Whether these two tools screen for the same constellation of symptoms is unclear, given the conflicting results in the publications on the subject.[27,28] Because of the numerous methodological issues described above, comparisons of sensitivity and specificity of delirium screening scales to mechanically ventilated patients in and outside the ICU are difficult to address.

Awareness as to which patient is more likely to develop delirium in the ICU will identify patients most likely to benefit from preventive strategies and alert caregivers as to which patients will require more thorough evaluation for delirium symptoms. These risk factors for delirium cannot identify patients who will respond to therapeutic intervention. Different clinical features have been associated with a higher incidence of delirium.[29] The incremental likelihood of delirium symptoms increases with severity of illness and with excessive alcohol consumption.[29] Hypertensive patients are more likely to become delirious in the ICU,[25] as are patients with preexisting dementia and patients who are heavily sedated.[25,29] In contrast to patients admitted to a hospital ward, age is not consistently related to the likelihood of developing delirium among ventilated patients,[25,30] although there may be an association with age in mostly nonventilated patients older than 65 years when the CAM-ICU delirium detection tool is used.[31,32]

There are significant gaps in our knowledge regarding delirium in ventilated patients. Despite reports that mechanical ventilation confers a risk for delirium,[33] the question of whether the association is with mechanical ventilation per se or an independent feature linked to severity of illness or drugs administered has not been addressed in studies where known risk factors are taken into account. Cardiovascular patients, who are burdened with cognitive dysfunction after cardiac surgery and ICU discharge, remain understudied, as do neurologic patients, and trauma patients (including those with traumatic brain injury), perhaps because of the inherent difficulties in making an assessment as a result of confounding clinical features.

Prevention

Early physiotherapy and mobilization, when implemented to aid myopathy, significantly reduce delirium rates.[34,35] These results raise the question of whether nonpharmacologic interventions, which encourage patients to focus on their autonomy, may prevent or alleviate delirium. Sedatives and analgesics, when carefully titrated and administered

according to symptoms, are associated with lower rates of subsyndromal delirium and an increase in the probability of a patient being able to return home.[36] Whether the particular type of sedative agent makes any difference to the probability of delirium is not clear. Once delirium develops, however, continuous sedation with dexmedetomidine is associated with lower duration of delirium than continuous intravenous sedation with midazolam, a short-acting benzodiazepine,[37] in medical and surgical patients. It is not clear whether these results reflect an inherent problem with midazolam infusions or a therapeutic benefit of dexmedetomidine.[38] In cardiac surgery patients, the use of propofol as a sedative did not alter the risk of delirium as compared with dexmedetomidine.[39]

Treatment

Although administration of antipsychotics has been a mainstay in the pharmacologic management of delirium in critically ill patients,[40] there is no scientific basis for this practice or evidence of benefit of administering antipsychotic agents in delirious critically ill ventilated patients[41]: neither the duration of delirium nor its severity is reduced. A possible exception is the atypical antipsychotic, quetiapine,[42] which, in contrast to other pharmacologic agents,[8,41] produced a reduction in the duration of ICU delirium, albeit in a single pilot study.

Descriptions by observers, and stories[43] told by individual patients,[44] describe the anguish, fear, and harrowing nature of patient perceptions in a delirious state. Some narratives and recall studies describe the positive impact of reassuring or reality-orienting caregivers[45] within the critical care setting. The added contribution made by visiting family members and loved ones[29] are in keeping with the positive impact of nurse-facilitated family participation in the care of a delirious patient.[46]

Some investigators have made links between delirium in the ICU and long-term cognitive dysfunction.[47] These data should be considered with caution given the frequency of cognitive dysfunction in nondelirious patients,[48] given our difficulties in establishing the diagnosis of delirium, and given its many potential confounders, such as the risk of dementia in patients older than 65 years, which doubles every 5 years between the ages of 65 and 85 years.

DEPRESSION

On morning rounds, the patient whose ICU stay was marred by multiple septic complications of his intraabdominal surgery does not look interested in your informing him he is finally ready to be extubated. After the extubation and despite no longer receiving sedatives, he is lying in bed immobile, and answers questions monosyllabically. He tells the nurse he is not interested in sitting up in a chair or in spirometry with the physiotherapist. No amount of encouragement seems to make a difference. His wife tells you he is "not himself," and is concerned.

Is this patient depressed? Or is he reacting normally to a near-death experience during which his mood was affected by circulating inflammatory mediators and the sedatives he received? The patient's hypoactive reaction and mood alteration is not unusual, especially because he was septic. A diagnosis of depression cannot be excluded, and the patient's evolution should be monitored with careful attention to psychological symptoms. Depression is not reported in ventilated ICU patients; descriptions exist primarily in ICU survivors[49] and in patients who have been transferred from a critical care setting to a specialized center that focuses on weaning from prolonged mechanical ventilation.[50] To assess whether patients are depressed or at risk for depression, questionnaires, such as the Hospital Anxiety and Depression Scale (HADS),[51] have been used as substitutes or complements to clinical assessments.[52] Studies that describe clinical assessments, such as one-on-one interviews by an experienced caregiver (a psychologist or a psychiatrist) of ICU patients, weaning patients,[50] or survivors are rare. Depression in critically ill patients, whether mechanically ventilated or not, is associated with both the severity of illness on admission[53] and with the administration of benzodiazepines.[54] Observational studies are few, and potential confounders in making a diagnosis of depression are numerous.

Sickness behavior is a term coined to describe the behavioral changes that develop in ill individuals during the course of an infection. This sickness behavior,[55] described in sepsis, is associated with lethargy, sleepiness, inability to concentrate, and apathy. Whether these symptoms are a manifestation of underlying medical illness or related to depression per se is not clear.

Risk factors for developing depression in association with mechanical ventilation or ICU admission have not been well established; patients with different profiles may be at different risk and have a different prognosis. For instance, 28% of more than 66,000 veterans admitted to nonsurgical ICUs[56] had a history of an earlier psychiatric diagnosis, a feature associated with a greater likelihood of being subsequently diagnosed with depression or with posttraumatic stress disorder. Patients with diabetes who have experienced depression are more likely to end up in an ICU than are patients with diabetes who have no baseline psychiatric history.[57] ICU admission in patients with diabetes is independently associated with a higher probability of subsequent major depression.[58] These large descriptive studies included both ventilated and nonventilated patients. No validated assessment tools exist to screen for the presence or severity of depression in mechanically ventilated patients. In specialized critical care settings where psychologists are part of the ICU team, clinical assessments of depression are probably reliable. Most intensive care units do not include such experts. Longitudinal studies suggest post-ICU depression is frequent. Early expert screening may benefit patients and their familiesy. No clear epidemiologic descriptions of depression and its outcomes in ventilated patients have been published. Whether any particular form of therapy or none is preferable in the management of depression in ventilated patients is not clear from the literature to date.

POSTTRAUMATIC STRESS DISORDER

The patient you discharged from the ICU 5 weeks ago with epiglottitis comes to your clinic for a follow-up appointment. Since her return home, she describes waking up several times each night in a cold sweat from a recurrent dream that involves attempts at intubating her while she is developing an obstructed airway. She is jumpy and frightened when she goes about the simplest of her daily tasks, and lashed out at a grocery store attendant who asked her at the checkout whether she had change. Her sister confirms how unusual this behavior is for her, and expresses concern because the patient is not functional.

Posttraumatic stress disorder (PTSD) symptoms, such as those described here, is an anxiety disorder associated with a traumatic event that involved the threat of injury or death. Diagnostic symptoms for PTSD include reexperiencing the original trauma(s) through flashbacks or nightmares, avoidance of stimuli associated with the trauma, and increased arousal, such as difficulty in falling asleep or staying asleep, anger, and hypervigilance. Formal diagnostic criteria (both DSM-IV-TR and ICD-10) require that the symptoms persist for more than 1 month and cause significant impairment in social, occupational, or other important areas of functioning. Stressors believed to trigger PTSD include myocardial infarction and critical illness.

Increasing numbers of publications have addressed PTSD in mechanically ventilated and nonventilated ICU survivors[59,60] over the last decade. Its reported incidence varies from 8% to 51%. The amount of literature is low, particularly when one considers the frequency with which the disorder is diagnosed.

Questionnaire-based screening, telephone-based screening, and clinical assessments with and without questionnaires to aid in establishing the diagnosis have populated the studies to date. Questionnaires and clinical assessments, however, may not have the same correlation in mechanically ventilated critically ill patients as they do in other patients. When patients admitted to a weaning center (who had been or still were being mechanically ventilated) were assessed with a standardized PTSD questionnaire and a clinical assessment by a clinical psychologist,[61] the results revealed that the threshold on the questionnaire, which had been validated to predict PTSD in non-ICU patients, was in fact lower than the scoring threshold that corresponded to the clinical diagnosis of PTSD in ICU survivors. These data raise concerns about underestimating the prevalence of PTSD in ventilated patients if standard thresholds are applied.

The only study addressing the link between psychopathology in the ICU and PTSD did not document a link between delirium and PTSD, albeit in a cohort where the incidence of PTSD was low.[62]

PTSD seems to be a risk factor for fatal and nonfatal cardiac events after discharge from hospital.[33] ICU-related associations include lower factual recall and its corollary, higher sedative administration,[63] during the ICU stay.

One study suggests that early and targeted psychological intervention, consisting of five or six face-to-face meetings involving direct ICU patient counseling, stress management, support, and education by a clinical psychologist,[64] offers better outcomes from PTSD than standard ICU care.

What remains surprising is that this condition, which requires a profound precipitant, commonly of a life-threatening magnitude, has been so poorly studied in critically ill patients where exposure to this type of stressor is so predictable.

NONPHARMACOLOGIC INTERVENTIONS

Nonmedical interventions can be helpful in many psychiatric and psychological disturbances. Outside the ICU, prevention of syndromes such as delirium through the use of interventions such as rehydration, reorientation, and warm milk and massages in the evening can sometimes yield spectacular results[65] and are extremely cost-effective. Physiotherapy and early mobilization certainly appear to have a beneficial impact on ICU delirium.[34,35] Interventions such as music may help, and are extremely unlikely to do harm.[66] A bedside diary may aid the most severely traumatized survivor make sense of his or her experience.[67] Finally, opportunities for ICU survivors to tell their tale in a structured fashion may be therapeutic.[68] The narrative has also been described as a tool for healing in the context of illness[69,70] and as a crucial instrument in transforming suffering for the individual who is telling the tale.[71]

Which type of follow-up care, with narratives or without, would best profit ICU survivors is uncertain,[72] although routine screening after ICU discharge and as-needed referral services may be of benefit.[73,74]

SUMMARY

Psychological and psychiatric disturbances are extremely common in the mechanically ventilated critically ill patient. The natural history of such disturbances is not well understood. To date, three disorders have been described in some detail: delirium, depression, and PTSD. Nonpharmacologic approaches, such as early mobilization, adjustment and minimization of sedation, and psychological support, appear to offer some promise. No pharmacologic approach can be endorsed unequivocally.

CONCLUSION

Mechanically ventilated patients are now the subject of more focused investigations with regard to their psychological and psychiatric well-being, both in the acute setting and in terms of outcomes. Regardless of the specific psychological disturbance or psychiatric diagnosis, there appears to be a

link between psychological abnormalities and the severity of illness.[75] The probability of developing psychological or psychiatric complications may depend on vulnerabilities such as prior psychiatric diagnosis[76] or variability in what is referred to as cognitive reserve. Although the severity of illness on ICU admission and some clinical features, such as excessive alcohol consumption, are associated with the development of delirium, the risks or associations with other disorders are not known. Diagnostic categories (delirium, depression, and PTSD) have not been simultaneously and comprehensively compared with patient outcomes. Less discrete but important syndromes, such as adjustment disorder, generalized anxiety, and panic disorder, remained unexplored in this population. Better, more thorough, and more holistic explanations and approaches await future investigations.

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ADDRESSING RESPIRATORY DISCOMFORT IN THE VENTILATED PATIENT

Robert B. Banzett
Thomas Similowski
Robert Brown

Although respiratory discomfort (dyspnea) is as common as pain in seriously ill patients,[1] there is no formal requirement to assess and manage it, such as the "fifth vital sign" requirement for pain assessment and management.

Mechanical ventilation is the most frequently used life-support measure in the intensive care unit (ICU). It is also used during anesthesia and the initial phase of postanesthesia awakening, and at home in patients with chronic respiratory failure. Many patients who are mechanically ventilated are thus conscious (or even fully awake), yet they can experience rapid and important changes in their respiratory status and metabolic needs. It is thus not surprising that ventilated patients do experience respiratory discomfort. They can report and quantify it, and there are strategies to address it. In this chapter we (a) propose that respiratory discomfort be routinely assessed in ventilated patients, and (b) suggest some approaches to managing this discomfort with minimal sedation. Together, these could be termed *patient-centered ventilation*.[2] There is, however, a paucity of studies directly addressing prevalence, outcomes, and mechanisms of dyspnea and its relief in acutely ventilated patients.

OCCURRENCE AND SEQUELAE OF RESPIRATORY DISCOMFORT IN VENTILATED PATIENTS

Although we lack large-scale studies on the prevalence of dyspnea in mechanical ventilation, there have been a few studies in which a small sample of acutely ventilated patients have been asked to rate dyspnea.[3–8] In three studies the severity of dyspnea was stratified: In a combined total of 204 patients, 19% of the respondents reported moderate to severe discomfort.[3,6,7] In one study, patients were asked to characterize the quality of their discomfort: 69% reported experiencing air hunger; 51% reported excessive work/effort. About a third of the foregoing patients experienced both air hunger and work/effort.[7] In another study, 29% of ventilated patients recalled after their stay in the ICU that

they had been moderately to extremely bothered by not getting enough air from the endotracheal tube, which we equate to air hunger.[9] Many patients, however, were too heavily sedated to respond; many of these latter patients had probably been heavily sedated in an attempt to alleviate respiratory discomfort. This clearly indicates that there is a problem to address. As discussed below, heavy sedation is not necessarily an adequate solution and may be harmful.

There is a clear association between anxiety and dyspnea in patients.[10–12] In laboratory subjects, experimentally induced air hunger produces more discomfort and more anxiety than tasks that require a great deal of respiratory work and effort.[13] In critically ill patients, emotional reactions such as panic, anxiety, and fear are significantly correlated with patient–ventilator dyssynchrony.[14] Dyspnea can cause anxiety, even in healthy subjects who experience dyspnea in a safe laboratory situation.[13,15,16] Conversely, anxiety can cause dyspnea. This is true even in the absence of cardiopulmonary pathology; for example, dyspnea is the most common symptom in anxiety and panic disorders.[17] Because of this reciprocal causation, the possibility of positive feedback exists in ventilated patients, with dyspnea causing anxiety, which then exacerbates the dyspnea. In a series of mechanically ventilated patients reporting dyspnea, multivariate analysis showed that the strongest statistical association with respiratory discomfort was with anxiety.[7] In the subset of these patients whose dyspnea was lessened by changes in ventilator settings, anxiety was also reduced, suggesting that the dyspnea caused the anxiety.

Survivors of mechanical ventilation in the ICU often carry surprisingly dark recollections of the experience. A recent study reported that 15% of patients recalled feeling at risk of being murdered, 17% felt betrayed, 39% felt at risk of imminent death, and 55% felt they were being suffocated.[18] Thus, it should not be surprising that posttraumatic stress disorder (PTSD) is now recognized as a common sequela of ICU experience.[18–21] PTSD symptom scores in the post-ICU population are significantly correlated with duration of mechanical ventilation,[19] and with recalled memories of respiratory distress.[20] A number of reasons for these connections can be postulated, but the possibility cannot be ignored that inescapable dyspnea is one of the traumatizing events leading to PTSD in this population.

ASSESSMENT OF DISCOMFORT IN THE VENTILATED PATIENT

Ask the Patient

The first step in addressing dyspnea is to determine how much and what kind of discomfort the patient is experiencing. A full assessment requires that the patient be alert enough to respond to simple direct questions regarding the intensity and quality of discomfort. In heavily sedated patients, the daily wake-up practiced in many ICUs[22] provides an opportunity to assess the intensity of dyspnea and attempt to reduce it with nonpharmacologic approaches before evaluating the need for further sedation.

TABLE 55-1: SAMPLE PATIENT ASSESSMENT QUESTIONNAIRE

Please indicate on this 10-point scale how your breathing feels:
10 EXTREMELY SHORT OF BREATH
9
8
7
6
5
4
3
2
1
0 BREATHING IS COMFORTABLE
Which of the following phrases describes the way you feel?
1. Not getting enough air (if yes, ask a and b and skip 2; if no, ask 2)
   a. Breaths are not deep enough
   b. Breaths are not fast enough
2. Getting too much air (if yes, ask a and b)
   a. Breaths are too deep
   b. Breaths are too fast
3. Too much effort to breathe
4. Chest feels tight or constricted

Several rating methods have been shown to be feasible in intubated and ventilated patients. Patients who are alert enough to respond but who cannot speak can provide information through simple number, word, or visual analog scales, similar to those routinely used in clinical pain assessment.[3,5,23] Patients can point to the appropriate responses but in some cases the interviewer will need to say or point to responses in succession and stop when the patient indicates with a blink or other sign. The intensity scale may be combined ad hoc with a list of descriptors from which the subject can choose; descriptor lists often make the process easier for patients who find it difficult to describe unfamiliar internal sensations.[24] Table 55-1 shows a brief sample assessment procedure. More extensive and sophisticated assessment may be required for research purposes.[25]

Physical Signs May Correlate Poorly with Discomfort Level

Many caregivers rely on physical signs such as respiratory rate, heart rate, use of accessory muscles, synchrony with mechanical ventilation, diaphoresis, and facial expression. Recently, a systematized Respiratory Distress Observation Scale (RDOS) was developed and validated in spontaneously breathing subjects.[26] This scale comprises measures of heart rate, respiratory rate, accessory muscle use, paradoxical breathing pattern, restlessness, grunting at end-expiration, nasal flaring, and fearful facial display. Some of these signs are likely to be altered by mechanical

ventilation, so adaptation and validation of the scale for ventilated patients is needed. Signs can be very useful when patients are unable to communicate, but they can be misleading.[5] Patients vary widely in their behavioral responses to discomfort; thus, as with pain, physical signs may overestimate or underestimate the degree of discomfort, and they give little information regarding its cause. Reliance on inconsistent physical signs was also a problem in pain assessment until accrediting organizations, such as Joint Commission on Accreditation of Healthcare Organizations (JCAHO), began to require more direct assessment and management of pain.[27] Caregivers should ask the patient whenever feasible.

Dyssynchrony of patient and ventilator is associated with discomfort. It has been suggested that it is a cause of discomfort and conversely that it is a result of discomfort (both may be true). The interaction between modern ventilators and patients is a result of the interface between two complex control systems, and the resulting pressure and flow waveforms can be complex. Dyssynchrony is usually assessed qualitatively by visual inspection of waveforms, but some investigators are attempting to formally quantify dyssynchrony.[28] When such methods have matured, they must be validated against subjective reports of patients. Again, we emphasize that when patients can report their discomfort, their reports should be weighed more heavily than physical signs. To date, the available studies of patient–ventilator synchrony have not measured its relationship to respiratory discomfort.

NEUROPHYSIOLOGIC SURROGATES OF DYSPNEA

There are a number of circumstances under which a ventilated patient will be unable to communicate verbally with caregivers and where physical signs of respiratory distress will be difficult to interpret. A particularly difficult instance is the patient paralyzed with neuromuscular blockers. Neurophysiologic surrogates of dyspnea would be particularly useful in this setting. Although in theory one might be able to assess respiratory discomfort using functional magnetic resonance imaging of the brain,[29] this is unlikely to become practical for clinical use in the foreseeable future.

Electroencephalography, however, may provide a more practical method. In normal volunteers under experimental conditions, preinspiratory potentials become apparent during noninvasive mechanical ventilation when respiratory discomfort is induced through the use of inappropriate ventilator settings.[30] Preliminary observations in mechanically ventilated patients suggest that similar monitoring of respiratory-related electroencephalography activity could help detect respiratory discomfort in noncommunicant patients. This approach would allow a continuous surveillance that would be particularly useful in patients liable to experience frequent changes in respiratory status. The clinical utility of these techniques and the spectrum of their applicability are important research targets.

In addition, assessing the electromyographic activity of inspiratory muscles can be useful as a measure of respiratory drive, one of the determinants of respiratory sensation discussed in the air hunger section. There is experimental and clinical evidence that "ventilator fighting" or patient–ventilator dyssynchrony can be associated with visibly increased activity of inspiratory neck muscles, parasternal intercostals, and upper airway dilators including the tongue.[31–33] Correlations between respiratory muscle activity and dyspnea have been observed.[31,33] The clinical usefulness of respiratory muscle electromyography to assess and monitor respiratory discomfort is another likely research topic.

Discomfort Can Be Caused by Dyspnea Combined with Other Sensations

A particular patient's discomfort may be caused by a mix of respiratory discomfort and nonrespiratory sensations, such as pain and nausea. Little is known about how these sum into total discomfort; in some cases, one noxious stimulus can occlude perception of another. The limited data available suggest that simultaneous dyspnea and pain can be separately scaled, and that the presence of one does not strongly affect the other, at least under controlled circumstances.[34] Sensations of respiratory discomfort other than dyspnea (e.g., secondary to cough or irritation from the endotracheal tube) may also be present. Different forms of dyspnea such as air hunger and excessive work of breathing may be simultaneously present, and are thought to be additive.[35] The problems of ventilated patients are therefore varied and complex; there is no single approach that will work in all patients.

PRIMER ON DYSPNEA

Different Forms of Dyspnea

Several different mechanisms give rise to respiratory discomfort; the mechanism(s) operating in an individual patient will guide the treatment approach selected. The quality of discomfort is one guide to understanding which mechanisms are in play; other clues come from physical examination and measurement of ventilatory variables (see "Approach to the Ventilated Patient with Dyspnea" below). There are at least three distinct qualities of uncomfortable breathing sensations: *air hunger, effort* or *work,* and *tightness.* These different forms of dyspnea are caused by different afferent mechanisms and are evoked by different physiologic stimuli.

Theories developed in the late 1960s and early 1970s attributed all dyspnea to excessive work or effort of breathing.[36] Although work of breathing has since been disproved as the sole origin of dyspnea,[37–39] this model still dominates thinking in the realm of clinical mechanical ventilation.[40,41] Attempts to understand a patient's discomfort based only on work of breathing will not be fully effective; in fact, extremely unpleasant dyspnea can be evoked in the absence of any respiratory work.

AIR HUNGER

Air hunger is the conscious perception of the need for more air that is typically described by subjects as "not getting enough air," "uncomfortable urge to breathe." This is the sensation felt by normal subjects at the end of a long breathhold.[15,38] Subjects comment that air hunger is a threatening or frightening sensation. Healthy subjects exposed briefly to air hunger in our laboratory have reported that "it's a feeling…you're going to die because you're not getting enough air." Even moderate air hunger is highly aversive if prolonged, with one subject commenting that "if I felt I had to live my life feeling like that I would jump out the window [commit suicide]." Quotes from patients with dyspnea can be remarkably similar: "When the shortness of breath was at its extreme I thought I was going to die," and "…wouldn't want to live if it continued."[42]

Air hunger arises from stimulation of arterial chemoreceptors and from other drives to breathe; a rise in partial pressure of arterial carbon dioxide (Pa_{CO_2}) or a fall in partial pressure of arterial oxygen (Pa_{O_2}) will evoke air hunger.[37,43–46] Air hunger is not caused by contraction of respiratory muscles; complete respiratory paralysis does not abolish or even diminish the air hunger response to CO_2.[37–39] It is hypothesized that air hunger is transmitted to the cerebral cortex by a corollary discharge of medullary respiratory center activity (also known as *ventilatory drive*). Such a corollary discharge has been described in the midbrain and thalamus of decorticate cats, presumably en route to the cortex.[47–49] Although air hunger is stimulated by medullary drive, the two are not equivalent; other processes modify the translation of drive into the perception of air hunger in the cerebral cortex. Air hunger is associated with activation of the paralimbic cortex in humans, a region of the brain long associated with emotional responses and learning. The principal activation reported in studies of experimental dyspnea is the anterior insula, with stronger activations on the right than on the left (Fig. 55-1A and B). The anterior insula is activated by several other unpleasant sensations that provide information on primal biologic drives, such as pain, thirst, and hunger.[29,50,51] Air hunger also activates the amygdala, which is implicated in the perception of fear and anxiety (Fig. 55-1C and D).

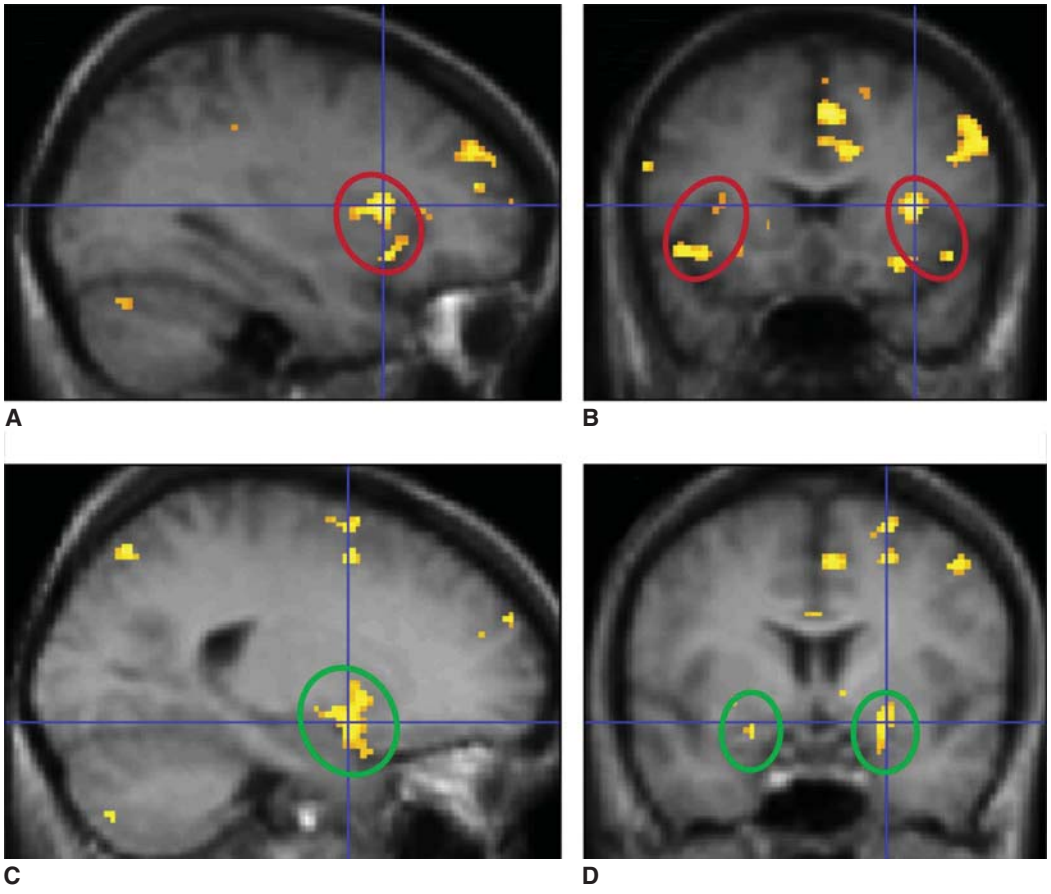

FIGURE 55-1 Functional brain images showing some important paralimbic activations during laboratory-induced air hunger (data from Evans et al[29]). Air hunger was induced during volume-control ventilation by lowering tidal volume (V_T); *red ovals* in *A* and *B* indicate activations in the anterior insular cortex (IC). The sagittal section (**A**) is in the right hemisphere, 34 mm from the midline; the coronal section (**B**) is 16 mm forward of the anterior commissure. The anterior insula is also involved in hunger, thirst, and pain. *Green ovals* in *C* and *D* indicate activations in the amygdala. The sagittal section (**C**) is in the right hemisphere, 24 mm from the midline; the coronal section (**D**) is 4 mm forward of the anterior commissure. The amygdala is implicated in states of fear and anxiety. These images were obtained using blood oxygen level dependent functional magnetic resonance imaging. All activations shown were statistically significant after correction for multiple comparison.

EFFECT OF BLOOD GASES ON AIR HUNGER

There is a substantial amount of information on the interaction of blood-gas levels, level of minute ventilation, and air hunger during mechanical ventilation in normal subjects and in patients who are ventilator-dependent secondary to neuromuscular paralysis. In a study of sixteen healthy subjects ventilated at 10 L/min, end-tidal carbon dioxide tension ($P_{ET}CO_2$) was raised by increasing inspired CO_2. An increase of 10 torr produced a level of respiratory discomfort that subjects could not tolerate even for a few minutes (Fig. 55-2).[15] This occurred despite a background of high oxygen and with minute ventilation ($\dot{V}_E$) greater than 150% of the normal resting level. In practical terms, this implies that modest acute increases in partial pressure of carbon dioxide (P_{CO_2}) that may seem clinically unimportant can be a source of profound discomfort.

An acute rise in Pa_{CO_2} evokes severely uncomfortable air hunger during volume-control ventilation in both healthy subjects and in alert patients ventilated for respiratory muscle paralysis.[23,38,39] The sensations of air hunger and work/effort produced by mild hypercapnia in spontaneously breathing healthy subjects are increased by partial neuromuscular block, even at $P_{ET}CO_2$ and $\dot{V}_E$ levels similar to those present before the block.[52,53] This may explain why exertional dyspnea occurs in patients with profound neuromuscular weakness.

How do responses to chronically altered blood gases compare to the acute stimulus–response relationships for air hunger detailed above (which were obtained in exposures of 10 minutes or less)? Common clinical experience leads to the hypothesis that there is adaptation to chronic changes in blood gases; for instance, the common observation that some patients with chronic obstructive pulmonary disease do not report dyspnea at resting P_{CO_2} in excess of 50 torr, a level that is intolerable to normal subjects at comparable ventilation levels. A direct test of the hypothesis was obtained in mechanically ventilated patients who adapted to a gradual 15-torr rise in Pa_{CO_2} produced by slowly raising inspired P_{CO_2} while holding ventilation and partial pressure of arterial oxygen (Pa_{O_2}) constant.[23] The air hunger response to acute hypercapnia was tested before and after the adaptation period. Within 2 to 3 days, the acute response to hypercapnia had also shifted by 15 torr, essentially complete adaptation (Fig. 55-3). The authors attributed this shift to neural adaptation, rather than acid–base compensation; thus, it may apply to other stimuli such as hypoxia.

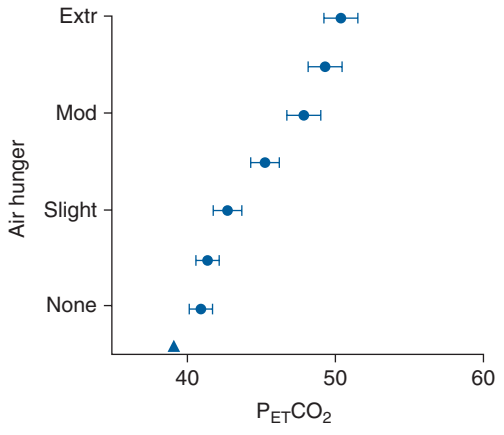

FIGURE 55-2 Air hunger response to an acute rise in end-tidal carbon dioxide tension ($P_{ET}CO_2$) produced by inspired CO_2 in normal healthy men and women (*closed circles*). The prevailing chronic level of $P_{ET}CO_2$ is indicated by *a triangle*. *Bars* indicate standard error of the mean. Volume-control ventilation was delivered via a mouthpiece at 0.16 $L \cdot min^{-1} \cdot kg^{-1}$. Subjects in these experiments were instructed to rate "discomfort due to your urge to breathe." "Extreme" (*Extr*) on the rating scale was defined to the subjects as an intolerable level, and "moderate" (*Mod*) was defined as a level that could be tolerated for several minutes. (Data were replotted from Banzett et al.[15])

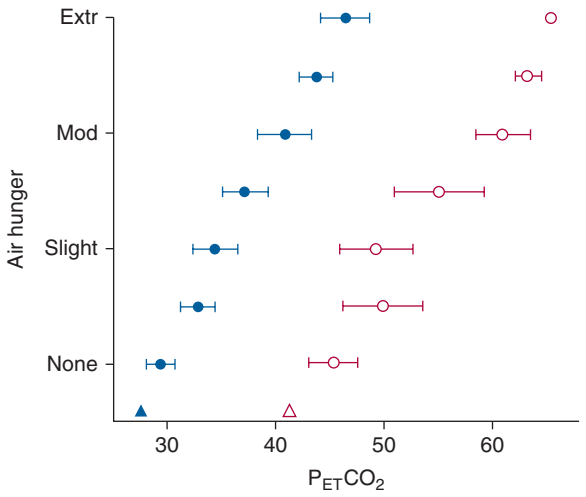

FIGURE 55-3 Adaptation of air hunger response to prevailing chronic level of $P_{ET}CO_2$ (*triangles*) in four ventilator-dependent patients. Response to acute hypercapnia (*circles*) is shown at baseline chronic level of $P_{ET}CO_2$ (*filled symbols*; mean of 27 torr in these chronically overventilated patients), and after adaptation for several days to a mean $P_{ET}CO_2$ of 41 torr (*open symbols*). Bars indicate standard error of the mean. The increase in chronic partial pressure of carbon dioxide (P_{CO_2}) was effected by adding inspired CO_2 at the same minute ventilation ($\dot{V}_E$). (Data replotted from Bloch-Salisbury et al.[23])

Subjects report little or no difference between the quality of air hunger evoked by hypoxia versus that evoked by hypercapnia.[46] If P_{CO_2} and ventilation are near normal, pronounced hypoxia is required to evoke air hunger; in healthy subjects an arterial partial pressure of oxygen (P_{O_2}) of 40 to 50 torr produces only mild air hunger if Pa_{CO_2} remains at eucapnic levels.[46] The effects of hypoxia are enhanced by hypercapnia.

EFFECT OF LUNG INFLATION ON AIR HUNGER

Mechanoreceptor input arising from breathing can dramatically reduce air hunger, as demonstrated by the classic experiment in which subjects held their breath until breakpoint and then breathed from a bag containing gas with alveolar concentrations of CO_2 and O_2, preventing improvement of arterial

blood gases.[16,54] Subjects reported immediate relief and could even continue with another breathhold. This phenomenon is manifested during mechanical ventilation as a decrease in dyspnea when tidal volume is increased, as was initially shown in polio patients.[55] Subsequently, mechanoreceptor relief of air hunger has been shown in normal subjects.[29,50,56] Studies of healthy subjects on volume-control ventilation, who have been initially made uncomfortable with mildly elevated P_{CO_2}, show that there is a decline in discomfort (air hunger) as $\dot{V}_E$ is increased with constant blood-gas levels (the solid line in Fig. 55-4). In these subjects, zero discomfort can be achieved, and further increases have no effect, or produce a different form of discomfort, "too much pressure." In normal subjects, the relationship between ventilation and air hunger is linear (A.P. Binks, personal communication). This relief is undiminished in C1–C2 quadriplegic patients who have no motor or sensory innervation of the rib cage and diaphragm, showing that pulmonary stretch receptors that send impulses via the vagus nerve, are able to produce the full response[57] (*dotted line* in Fig. 55-4). It is not clear, however, whether chest wall receptors form a fully redundant pathway capable of providing relief. Tidal volume provided somewhat less relief in double-lung transplant patients than in normal subjects;[56] however, even the diminished response present in these transplant patients may have been caused by reinnervation of the transplanted lung, because the patients were studied 1 to 9 years posttransplantation.[58]

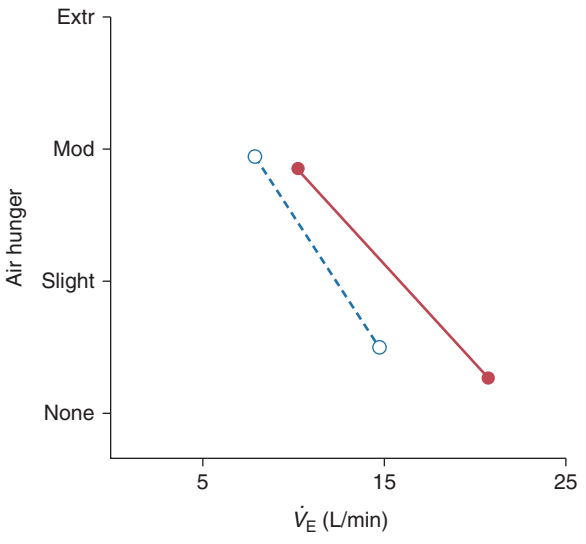

FIGURE 55-4 Relief of air hunger by increased minute ventilation at constant $P_{ET}CO_2$ in normal subjects (*solid line, closed symbols*) and patients with high cervical quadriplegia (*dotted line, open symbols*). In all cases, air hunger was generated by adding inspired CO_2 to increase $P_{ET}CO_2$ above the subjects' baseline $P_{ET}CO_2$. (Mean $P_{ET}CO_2$ in normal subjects was 44 torr and in quadriplegic patients, 34 torr, owing to their lower baseline P_{CO_2}.) $P_{ET}CO_2$ and respiratory frequency were held constant as ventilator tidal volume was varied. (Data for normal subjects combined from Harty et al[56] and Banzett et al[50]; data for quadriplegic patients combined from Manning et al[57] and Bloch-Salisbury et al.[90])

WORK OR EFFORT OF BREATHING

The sense of breathing work or effort arises both from muscle receptors and from corollary discharge arising from cerebral motor cortex activation during volitional respiratory efforts.[59] (Corollary discharge from medullary respiratory centers probably does not give rise to increased work or effort of breathing.) Although some studies of well-trained subjects have shown a distinction between effort and work, most normal subjects and patients do not distinguish the two; thus, we use work/effort to denote the sensation. Work/effort of breathing is perceived when the physical work of breathing is increased by loading the respiratory muscles with high $\dot{V}_E$ or increased impedance, or when increased cortical motor drive is necessitated by respiratory muscle weakness.[53,60–62] Breathing at high lung volume both weakens the muscles (by placing them at a disadvantageous point in the length–tension curve) and loads them by increasing preload and system elastance; this is thought to be an important source of dyspnea in obstructive pulmonary disease.[63–65] In normal subjects, high levels of respiratory work/effort unaccompanied by blood-gas derangements are not as unpleasant or threatening as air hunger.[13,60,62]

In theory, the ventilated patient need not do any respiratory work; ventilators have ample power to assume all work of breathing. Two sources of work, however, commonly arise in ventilated patients. The first we term *wasted work* (i.e., work that does not result in air movement); this includes respiratory efforts that are ineffective because they are out of synchrony with the ventilator, or efforts (although in synchrony) that do not alter airflow (e.g., inspiratory efforts during volume-control inspirations). The second, *productive work,* is performed to lower airway pressure to trigger inspiration during assist control, or to trigger and prolong inspiratory flow during pressure support. Some respiratory work may prevent deconditioning of respiratory muscles.[66,67] Even productive work, however, may be excessive, if for instance the trigger pressure or flow thresholds are set too high especially in the face of high respiratory impedance or respiratory muscle dysfunction. Dynamic hyperinflation (intrinsic positive end-expiratory pressure [PEEP]) is a typical cause of excessive work; in this case the patient must generate inspiratory muscle pressure to overcome the difference between ventilator PEEP and intrinsic PEEP before the ventilator can be triggered. In addition, dynamic hyperinflation is associated with elastic loading caused by flattening of the respiratory system pressure-volume relationship at high lung volumes, and with decreased inspiratory muscle effectiveness secondary to sarcomere shortening and geometry changes. Thus, the effort required to trigger the ventilator and sustain flow above the cutoff level can give rise to excessive work/effort at a time where muscle output is diminished. Depending on the ventilator setting, it can also cause inadequate ventilation, giving rise to air hunger. It is thus likely that dynamic hyperinflation can give rise to a mixed respiratory discomfort combining air hunger and an excessive work/effort.

DYSPNEA ARISING FROM PULMONARY AFFERENTS

There are several diseases in which dyspnea seems to arise from derangements of pulmonary afferent traffic; less is known about the neurophysiology of these forms of dyspnea. *Tightness* arises during bronchoconstriction.[68,69] Tightness is undiminished by mechanical ventilation, and preliminary evidence suggests that it is present during bronchoconstriction in quadriplegic patients with denervated chest walls, suggesting that it arises from pulmonary afferents.[70,71] Pulmonary embolism, pulmonary hypertension, and congestive heart failure all give rise to dyspnea that is disproportional to blood-gas changes or to increased work of breathing. All directly impinge on the lung or its vasculature. It has thus been speculated that these conditions give rise to dyspnea via pulmonary receptors, and there is some evidence implicating vagal afferents, perhaps unmyelinated J-receptors.[72–74]

APPROACH TO THE VENTILATED PATIENT WITH DYSPNEA

If the ventilated patient is experiencing dyspnea, steps should be taken to establish the reason for the dyspnea and corrective measures should be attempted. It may be useful to establish a routine protocol to suit the needs of the unit. If diagnosis and corrective measures are expected to take more than a few minutes, interim relief can usually be obtained by increasing the level of ventilator support. Sedation should be used as a last resort because of the related risks. There are several avenues to pursue before resorting to sedation: assess and remedy problems with obstructed airways, a stiff respiratory system, or weak respiratory muscles; improve ventilator settings; and address neuropsychiatric problems.

Essential information can be obtained from the physical examination (e.g., onset of wheezing, absence of breath sounds, new crackles, use of accessory muscles of ventilation, or pulsus paradoxus) and by measuring airways resistance (Raw), intrinsic PEEP, spontaneous and ventilator-assisted tidal volume, maximal inspiratory and expiratory pressures, and compliance of the respiratory system (sometimes with the use of an esophageal balloon-catheter system to obtain compliance of the lung and chest wall separately).

Reduce Respiratory Drive

Respiratory drive in excess of achieved ventilation is the cause of air hunger, the most common respiratory discomfort reported by mechanically ventilated patients.[7] The most straightforward way to address air hunger is to increase ventilation. When it is not possible or not advisable to increase achieved ventilation, other steps should be taken to reduce drive. Factors such as acidosis, hypoxia, hyperthermia, and anemia should be corrected.[75] Although patients may adapt to hypercapnia over the course of several days, acute increases in Pa_{CO_2} of only a few torr can cause substantial discomfort.[23] When addressing acidosis, it may be possible to use buffers such as tris-hydroxymethyl aminomethane (THAM) that do not increase P_{CO_2}.[76–78]

Correct Increased Respiratory Impedance

Increased resistive or elastic impedance may give rise to air hunger in the ventilated patient by reducing ventilation, either by causing patient triggering efforts to fail, or by reducing tidal volumes delivered by pressure-targeted ventilators. Increased impedance may also give rise to a sense of excessive effort by increasing both wasted and productive work.

EXCESSIVE RESISTANCE

Airways obstruction in ventilated patients as reflected by Raw greater than 10 cm H_2O/L/s is a frequent cause of dyspnea. Table 55-2 lists common causes of high Raw.

In addition to resistance and compliance measures, the pressure and flow waveforms from the ventilator can provide useful diagnostic clues: A sawtoothed pattern is usually caused by retained secretions or condensed water in the expiratory line. Interruption of exhalation by a new inhalation before flow reaches zero indicates the presence of intrinsic PEEP, the magnitude of which should then be measured. Intrinsic PEEP secondary to flow limitation can be distinguished by pressing on the patient's abdomen during expiration. If there is flow limitation, the expiratory waveform will not change. Many of the causes of high Raw listed in Table 55-2 can be identified easily by bronchoscopy. In other instances, the quality of dyspnea reported by the patient can provide important diagnostic clues. For example, our experience is that when bronchoconstriction is the cause, patients complain of chest tightness, whereas other causes of obstruction are usually associated with a sense of increased effort or work to breathe.

The goal is to reduce or eliminate excessive Raw if possible, for instance by suctioning, replacement of the obstructed endotracheal or tracheostomy tube, administration of

TABLE 55-2: COMMON CAUSES OF HIGH AIRWAY RESISTANCE

- Bronchoconstriction
- Inspissated debris in the endotracheal or tracheostomy tube
- Retained secretions in the trachea or bronchi
- Obstruction of the orifice of the endotracheal or tracheostomy tube by the posterior membranous sheath of the trachea secondary to tracheomalacia or a poorly fitting tube
- Granulation tissue (most often at the site of the cuff or tip of the tube or at the anastomosis site of a transplanted lung or lobe)
- Dislodged tracheostomy tube (most common in obese patients in whom selection of the proper size and shape of the tracheostomy tube can be difficult)

bronchodilators or corticosteroids, or removal of granulation tissue. Until these measures are successful in alleviating intrinsic PEEP, however, an important step in achieving relief is to set the PEEP to equal the intrinsic PEEP (which reduces the preload the patient must overcome before triggering inspiration).[79] An alternative is to switch to mandatory volume-control ventilation, in which intrinsic PEEP does not affect delivery of tidal volume.

LOW COMPLIANCE

Stiffness of the respiratory system, as reflected by compliance (Crs) values less than about 40 mL/cm H_2O, is also a common cause of dyspnea. Common causes of low Crs are disorders involving the parenchyma (airspace diseases, fibrosis, and pulmonary edema), pleura (large pleural effusions, pleural thickening secondary to empyema, fibrosis, and tumor), or chest wall (kyphoscoliosis, ankylosing spondylitis, thoracoplasty, or obesity, especially in supine patients). These problems tend to be associated with a sense of effort to breathe, and with air hunger if hypoxemia or hypercapnia occurs. Many of the causes can be identified by chest computed tomography scan. Relief is obtained by reversal of the problem when possible.

FIGHTING THE VENTILATOR

Respiratory efforts out of phase with the ventilator often reduce its effectiveness by increasing effective impedance. These counterproductive efforts can be both an effect of dyspnea and resultant anxiety, and conversely, the efforts and consequent reduction in ventilation can be a cause of further dyspnea.

Dyspnea Associated with Care Activities

Dyspnea is frequently associated with normal care activities such as planned turns, transfers, bathing, and suctioning.[5] Good oxygenation should be assured before the activity, and it may be desirable to administer a preemptive dose of a very short-acting sedative or narcotic agent before commencing. A hazard of using even short-acting drugs repeatedly is that the drug will accumulate and produce prolonged sedation.

Ventilator Settings

Very few research papers have reported measures of dyspnea in patients during mechanical ventilation, and fewer still report the effect of systematic manipulations designed to reduce dyspnea. In most of these studies, respiratory discomfort was not the primary outcome measure, and ventilator settings were optimized according to the investigators' criteria, not according to subjects' reports of comfort.[40,41,80,81] A few studies in normal subjects and none in patients have systematically examined independent variables such as flow rate while holding other known stimuli for dyspnea constant. Usually several mechanoreceptor stimuli changed simultaneously; for instance, in one study when flow rate was changed, tidal volume also changed. In other cases, important physiologic variables secondary to ventilation were not controlled, and were often not even measured. For instance, although it is well known that Pa_{CO_2} and Pa_{O_2} have a powerful effect on air hunger, these variables are frequently not controlled or reported. Despite these limitations, it is clear from these studies that changing ventilator settings can reduce dyspnea, and that patients can report these changes in dyspnea—the two essential features to enable patient-centered ventilation. In an observational study of ninety-six patients mechanically ventilated of whom forty-five (47%) reported dyspnea, altering ventilator settings and/or increasing the level of ventilator support partially alleviated dyspnea in 35% of cases. This corresponded to a median reduction of reported dyspnea by 40% of full scale.[7]

LEVEL OF VENTILATOR SUPPORT

Major relief of dyspnea in ventilated patients can be obtained by increasing the level of ventilator support.[7] There is, however, very little systematic information on this phenomenon; we are aware of only one study in which ventilator variables, work of breathing, and dyspnea were measured at different levels of support by invasive ventilation.[41] This study of patients with chronic obstructive pulmonary disease presents data on respiratory sensation at graded levels of assistance. Increasing the percentage of respiratory work done each minute by the ventilator proportionally decreased ratings of "difficulty breathing" (Fig. 55-5). The effect was large, with breathing difficulty ratings falling from 60% of scale with no support to 30% of scale with 80% support (ratings were not

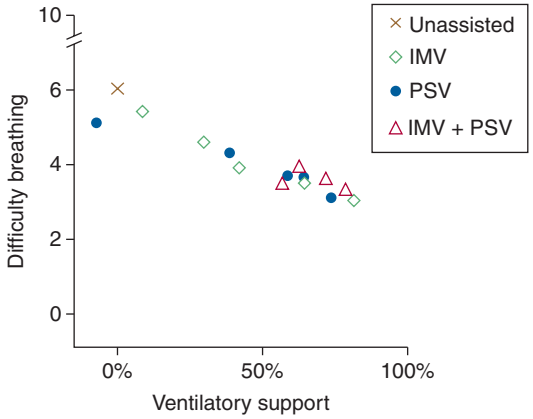

FIGURE 55-5 Effect of ventilator support on dyspnea. Subjects were instructed to rate "difficulty breathing" on a ten-point scale. Work of breathing was measured as the pressure-time product of inspiratory muscles, including all breaths, spontaneous and mandatory. Ventilator support is calculated as the difference from work of breathing in the unassisted control state. Data are shown for unassisted breathing, pressure-support ventilation (*PSV*), intermittent mandatory volume ventilation (*IMV*), and a combination of modes (*IMV+PSV*). (Data reanalyzed and redrawn from Leung et al.[41])

reported for full support). There were equally good correlations when ratings were replotted against a number of relevant physiologic indices (average tidal volume, frequency, minute ventilation, and work of breathing), so the afferent mechanism cannot be deduced from this experiment alone.

There are several mechanisms that could account for the relief achieved by increasing support. When support was increased in the above study, tidal volume also increased, as it would in most clinical situations. Relief correlated with tidal volume equally well as with percentage of support, and it is well known that increasing tidal volume can profoundly decrease air hunger (see the section above Effect of Lung Inflation on Air Hunger). Alveolar ventilation also increased with ventilator support in this study, presumably causing an improvement in blood gases, although these were not measured. Lowering Pa_{CO_2} has also been shown to have a profound effect on air hunger (see the section above Effect of Blood Gases on Air Hunger), providing another possible relief mechanism (not mutually exclusive).

OTHER ASPECTS OF VENTILATOR SETTINGS

Rate of inflation has been shown to have an effect on comfort. In healthy subjects on volume-control ventilation, inflation rates higher or lower than an optimum rate were less comfortable; there was, however, a broad range of comfortable inspiratory flow rates—the minimal comfortable flow, on average, was 0.6 L/s.[82] At inflation rates below the optimum, subjects reported air hunger. At inflation rates well above this minimal flow (average 1.8 L/s), subjects reported sensations of too much pressure. Optimal flow rate has also been shown in patients on pressure-support ventilation for conditions ranging from pneumonia to stroke; discomfort increased above and below the preferred setting.[40] In this latter study, however, there were concomitant changes in tidal volume that may have contributed to changes in discomfort ratings. Another study of ICU patients found a higher prevalence of dyspnea at inspiratory flow rates below 60 L/min (1 L/s), but concomitant changes in other key variables were not reported.[7] In a third study, a minimum inspiratory flow rate of 60 L/min was required to assure respiratory muscle relaxation in patients receiving assist-control ventilation.[83]

There is also evidence that PEEP level affects comfort via two distinctly different mechanisms: triggering effort and mean lung volume. The first, and best understood, arises from the interaction between ventilator PEEP and intrinsic PEEP in determining the effective trigger threshold. In this case, dyspnea can be reduced with little or no change in tidal volume by adjusting PEEP to minimize inspiratory muscle preload. The second effect is through the effect of lung volume on comfort. There is some evidence that chronic ventilator patients and mechanically ventilated healthy subjects are more comfortable (or require less tidal volume to achieve comfort) when end-expiratory lung volume is raised with PEEP,[84,85] possibly secondary to increased pulmonary mechanoreceptor activity.

EFFECT OF VENTILATOR CONTROL MODE

Most comparisons of sensation during different ventilator modes have not controlled the relevant physiologic variables. Leung et al[41] compared respiratory sensation during graded levels of support in two ventilator modes, pressure-support and intermittent mandatory ventilation, allowing meaningful comparisons of the two modes. The ratings of dyspnea ("difficulty breathing") depended only on the amount of assistance, not on the mode of ventilation (see Fig. 55-5). Both modes provided equivalent relief of dyspnea when ratings were replotted against a number of relevant physiologic indices. We conclude that judicious setting of volume-control ventilation parameters (see below) is likely to reduce dyspnea as effectively as subject-controlled ventilation when ventilatory demand is relatively constant.

A great deal of attention is paid to allowing patients to control the inspiration delivered by the ventilator; several clever schemes have been devised to perfect this control. It is thought by many that patient control of the ventilator is more comfortable, either because it ensures coincident timing of lung inflation with neural inspiration, or because it provides a sense of control to the patient. There is, however, no direct evidence that patient-triggered ventilation is inherently more comfortable than the same ventilator parameters set externally; differences appear to be more dependent on the parameter values chosen, and perhaps on the preference and familiarity of the operator for one mode versus another. There is growing evidence to show that use of the diaphragmatic electromyogram to initiate, control, and terminate pressure support (neurally adjusted ventilatory assist) improves patient–ventilator synchrony and allows more natural breathing variability.[86] The impact of neurally adjusted ventilatory assist on respiratory comfort, however, has not yet been determined.

If timing ventilator inflation to coincide with neural inspiration were crucial, spontaneous breathing in healthy subjects would be more comfortable than volume control; this is not the case. During hypercapnia in healthy subjects, spontaneous breathing was no more comfortable than volume-control mechanical ventilation at the same $\dot{V}_E$.[87] This may be because timing is irrelevant, or because neural timing adapts quickly to reasonable ventilator timing.[88,89]

If a psychological sense of control were important, giving the patient direct control of ventilator parameters would improve comfort; this is not the case, at least in chronically ventilated patients. When paralyzed patients on volume-control ventilation were allowed to control the tidal volume setting of the ventilator using a "sip/puff switch," they obtained no more relief from hypercapnia-induced discomfort than when the experimenter surreptitiously increased the volume.[90]

Patient-controlled ventilation may, however, have important advantages when ventilatory demand is highly variable. Two such instances are ambulatory patients assisted with noninvasive positive-pressure ventilation, whose ventilatory demand changes with physical activity,[80] and patients who use ventilator-delivered air to generate speech.

CHRONICALLY VENTILATOR-DEPENDENT PATIENTS

An illustrative case is that of the chronically ventilator-dependent neuromuscular patient. These patients are nearly always comfortable with their usual ventilator settings. The reason for this is that they are not sedated, and thus they clearly and insistently communicate their ventilatory desires to caregivers. In response, the caregivers set the ventilator to satisfy the patient. In our experience, this always results in high tidal volumes, frequencies of 10 to 15 breaths/min, and very low $P_{ET}CO_2$. In general, nearly all breaths are delivered by the ventilator as mandatory breaths, even when triggering is possible. Presumably this is because ventilation is high enough to suppress spontaneous efforts. Studies in which $P_{ET}CO_2$ is slowly raised show that complete comfort is maintained at normal $P_{ET}CO_2$, leading us to conclude that the factor suppressing dyspnea and spontaneous efforts is large tidal volume, rather than low P_{CO_2}. Patients with lung and heart disease present additional constraints that complicate the issue, but the general principle of obtaining feedback from the patient as part of the ventilator-setting process can probably be applied to most awake patients.

UNWANTED EFFECTS OF VENTILATOR ADJUSTMENTS

Ventilator-induced lung injury can be caused by overly high tidal volumes in vulnerable patients. It may not be necessary to give excessively high tidal volumes to achieve patient comfort. Although one observational study suggests that the tidal volume limit should be reduced in all patients, the study design limits the strength of the conclusions.[91] We also note that chronically ventilator-dependent neuromuscular patients are routinely maintained for years with much larger tidal volumes without experiencing ventilator-induced lung injury.[23,57,84,92] More restrictive limits should be observed in patients at risk for the acute respiratory distress syndrome, in which case other means must be used to avoid dyspnea. Clinicians should be sure to apprise themselves of the current state of the art for tidal volume limits, as this is a rapidly changing field. It seems particularly important not to extend attitudes and recommendations that have been developed for patients at high risk of lung injury to situations where their relevance is unknown. Exposing a patient to dyspnea and psychological trauma is not warranted if this patient is not at risk of acute lung injury.

Some clinicians become concerned if arterial P_{CO_2} falls below normal values. Again we note the experience of chronically ventilator-dependent neuromuscular patients, who invariably have arterial P_{CO_2} 10 to 20 torr lower than normal for many years without apparent ill effect.[57,83] It is important, however, to avoid acute increases in Pa_{CO_2} that give rise to dyspnea. Thus, for instance, if a patient is preparing to wean and is unlikely to have the ventilatory capacity to sustain low P_{CO_2}, the P_{CO_2} should be slowly raised over the course of a day or more to a level the patient is likely to be able to sustain with spontaneous breathing.

Sedation

It is commonly believed that heavy sedation is the best method to deal with patients who are uncomfortable during mechanical ventilation.[93,94] This is the usual approach in many hospitals. Mounting evidence suggests that this is a poor solution to the problem. It is intuitively evident that the loss of communication with loved ones and health care professionals is a serious disadvantage of sedation. It is also reasonably well established that heavy sedation worsens several outcome measures, such as length of ICU stay, length of hospital stay, and incidence of serious complications.[95] More recently, and more surprisingly, evidence has emerged suggesting that sedation worsens psychological outcome following discharge.[96,97]

Sedation may not eliminate discomfort even though it reduces outward signs of discomfort. What is known about the effect of sedation on pain suggests that some sedatives are ineffective in eliminating discomfort. For example, ratings of the discomfort of a controlled cutaneous pain stimulus were unaffected by propofol plasma concentrations up to 1.5 μg/mL (moderate sedation). Even at propofol concentrations that rendered subjects unresponsive, strong pain-related activations were seen in cortical regions associated with pain.[98,99] Although no similar studies exist for dyspnea stimuli, it is possible that cortical activation by dyspnea also persists during heavy sedation, providing a substrate for psychological trauma. It has been hypothesized that sedated patients can experience discomfort at some level, yet not have explicit recollections of stressful events.[100] They are therefore unable to construct a rational understanding of their discomfort, and are left with nightmarish recollection of the episode.[96,101]

Opioids are the only drugs recognized as effective in providing symptomatic relief of dyspnea. Relatively low doses of opioids can be effective. A recent meta-analysis showed a significant effect of opioids on clinical dyspnea, but the effect size was variable, probably because most of the included studies used oral dosing.[102] Parenteral doses are more consistently effective than oral doses.[103] In laboratory tests, morphine has been shown to specifically reduce air hunger,[103] the predominant symptom in ventilated patients.[7] Strom et al showed that it is possible to maintain ventilated patients with low doses of morphine and no other sedative; although no direct measurements of discomfort were reported, approximately 20% of patients required dedicated personal reassurance.[95] The duration of ventilation and ICU stay were shorter than in control patients sedated with propofol or midazolam.

COMFORT IMPLICATIONS OF THE PATIENT–VENTILATOR INTERFACE

Mechanical ventilation can be provided through a variety of patient–ventilator interfaces, including body tanks ("iron lungs"), endotracheal tubes, tracheostomy, masks, and helmets. It is customary to call support that does not involve tracheal cannulation as "noninvasive ventilation." Noninvasive ventilation is efficient as a life-support and symptomatic measure both during acute and chronic ventilatory failure. Noninvasive ventilation, when feasible, can

provide distinct advantages over endotracheal intubation for physical outcome,[104,105] and avoids major discomfort caused by the endotracheal tube.[106] Where conditions are suitable for noninvasive ventilation, it may even reduce posttraumatic stress disorder.[107] Patients supported by noninvasive ventilation, however, are not free from psychological trauma events.[18] It can be difficult to achieve both adequate gas exchange and comfort in the presence of leaks. Leaks promote patient–ventilator dyssynchrony[108] and may require the use of uncomfortable measures including high insufflation pressures and excessively tight application of masks.

Tracheotomy is probably the most ancient patient–ventilator interface. ICU mortality and morbidity are unaffected by tracheotomy;[109,110] although it has been associated with significant improvement of comfort in ventilated patients.[109,111] Tracheotomy can also allow spoken communication with caregivers and loved ones; more intubated patients are bothered by the inability to speak than by endotracheal tube discomfort,[112] although tracheotomy is often considered as very invasive by caregivers, patients, and relatives.

IMPORTANT UNKNOWNS AND THE FUTURE

Epidemiology

There are only a few small studies of the prevalence of dyspnea in mechanically ventilated patients. These pilot studies strongly suggest there is a reason for concern, but studies defining the extent of the problem and its variation in different categories of patients and in different care settings are needed. In addition, the connection between dyspnea in ICU patients and poor psychological outcomes needs to be more carefully studied. Having defined the extent of the problem, it will be necessary to study the effectiveness of patient-centered ventilation strategies on both immediate comfort and long-term medical and psychological outcomes.

Respiratory Interventions

Systematic studies of the effect of each of the multitude of ventilator setting modes on patient comfort are needed. These should be accomplished with state-of-the-art methods for dyspnea measurement, and with proper measurement and control of interrelated physiologic variables that may change. To date, there are no studies of ventilator settings that report measurements of discomfort together with measurements of the salient physiological variables that determine comfort (tidal volume, inspiratory time, frequency, blood gases, and so on). Further investigation is also needed to determine whether feedback on magnitude of discomfort will suffice as a practical guide to treatment of the mechanically ventilated patient, or whether obtaining further descriptions of the nature of discomfort will be useful.[13,69] On the basis of this mechanistic knowledge, a more systematic approach to achieving comfort can be devised.

Nonrespiratory Interventions

There are several potential schemes for altering afferent input without actually altering ventilatory variables, in a sense "fooling" the system to reduce perception of dyspnea. These have not been studied in the context of mechanical ventilation. Cool air directed over the face has a significant effect on dyspnea.[113] In some studies, phasic vibration of intercostal spaces has been shown to have an effect on work/effort dyspnea,[114–116] but no effect on air hunger.[117] Aerosolized furosemide has also been shown to reduce air hunger dyspnea.[118–120]

A complementary approach may be the provision of psychological support during the ICU stay. In one study, provision of a staff member to reassure and comfort those patients having difficulty with discomfort allowed lighter sedation. Such extra support was needed in only 20% of lightly sedated patients.[95]

SUMMARY AND CONCLUSION

Substantial respiratory discomfort is common in mechanically ventilated patients and is likely responsible for important emotional reactions, such as anxiety, fear, and PTSD. There is some irony in this, as mechanical ventilation is often instituted to relieve respiratory distress. Unfortunately, the current trend toward using low tidal volume ventilation in all patients exposes patients to dyspnea more often and for more prolonged periods. It will be of the utmost importance to explicitly recognize this trade-off, and to balance the clinical need for lung protection against the suffering that low tidal volume may engender.

Although it is not common current practice, we have recommended that, in ventilator units, there be routine formal assessment of the quality and intensity of the discomfort, for example, when vital signs are obtained. The cause(s) of the dyspnea should be sought and corrective measures attempted. The patient's description of the discomfort, the physical examination, and physiologic measurements, such as airways resistance and respiratory system compliance, provide important clues about the cause of the dyspnea. Increasing the level of mechanical support usually provides relief, but the best method for this is not yet known and may vary with the cause. Heavy sedation should be used only when necessary because it is associated with an increase in days requiring mechanical ventilation, occurrence of pneumonia, and length of stay in the hospital. Whether the patient-centered ventilation approach that we have recommended will yield beneficial outcomes remains to be determined and should be the subject of future research.

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VENTILATOR-SUPPORTED SPEECH

Jeannette D. Hoit
Robert B. Banzett
Robert Brown

Under normal circumstances, the respiratory system supplies the aeromechanical drive that allows the vocal folds, tongue, lips, and other structures to create the sounds of speech. Although a simplification, this drive can be understood as the tracheal pressure. Usually this pressure is exquisitely and actively controlled by muscles of the chest wall. When speech is produced with ventilator support, however, the ventilator and the respiratory system must work together to produce the pressure that drives speech production. In most cases, this pressure is markedly different from that of normal speech production. As a result, the act of speaking can be challenging for patients, and they often require assistance from their pulmonologists, respiratory therapists, and speech-language pathologists. The views presented here are that patients should be enabled to speak whenever possible, and that ventilator-supported speech can often be improved by using interventions such as those described in this chapter.

THE IMPORTANCE OF SPEECH

Communication is critical to maintaining good quality of life. Communication is the key to being able to express needs, participate in social activities, and retain control over important life decisions.[1–5] It can be especially important in intensive care or during end-of-life care.[6,7] There are many ways to communicate, but of these, speech is the fastest and most convenient. It works in the dark and across telephone lines, and it conveys meaning and emotions through words and tone of voice (i.e., pitch, loudness, quality, and timing).

Patients who are ventilator-supported often complain of speech problems, especially unwanted pauses and inadequate loudness.[8] This is illustrated in the following quotation,[9] which comes from a patient who was asked, "Do you have any problems with your speech?" Note that the pauses between phrases were 3 to 4 seconds (• = 1 second),

and that some words were produced without voice (shown in parentheses). To appreciate the severity of the speech problem, this quotation should be read aloud with timed pauses:

"Yes •••• Um, getting cut (off) •••• people interfering with me ••• trying to finish my sentences (for me) •••• that's the most frustrating (part)."

Fortunately, it is nearly always possible to improve ventilator-supported speech. The following quotation comes from the same patient, after she received speech interventions. Pauses were reduced to approximately 1 second, and the amount of speech per breath increased by approximately 50%.

"Since I've been able to talk better • I've par- participated in talking with more people and • and in conversation instead of just doing the listening • and talking as little as possible • I've joined in and, and • I don't know, I've just been part of a group more • Very few people try to finish my sentences now and • second guess what I'm going to say • It's, it's helped a lot."

FUNDAMENTALS OF SPEECH BREATHING

Speech comprises the tones, hisses, pops, and buzzes that are the acoustic representation of language.[10] Speech is usually produced by the coordinated efforts of more than 100 muscles spanning the chest wall, larynx, and upper airway structures (pharynx, velum, jaw, lips, and tongue). Speech breathing is the process by which the driving forces are supplied to downstream structures to generate speech, and it is tailored to simultaneously serve speech-related functions and meet gas exchange requirements.[11]

The normal speech breathing cycle has an inspiratory phase ranging from 0.5 to 0.7 second.[12–16] Inspirations during speaking are so short that the pauses they create are hardly noticeable. The longer, more variable expiratory phase of the cycle is the speaking phase. Its duration averages 3 to 5 seconds, but varies substantially as a function of linguistic factors, cognitive variables, mechanical constraints, and ventilatory needs.[13,14,16–18] Speech is usually produced throughout most of the expiratory phase, although nonspeech expirations are likely to occur in senescent subjects,[19] with high cognitive-linguistic demands,[20] and under conditions of elevated ventilatory drive.[16,21,22] The tidal volumes used in speech breathing are typically about twice as large as those of resting tidal breathing.[23]

The normal speech breathing cycle has a characteristic tracheal pressure profile. During inspiration, pressure is substantially and briefly negative, and during expiration (speaking), it is moderately positive and relatively steady. For speech of conversational loudness, pressure is generally in the range of 5 to 10 cm H_2O.[24,25] Pressure usually remains relatively constant throughout expiration so that loudness and voice quality remain relatively constant.[26,27] An increase in pressure generally causes an increase in loudness. To produce voiced speech sounds (such as vowels), the vocal folds must oscillate, which requires a minimum pressure of approximately 2 cm H_2O.[28,29] When voiced sounds are produced with a constricted oral airway (such as the plosive /d/ or the fricative /v/), slightly higher pressures are needed.

The pressures of normal speech breathing are controlled actively throughout the cycle by muscles of the chest wall.[27] Inspiration is driven by the diaphragm (with activation of other muscles that serve to stabilize the chest wall), and expiration (speaking) is driven by both expiratory rib cage and abdominal muscular pressures (with the latter predominating) when in upright body positions, and by expiratory rib cage muscular pressure alone when in the supine body position. These muscular pressures are usually supplemented by positive recoil pressure, because most conversational speech is produced above the resting expiratory level. On rare occasions, when speech is initiated at a very large lung volume (i.e., near total lung capacity), positive recoil force may be so great that inspiratory muscular pressure must be called into play to counteract (i.e., "brake") the high positive pressure.

A FRAMEWORK FOR UNDERSTANDING VENTILATOR-SUPPORTED SPEECH

During ventilator-supported speech breathing, tracheal pressure reflects the combined contributions of the patient's prevailing respiratory recoil pressure, active muscular pressures (if the patient is able to activate chest wall muscles), and inspiratory and/or expiratory drive from the ventilator, among other factors. A useful framework for understanding, evaluating, and managing ventilator-supported speech is to relate speech to tracheal pressure.[9,11,30]

SPEECH WITH INVASIVE POSITIVE-PRESSURE VENTILATION

Invasive positive-pressure ventilation (InPPV) is used here to mean intermittent positive-pressure ventilation via tracheostomy. Because an endotracheal tube prohibits vocalizing and can damage the vocal folds, speech is one of several factors to consider when deciding whether and when to perform a tracheotomy (see Chapter 40). Speaking with InPPV is substantially different from speaking with other forms of ventilation, but it can be very successful. The primary differences stem from the fact that the ventilator-delivered air enters below the larynx.

Deflate the Tracheostomy Tube Cuff

For a patient to speak, the first and most critical step is to configure the tracheostomy tube so that flow (and thus pressure) can reach the larynx. This means that the cuff on the

tube must be deflated (and/or the tube must contain a fenestration). If cuff deflation or use of a fenestrated tube is deemed inadvisable, alternative forms of speech or communication must be sought (see Chapter 40 and "Alternatives to Ventilator-Supported Speech" below).

Cuff deflation is feasible in most chronically ventilated patients[31,32] and in acutely ventilated patients who are otherwise stable. Indeed, in some patients, the cuff can be deflated and speech training initiated on the first day after the tracheotomy has been performed. Unfortunately, cuff deflation and speech training are often delayed (or not performed at all) because of unfamiliarity with the procedure, concerns about aspiration, and fear of causing hypoventilation and hypoxemia. Hypoventilation and hypoxemia can be avoided by increasing the ventilator-delivered tidal volume. In many stable patients, the cuff can remain deflated all day (and inflated only for sleep). In less-stable patients, cuff deflation may need to be brief (to allow communication with family members or caregivers) and performed only in the presence of a pulmonologist or respiratory therapist (see Clinical Scenario 1). It is sometimes helpful to deflate the cuff only partially in patients who tend to lose too much of the inspired tidal volume through an open larynx. The recommended procedure for initial cuff deflation is described in "Important Cautions" below.

CLINICAL SCENARIO 1

Mrs. Z was a 52-year-old woman with breast cancer that had metastasized to her lungs, causing her to be very short of breath and unable to breathe on her own. She obtained relief from assisted ventilation via a tracheostomy and could not be weaned from the ventilator. She was frustrated by not being able to speak to her caregivers, husband, and daughters about the nature and intensity of the care she wished to receive and about her impending death. Communication by writing was tedious. She was advised that the cuff of her tracheostomy tube could be deflated so that she could speak, but that she would likely experience periods of breathlessness at first while ventilator adjustments were being made. She was very fearful of this, but with encouragement and reassurance the procedure was successful. For several minutes at a time, with only slight shortness of breath, she was able to speak and communicate her wishes to her family. She went home on the ventilator and died peacefully there.

After cuff deflation, the patient's voice should be assessed. If voice problems are noted, the resistance to "bypass" gas flow around the cuff should be estimated to determine if it is sufficiently low to allow good vocalizing. Bypass resistance can be estimated by blocking expiratory flow where it exits the ventilator and observing tracheal pressure during expiration. When the resistive pressure drop is less than 5 cm H_2O, cuff deflation is generally successful, but when pressure exceeds 10 cm H_2O, cuff deflation often fails. Bypass resistance can usually be reduced by downsizing the tracheostomy tube. If the patient still cannot vocalize, the upper airway, larynx, and upper trachea should be viewed via nasendoscopy to rule out conditions such as excessive secretions, laryngeal edema, granulation tissue, tracheal scar formation, or vocal fold paralysis.

Figure 56-1 illustrates the flow routes for inspiration and expiration with an inflated cuff (closed system) and deflated cuff (open system). When the cuff is inflated, no flow reaches the larynx. When the cuff is deflated, flow reaches the larynx during inspiration and expiration, making it theoretically possible to produce speech during both phases of the ventilator's cycle. The ventilator's settings, however, are strong determinants of when within the cycle speech can be produced. Speech produced with InPPV is often plagued by long pauses, short phrases, variable loudness, and variable voice quality.[30,33,34] These speech features are most easily explained by relating them to the tracheal pressure.

Speech Production with Volume-Controlled Ventilation

Figure 56-2 illustrates tracheal pressure with volume-controlled ventilation compared with that of normal speech production. During normal speaking pressure is low and constant. This steady pressure allows vocal fold oscillations to be relatively constant in amplitude and waveform, translating perceptually to relatively constant loudness and voice quality. Also, pressure remains above the vocalizing threshold throughout expiration.

By contrast, during volume-controlled InPPV pressure rises quickly during inspiration, falls sharply when the expiration valve opens, and then remains below the vocalizing threshold for a substantial portion of the cycle. The rapidly changing pressure is the primary cause of loudness and voice quality problems, and the periods of low pressure (below the vocalizing threshold) explain the long pauses and the short phrases.

Ventilator Adjustments That Can Improve Speech

Abnormal magnitude and time course of tracheal pressure are at the root of the speech problems associated with volume-controlled InPPV. Therefore, the unifying principle for improving speech is to adjust the ventilator so as to generate a pressure that is better suited for speech production, while accommodating the patient's respiratory needs and comfort. Ventilator adjustments to improve speech are designed to (a) increase the portion of the cycle during which pressure remains above the vocalizing threshold (i.e., at least 2 cm H_2O), and (b) reduce the rate and magnitude of pressure changes during the period in which speech is produced. Many adjustments are possible, and the optimal combination for a given patient must be determined empirically.

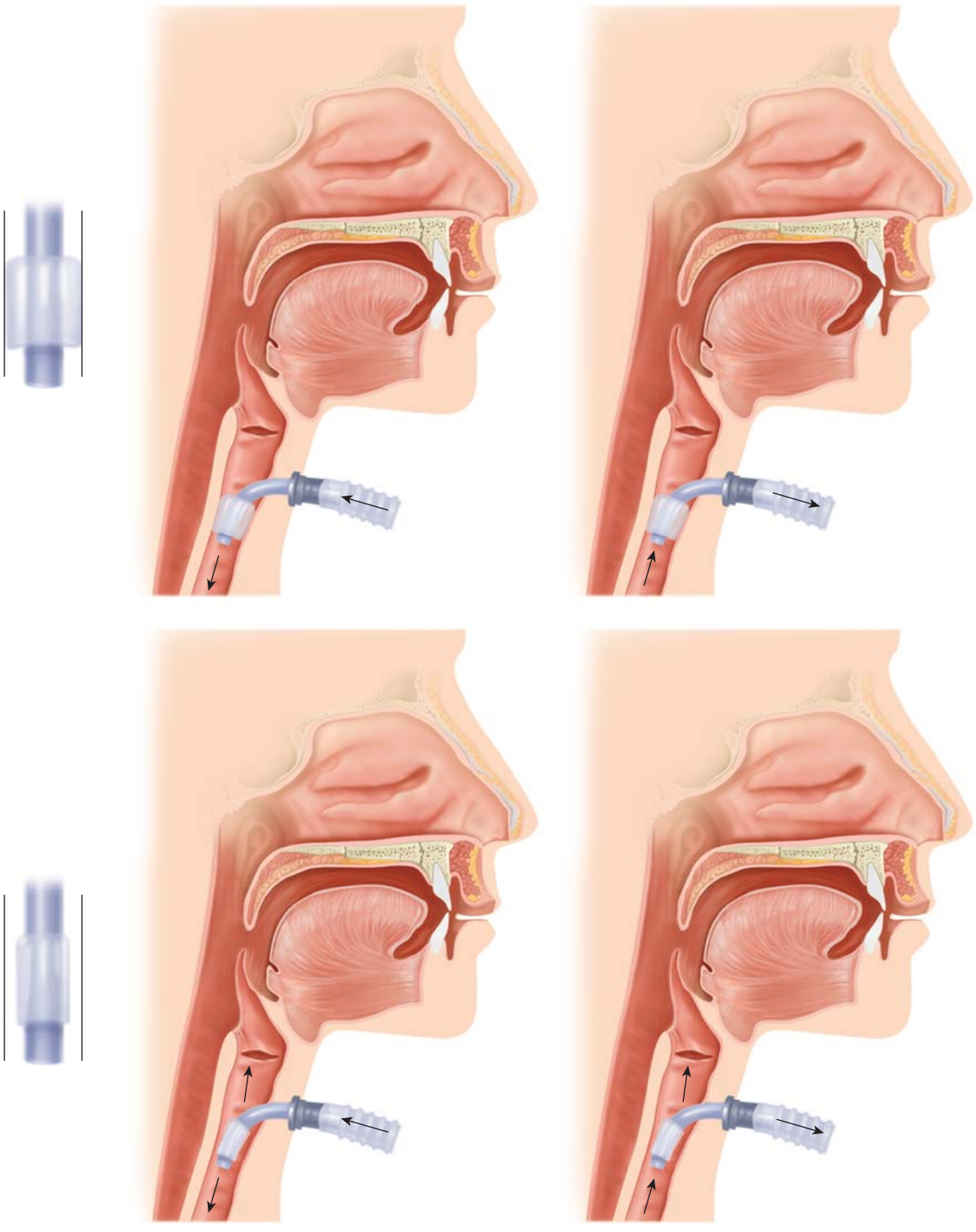

FIGURE 56-1 Inflated and deflated tracheostomy tube cuff during inspiration (*left*) and expiration (*right*). When the cuff is inflated, no flow reaches the larynx, and when the cuff is deflated, flow reaches the larynx during both inspiration and expiration. (Adapted and used, with permission, from Hixon and Hoit.[11])

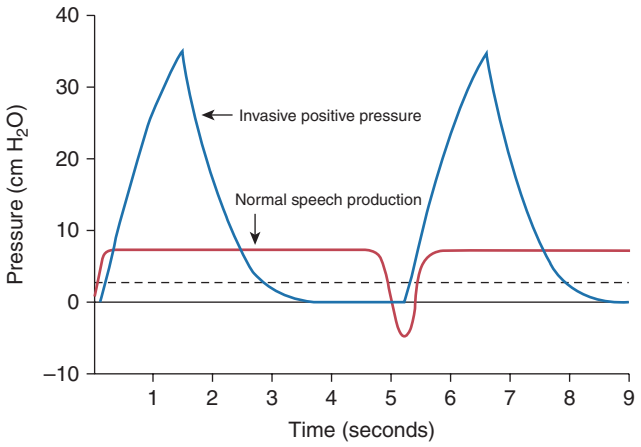

FIGURE 56-2 Tracheal pressure during volume-controlled InPPV and during normal speech production. The *dashed line* shows the minimum pressure needed for vocalizing. (Used, with permission, from Hixon and Hoit.[11])

The success of this approach has been well documented in patients with spinal cord injury and neuromuscular disease,[30,34–36] and is likely to be effective in others. Examples of ventilator adjustments and their predicted influences on speech are given below.

LENGTHENED INSPIRATORY TIME, POSITIVE END-EXPIRATORY PRESSURE, AND REDUCED TIDAL VOLUME

One of the easiest and most successful adjustment combinations is lengthened inspiratory time and the application of positive end-expiratory pressure (PEEP). When inspiratory time is lengthened, more speech can be produced during the inspiratory phase of the ventilator's cycle, because pressure is above the vocalizing threshold for a longer period. In general, as inspiratory time increases, the amount of speech produced during inspiration increases. Also, because the rate of pressure change is more gradual when inspiration is prolonged, loudness and voice quality variability may be reduced. The addition of PEEP extends speaking time during the expiratory phase by adding resistance to the ventilator's expiratory line, which keeps pressure above the vocalizing threshold longer. In most cases, pressure will eventually fall to zero secondary to flow through the larynx.

Sometimes it is physiologically appropriate to also reduce the ventilator-delivered tidal volume in patients whose tidal volumes are too large. When tidal volume is reduced, peak pressure is lowered, which helps to smooth out loudness and voice quality. Although patients are usually uncomfortable when tidal volume is reduced, they are often comfortable if PEEP is added first.

An example of the effect of these adjustments on tracheal pressure and the acoustic speech signal is shown in Figure 56-3 as a comparison of a patient's "usual" and "best" ventilator settings. Although the ventilator adjustments resulted in only subtle changes in the pressure waveform, the changes in speech were substantial and easily perceptible to listeners.[30] On average, an increase in inspiratory time of 17% to 25% combined with PEEP of 5 to 10 cm H_2O results in an increase in speaking time of 55% per cycle.[34] As shown in Figure 56-4, the increase in syllables/minute for lengthened inspiratory time and the PEEP adjustment is additive.

PRESSURE-CONTROLLED VENTILATION AND POSITIVE END-EXPIRATORY PRESSURE

Pressure-controlled ventilation (and its variants, such as pressure-support ventilation) target a given airway pressure (rather than a volume). Thus, inspiration may be associated with a relatively steady pressure, somewhat similar to that associated with normal speech production (except higher). With this form of ventilation, pressure remains above the vocalizing threshold throughout inspiration. And, when pressure is steady, loudness and voice quality are more apt to be constant. When PEEP is added, pressure can be maintained above the vocalizing threshold during expiration. Figure 56-5 shows that vocalizing can continue throughout the entire ventilator cycle[35] (as it can with appropriate volume-controlled adjustments).

POSITIVE END-EXPIRATORY PRESSURE REPLACES A ONE-WAY VALVE

A one-way valve can improve speech in a patient with a tracheostomy who breathes spontaneously with a tracheostomy (see Chapter 40). Such a valve can also improve speech in a patient with InPPV; however, its use with InPPV can be dangerous. For instance, if the tracheostomy tube cuff is inflated and the valve is inadvertently left in place, the patient cannot expire. This can be lethal by causing asphyxia, by impeding venous return, or, if the pressure-limit device fails, by rupturing the lungs. A safer approach is to add PEEP.[37] With PEEP (Fig. 56-6), speech can be indistinguishable from that produced with a one-way valve,[34] even with PEEP as low as 5 cm H_2O.[38]

RISKS AND BENEFITS OF VENTILATOR ADJUSTMENTS

Ventilator adjustments can have adverse effects if not properly chosen and implemented. For instance, when inspiratory time is lengthened with volume-controlled ventilation, the patient may hypoventilate while speaking, because there is more time for inspiratory flow to "bleed off." If this happens, most patients experience air hunger and intuitively stop speaking to catch their breath,[39,40] but patients with diminished chemosensitivity may be at risk. If too much of the total cycle is devoted to inspiration, the shortened expiratory time may lead to dynamic hyperinflation, especially in patients with severe obstructive airways disease. Any adjustment that excessively increases intrathoracic pressure may reduce cardiac output and impede venous return. To

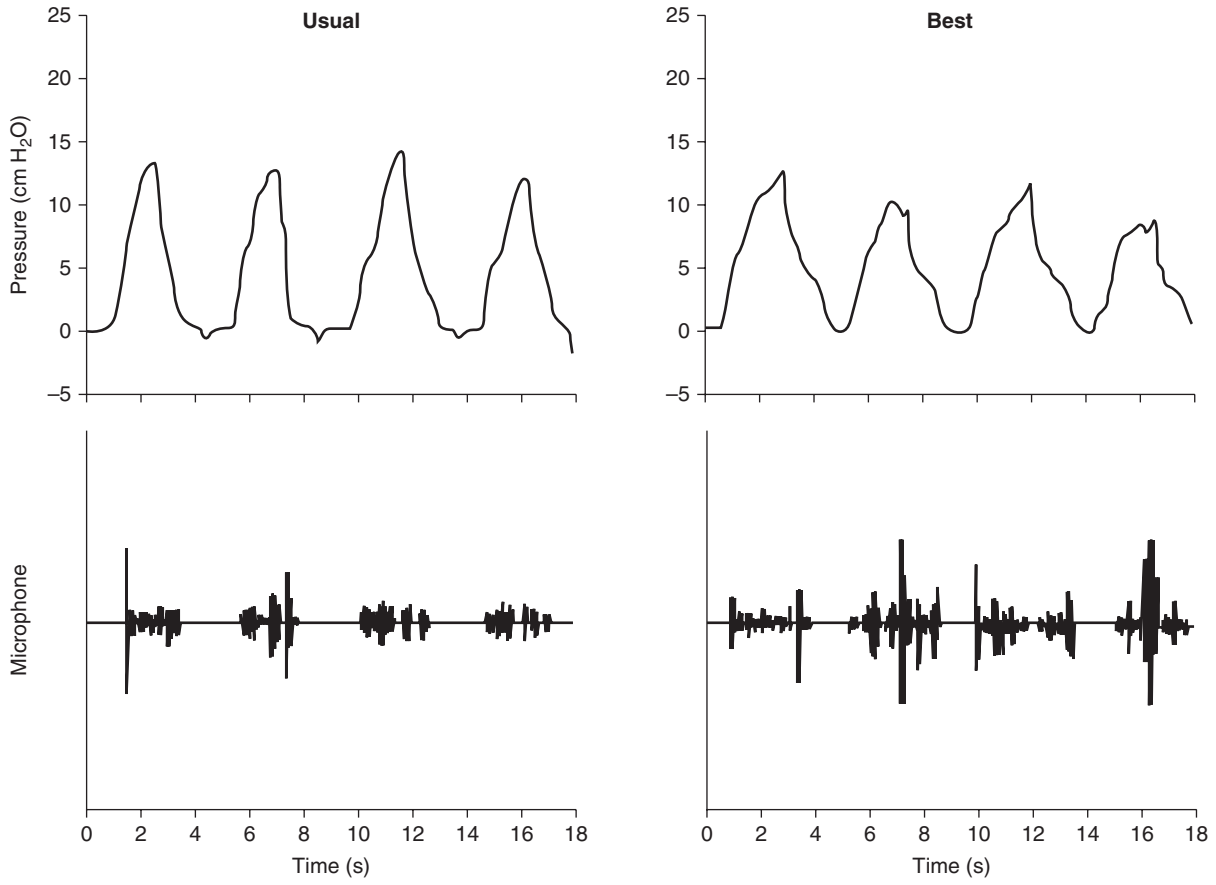

FIGURE 56-3 The tracheal pressure and speech signal under the usual (*left*) and best (*right*) ventilator conditions. The best settings represented the following adjustments: (a) inspiratory time was lengthened by 0.5 second; (b) 4 cm H_2O of PEEP was added; and (c) tidal volume was reduced by about 0.3 L. (Adapted and used, with permission, from Hoit and Banzett.[30])

minimize this risk, the lowest level of PEEP adjustment that reaps adequate speech improvement should be used, and dynamic hyperinflation (intrinsic PEEP) should be assessed following any changes to the ventilator. Also, ventilator adjustments can cause patient discomfort (e.g., "not enough air" or "too much pressure"). The potential for discomfort may be lessened if adjustments are made gradually and in small steps. Fortunately, most adjustments that improve speech also fortuitously improve comfort. Although there are risks to ventilator adjustments, they are usually minimal, especially when compared to the more serious risks posed by a one-way valve.

The most obvious benefits of these ventilator adjustments include improved speech, decreased speaking effort, and,

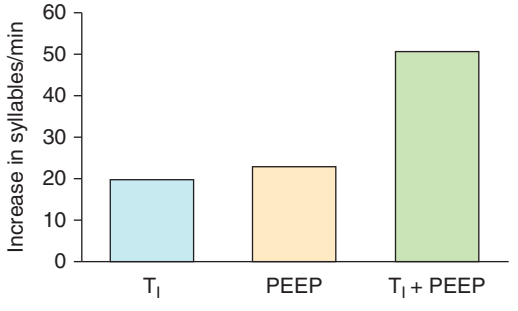

FIGURE 56-4 Changes (from usual) in syllables/minute for lengthened inspiratory time, PEEP, and combined lengthened inspiratory time (T_I) and positive end-expiratory pressure (PEEP). (Adapted and used, with permission, from Hoit et al.[34])

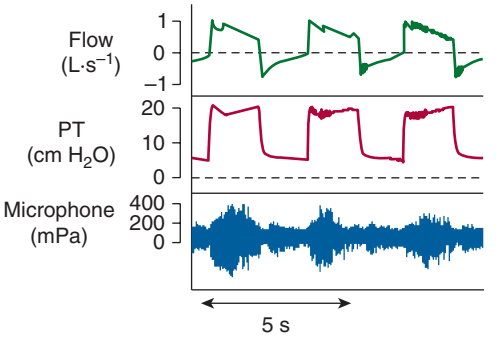

FIGURE 56-5 Flow, pressure, and speech signal during sustained vowel production with pressure-targeted ventilation and PEEP. (Reprinted with permission of the American Thoracic Society. Copyright © American Thoracic Society. Prigent H, Samuel C, Louis B, et al. Comparative effects of two ventilatory modes on speech in tracheostomized patients with neuromuscular disease. *Am J Respir Crit Care Med.* 2003;167:114–119. Offical Journal of the American Thoracic Society.)

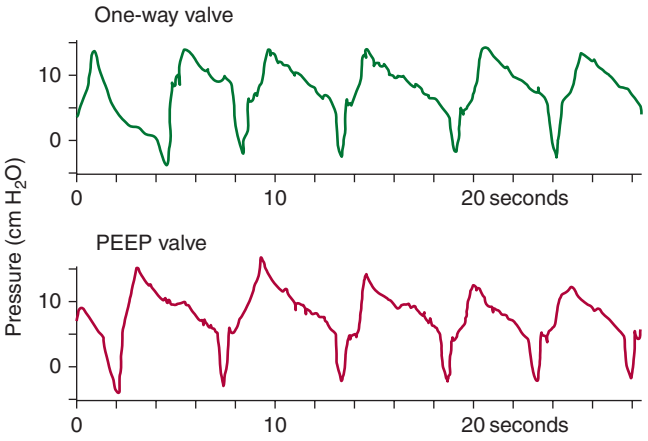

FIGURE 56-6 Tracheal pressure during speaking with a one-way valve and with positive end-expiratory pressure (PEEP) set to 15 cm H_2O. (Adapted and used, with permission, from Hoit et al.[34])

in some cases, increased breathing comfort. There may be other benefits as well. For example, if a patient is chronically hyperventilated,[41] speech adjustments may move ventilation toward normal (e.g., because the patient is comfortable with a smaller tidal volume if PEEP is applied; see Clinical Scenario 2).

CLINICAL SCENARIO 2

JT, a man with a C2 spinal cord injury and InPPV, was referred to the speech-language pathologist for a speech evaluation. The evaluation revealed that JT spoke in short phrases (three to four syllables per breath) with excessively long pauses (up to 5 seconds), and he complained that he was "interrupted all the time." The speech-language pathologist recommended to JT's pulmonologist that ventilator adjustments be tested to improve his speech. The pulmonologist agreed and wrote the order, adding that "if the ventilator adjustments can also reduce his ventilation, that would be a bonus." Ventilator adjustments were tested (with the pulmonologist, respiratory therapist, and speech-language pathologist present) and it was found that lengthened inspiratory time, a PEEP adjustment, and reduced tidal volume improved his speech dramatically. Preadjustment and postadjustment measures revealed a moderate increase in arterial partial pressure of carbon dioxide (P_{CO_2}) (from 22 to 29 torr) and greater breathing comfort. The patient, his speech-language pathologist, his pulmonologist, and his family and friends were delighted with the outcome.

Behavioral Interventions That Can Improve Speech

Once appropriate ventilator adjustments have been made, behavioral interventions, guided by a speech-language pathologist, may further improve speech (see reference 11 for an extensive discussion of this topic). For example, linguistic strategies may be helpful for patients who continue to have long pauses between phrases despite ventilator adjustments. These linguistic strategies might take the form of pausing at appropriate linguistic junctures (e.g., at phrase, clause, or sentence boundaries) when speaking didactically, but intentionally pausing at inappropriate linguistic junctures (e.g., within a phrase or following a conjunction) when speaking conversationally to reduce the likelihood of being interrupted. It may be useful to teach buccal speech (i.e., "Donald Duck"-type speech) as a compensatory strategy. This type of speech, which is produced entirely within the upper airway and requires no drive from chest wall muscles,[42] can be used to add a syllable or two after the pressure has fallen below the vocalizing threshold.

SPEECH WITH OTHER FORMS OF VENTILATOR SUPPORT

Whereas speech can be produced during both inspiration and expiration with InPPV, it is produced only during expiration with other forms of ventilator support (see Table 56-1 and Chapters 16, 17, 18, and 62). Although research is sparse, ventilator adjustments and behavioral interventions have strong potential to improve speech produced with these other forms of ventilator support. Noninvasive positive-pressure ventilation (NPPV) and phrenic nerve pacer ventilation are discussed below as illustrations of how this might be done.

TABLE 56-1: SUMMARY OF SPEECH PRODUCED USING DIFFERENT TYPES OF VENTILATOR SUPPORT

Type of Ventilator Support	Speech Production	Can Ventilator Adjustments Improve Speech?	Can Behavioral Interventions Improve Speech?
Invasive positive pressure	Inspiration/ expiration	Yes	Yes
Noninvasive positive pressure	Expiration	Yes	Yes
Negative pressure	Expiration	Yes	Yes
Phrenic nerve pacer	Expiration	Yes	Yes
Rocking bed	Expiration	No	Yes
Abdominal pneumobelt	Expiration	Yes	Yes

Included here are the phase(s) of the ventilator cycle during which speech is produced and whether or not ventilator adjustments and behavioral interventions have potential to improve speech.

Noninvasive Positive-Pressure Ventilation

An important speech consideration when using NIPPV is selection of the patient-ventilator interface.[43] Choices for interfaces include mouthpieces, nasal pillows, nasal masks, and face masks. Of these, the clear choice for speech breathing is a mouthpiece that is not secured to the patient's mouth. To use this interface, the patient places his or her lips around the mouthpiece during inspiration and pulls the lips away during expiration. Thus, the patient's face is completely unencumbered during speech production. The next best interface options are nasal interfaces, because they allow the lips and jaw to move freely during speaking. Nevertheless, they encumber the nasal airway and can distort nasal consonants (*m*, *n*, and *ng*, in English). By far the least desirable interface is the face mask, because it encumbers both the oral and nasal airways, dampens and distorts the speech signal, and removes visual cues that a listener might use to help compensate for reduced intelligibility.

For many patients who use NIPPV, one of the best strategies for improving speech is to increase inspiratory volume.[11] In the case of the patient with neurologically complete chest wall paralysis, pressure (and loudness) at the beginning of expiration is determined primarily by inspiratory volume and respiratory system elastance, and the rate at which pressure drops (and loudness decreases) is determined by the rate at which volume is expended during speaking. By increasing inspiratory volume, speech can be louder (at least at the beginning of expiration) and last longer.

One way to increase inspiratory volume is to adjust the ventilator's tidal volume. Another way is to train the patient to use glossopharygneal breathing. Glossopharyngeal breathing can be effective, not only for increasing tidal volume, but also for replenishing volume (and pressure) while speaking.[44]

Phrenic Nerve Pacer Ventilation

In patients with paralysis from cervical spinal cord injury, speech with phrenic nerve pacer ventilation may be characterized by low loudness, fading loudness, short breath groups, and long inspiratory pauses.[45] Phrenic nerve pacers can be adjusted, within limits, to alter tidal volume, breathing frequency, and inspiratory time.[46] Such adjustments can increase speech loudness and duration and decrease the length of inspiratory pauses.

Tidal volume can be increased by applying an abdominal binder.[47,48] An abdominal binder or truss can improve speech in patients with chest wall paralysis who use phrenic nerve pacers[49] as well as in those who can breathe on their own.[50,51] Speech improvements include louder speech, longer breath groups, and better voice quality. Glossopharyngeal breathing is also a good strategy for increasing tidal volume in patients who use phrenic nerve pacers.

WHICH PATIENTS ARE CANDIDATES FOR SPEECH INTERVENTIONS?

Many of the speech interventions described in this chapter have been tested systematically in patients with neuromotor impairments who were chronically ventilated. Nevertheless, acutely ventilated patients, including those with other medical conditions, are also candidates for these interventions, especially cuff deflation. Cuff deflation and speech training are performed routinely in the postcritical respiratory care stepdown unit and even in the intensive care units at Massachusetts General Hospital.

There are several issues to consider when determining if a patient is a candidate for ventilator adjustments. Most importantly, ventilator adjustments must be deemed medically safe and should not be attempted if the pulmonologist, cardiologist, or other physician judges them to be unsafe for a given patient. The patient should also have motivation to speak, functional cognitive and language skills, and adequate laryngeal and upper airway control to benefit from such adjustments.

Behavioral interventions can be even more broadly applied than ventilator adjustments. There is a vast repertoire of behavioral interventions that include strategies for improving speech intelligibility, use of augmented communication, and many others.

IMPORTANT CAUTIONS

The initial deflation of the tracheostomy tube cuff should be done in a cautious and organized manner. To begin, the patient should be advised to expect flow of air through the mouth (as many are surprised by the sensation). Before deflating the cuff, the patient's oropharynx should be suctioned thoroughly and adequate oxygen saturation should be assured (often by increasing the fractional inspired oxygen concentration). An anesthesia bag supplied by oxygen should be attached to the tracheostomy tube and, at the moment of cuff deflation, a positive-pressure breath should be given to propel secretions that lie between the larynx and cuff into the pharynx for further suctioning. This technique minimizes aspiration of the retained secretions.

Cuff deflation usually causes patients to cough, likely from secretions above the cuff that move distally. If the cough does not subside quickly, it is useful to instill 5 mL of 2% lidocaine into the tracheostomy tube and occlude the opening of the tube briefly. The lidocaine will anesthetize the distal trachea and, when the patient coughs, the lidocaine will be propelled above the cuff as well. Patients who have had endotracheal intubation before tracheostomy are at increased risk for aspiration secondary to laryngeal dysfunction and should be evaluated accordingly before more than brief cuff deflation.

Cuff deflation may cause hypoventilation, hypoxemia, or dyspnea because some of the ventilator-delivered inspiration exits through the larynx. Thus, it is important to increase the tidal volume during cuff deflation. In addition, it may be

beneficial to deflate the cuff only partially, rather than completely. The added resistance through the laryngeal pathway results in more of the ventilator-delivered tidal volume reaching the lungs.

Although dynamic hyperinflation and intrinsic PEEP are observed rarely when inspiratory time is lengthened, it is nevertheless a risk in patients with obstructive lung disease. Positive end-expiratory intrathoracic pressure can lead to decreased cardiac output and hypotension. Cardiovascular reflexes usually compensate, but may be impaired in patients with autonomic dysfunction. These include patients with diabetes or with neurologically complete cervical spinal cord injury (particularly during the phase of spinal shock).

Ventilator adjustments to improve speech should only be made with the approval and oversight of a pulmonary or critical care physician. While adjustments are being made, cardiopulmonary variables should be monitored (e.g., O_2 saturation, heart rate, and blood pressure), and the patient should be systematically asked about comfort (see Chapter 55).

ALTERNATIVES TO VENTILATOR-SUPPORTED SPEECH

Sometimes it is impossible for a patient to speak. When this results from severe laryngeal and/or upper airway impairment, it is usually necessary to provide the patient with augmentative and alternative communication (see Chapter 40). Some patients, however, with good laryngeal and upper airway function can benefit from a talking tracheostomy tube,[8,52,53] which provides a separate air source to produce speech while the tracheostomy tube cuff is inflated (Fig. 56-7). Flow is adjusted to determine what produces the best voice quality and is comfortable for the patient.[52,54,55] Common problems include discomfort from drying of the mucosa, crimping of the tubing, inability to vocalize, and inability to turn the air source on or off independently.[56]

Another device is called a voice tracheostomy tube.[57] The cuff on this specially constructed tracheostomy tube inflates during inspiration (preventing speech production) and deflates during expiration. Thus, nearly all of the ventilator-delivered inspiration reaches the patient's lungs, whereas some or all of the expired air can be used for speaking. A newer tracheostomy tube operates on similar principles and incorporates additional safety measures.[58] These devices may be useful for patients with poor laryngeal control, but most patients can speak using a conventional tracheostomy tube with a deflated cuff and some form of volume compensation.[59]

ROLES OF HEALTH CARE PROFESSIONALS

Speech management for patients who are ventilator-supported requires a team of health care professionals. Pulmonary and critical care physicians and respiratory therapists operating under them can make substantial improvements in speech. Speech-language pathologists can further optimize speech by evaluating speech, language, and communication, and recommending a management plan to the medical team. If evaluation or management includes ventilator adjustments, it is important for a physician or suitable proxy to be present to assess cardiopulmonary effects of the adjustments as they are made. The physician in charge must decide whether such adjustments should be made permanently or only when essential for communication. Behavioral interventions (such as glossopharyngeal breathing and linguistic strategies) can be offered by the speech-language pathologist.

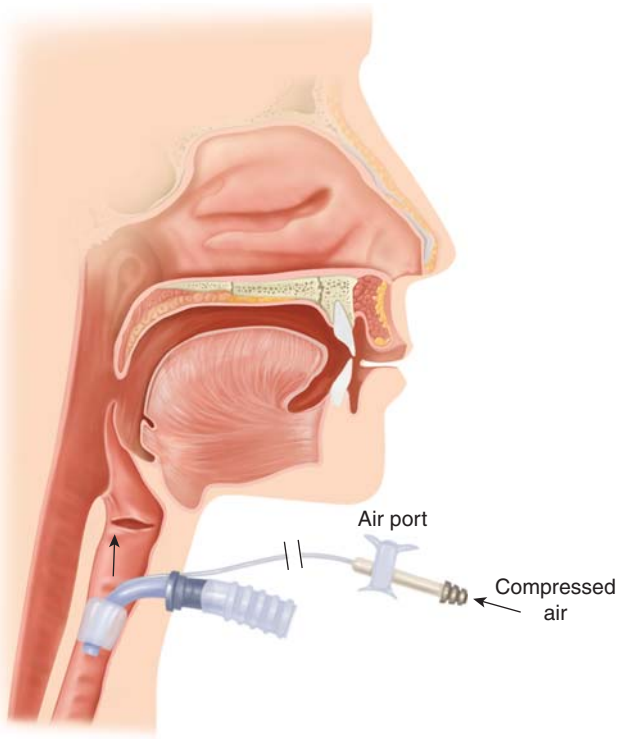

FIGURE 56-7 Talking tracheostomy tube. The air port is occluded to route flow from a compressed air source to the larynx for speaking. (Used, with permission, from Hixon and Hoit.[11])

IMPORTANT UNKNOWNS AND FUTURE RESEARCH

Research on ventilator-supported speech has largely been limited to patients with spinal cord injury and neuromuscular disease. Much needs to be learned about the influence of ventilator adjustments on speech in other patients, especially those with obstructive airways disease. The speech effects of ventilator adjustments with certain forms of ventilator support (such as NIPPV) and various behavioral interventions also have yet to be studied systematically.

SUMMARY AND CONCLUSIONS

For most people, speech is an important requisite to good quality of life. Thus, a patient should be given the opportunity to speak, if medically possible. For the patient who is ventilated invasively, this means deflating the tracheostomy tube cuff. For the patient who is already able to speak, there are often ways to improve speech by modifying the tracheal pressure. Ventilation requirements always have primacy over speech improvements, but these are often complementary, rather than competing, goals. A patient's speech can be optimized through the collaborative efforts of competent and creative physicians, respiratory therapists, and speech-language pathologists.

ACKNOWLEDGMENTS

This chapter is dedicated to the late Susan Kropoff, who used a ventilator for nearly 40 years, and who has taught us more about ventilator-supported speech than anyone else we know. We are grateful to Thomas J. Hixon and Robert W. Lansing for their helpful suggestions on this chapter.

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SLEEP IN THE VENTILATOR-SUPPORTED PATIENT

Patrick J. Hanly

It is well recognized that sleep is abnormal in mechanically ventilated patients in the intensive care unit (ICU). Although this has been described for decades, there is still no consensus on the underlying pathogenesis and the best way to manage it. Moreover, the assumption that abnormal sleep is not good for patients who are critically ill is based primarily on extrapolation from models of sleep loss and sleep disruption in other patient populations and not on evidence that abnormal sleep affects the clinical outcomes of patients in the ICU. Nevertheless, there is growing interest in this topic as the technology to measure sleep evolves and new ways are sought to improve patients' ability to recover from their critical illness. This chapter outlines the current understanding of the causes and potential consequences of sleep disruption in ventilator-supported patients and how this may be further researched and treated.

NORMAL SLEEP

Sleep is objectively assessed by means of polysomnography, the simultaneous recording of several electroencephalographic and physiologic parameters.[1] Sleep periods are classified as non–rapid eye movement (NREM) and rapid eye movement (REM) sleep. NREM sleep is further subdivided into four stages, with stages 3 and 4 also referred to as slow-wave sleep (SWS). Each sleep stage is recognized by characteristic changes on the electroencephalogram and, in addition, REM sleep has distinctive, intermittent rapid eye movements. During normal sleep, periods of NREM and REM alternate throughout the night in a recognizable pattern, so that most SWS occurs during the first half of the night and most REM sleep occurs during the second half (Fig. 57-1). The "normal" duration of sleep required and the proportion of time spent in each stage of sleep depends on many factors including age and genotype.[2] In healthy, middle-aged individuals, however, nocturnal sleep lasts 7 to 8 hours, and 5% to 10% of that time is spent in stage 1 NREM sleep, 50% in stage 2 NREM sleep, 15% to 20% in SWS, and 25% in REM sleep.[1] There are also standardized electroencephalographic criteria for identifying arousals and awakenings on the polysomnograph;[3,4] up to 10 arousals per hour of sleep is considered to be within normal limits.[5] The term *sleep architecture* refers to the amount of time spent in each sleep stage and *sleep disruption* is reflected by an increased frequency of arousals and awakenings.

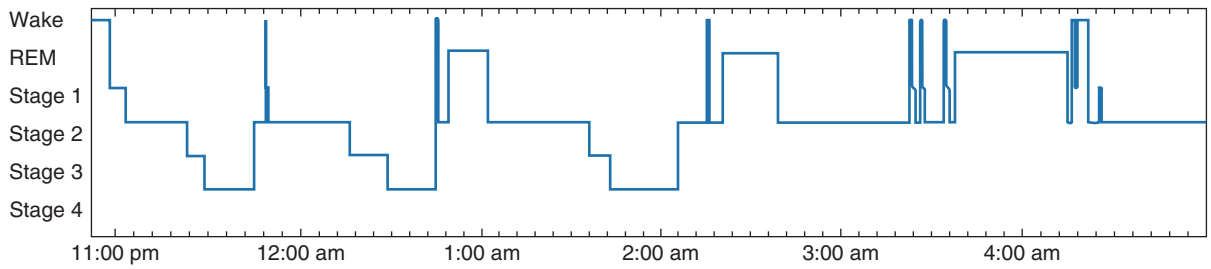

FIGURE 57-1 Normal sleep (nocturnal hypnogram). *Vertical axis: REM,* rapid eye movement sleep; *NREM,* non–rapid eye movement sleep stages 1, 2, 3, and 4. *Horizontal axis:* Time in hours.

SLEEP IN THE INTENSIVE CARE UNIT

Patient Perception

When questioned after discharge from the ICU, patients consistently report sleep disruption during their stay.[6–11] In one study,[10] 200 patients from four different ICUs received questionnaires that evaluated the quality of their sleep at home and in the ICU and the effect of noise and a variety of activities (such as nursing interventions, phlebotomy, and diagnostic procedures) on their sleep quality. Sleep quality in the ICU was perceived as significantly poorer than sleep quality at home. In addition, sleep quality did not change significantly over the course of the ICU admission, and no differences were reported between ICUs or between ventilated and nonventilated patients. Ventilated patients, however, reported greater daytime sleepiness, perhaps because of the greater administration of sedatives or more severe illness. Patients selected the recording of vital signs and phlebotomy as the most sleep-disrupting environmental factors. Noise was not rated as the primary cause of sleep disruption; of the many forms of environmental noise stimuli, however, communication between staff members and telemetry alarms were perceived as the most disruptive. Although very thorough in design and statistical analysis, the study was limited by potential recall bias, lack of objective sleep assessment by polysomnography, and the absence of a control group.

Polysomnography

Since the mid-1970s, numerous polysomnographic studies in ICU patients have consistently revealed both sleep fragmentation and sleep loss.[6,12–19] Hilton[6] studied nonventilated patients by 24-hour polysomnography and found a decreased total sleep time, an increase in stage 1 NREM sleep, and a concomitant decrease in SWS and REM sleep. Hilton also observed an apparent uncoupling of sleep from the day–night circadian pattern: Only 50% to 60% of sleep occurred at night.[6] These characteristic sleep patterns have also been observed in subsequent 24-hour polysomnography studies.[12,16,20]

Cooper et al investigated sleep in ventilated patients in the ICU and categorized patients into three groups based on polysomnographic findings: disrupted sleep, atypical sleep, and coma.[12] As seen in other ICU cohorts, patients in the disrupted sleep group (Fig. 57-2) showed the abnormal temporal distribution of sleep described earlier as well as reduced amounts of SWS and REM sleep and an increased frequency of arousals and awakenings. Patients in the atypical sleep group had electroencephalogram (EEG) features intermediate between sleep and coma, characterized by a virtual absence of stage 2 NREM sleep and REM sleep (Fig. 57-3). In addition, patients displayed "pathologic wakefulness," where behavioral correlates of wakefulness (such as saccadic eye movements and sustained chin muscle activity) coincided with EEG features of SWS (Fig. 57-4). The coma group was characterized by EEG features of coma according to the classification of Young et al.[21] The authors concluded that sleep could not be identified by polysomnography in all critically ill patients. They proposed the following criteria to select ICU patients in whom sleep can be reliably measured by polysomnography: acute physiology score less than 13, Glasgow Coma Scale score greater than 10, and sedative doses of lorazepam equivalents and morphine equivalents less than 10 mcg/kg per hour. These cutoffs approximated the point estimate of the atypical sleep group. Subsequent data suggest that sleep disruption can be measured by polysomnography in approximately 50% of patients in a general ICU.[22]

Once polysomnography has been performed, what is the most reliable way to score sleep in the ventilator-supported patient? Sleep is conventionally assessed by manual scoring of the EEG according to the criteria of Rechtschaffen and Kales.[4] The reliability, however, of this methodology to score sleep in the critically ill patient has been questioned.[23] Ambrogio et al compared manual scoring of sleep in fourteen ventilator-supported patients in the ICU and seventeen age-matched ambulatory patients in the sleep laboratory and reported that interobserver and intraobserver reliability was weaker for critically ill patients ($k = 0.52 \pm 0.23$) than for those in the sleep laboratory ($k = 0.89 \pm 0.13$; $P = 0.03$). Furthermore, they suggested that computer-based spectral analysis of the EEG with fast Fourier transformation is a better way to monitor sleep in this patient population. It appears that improved

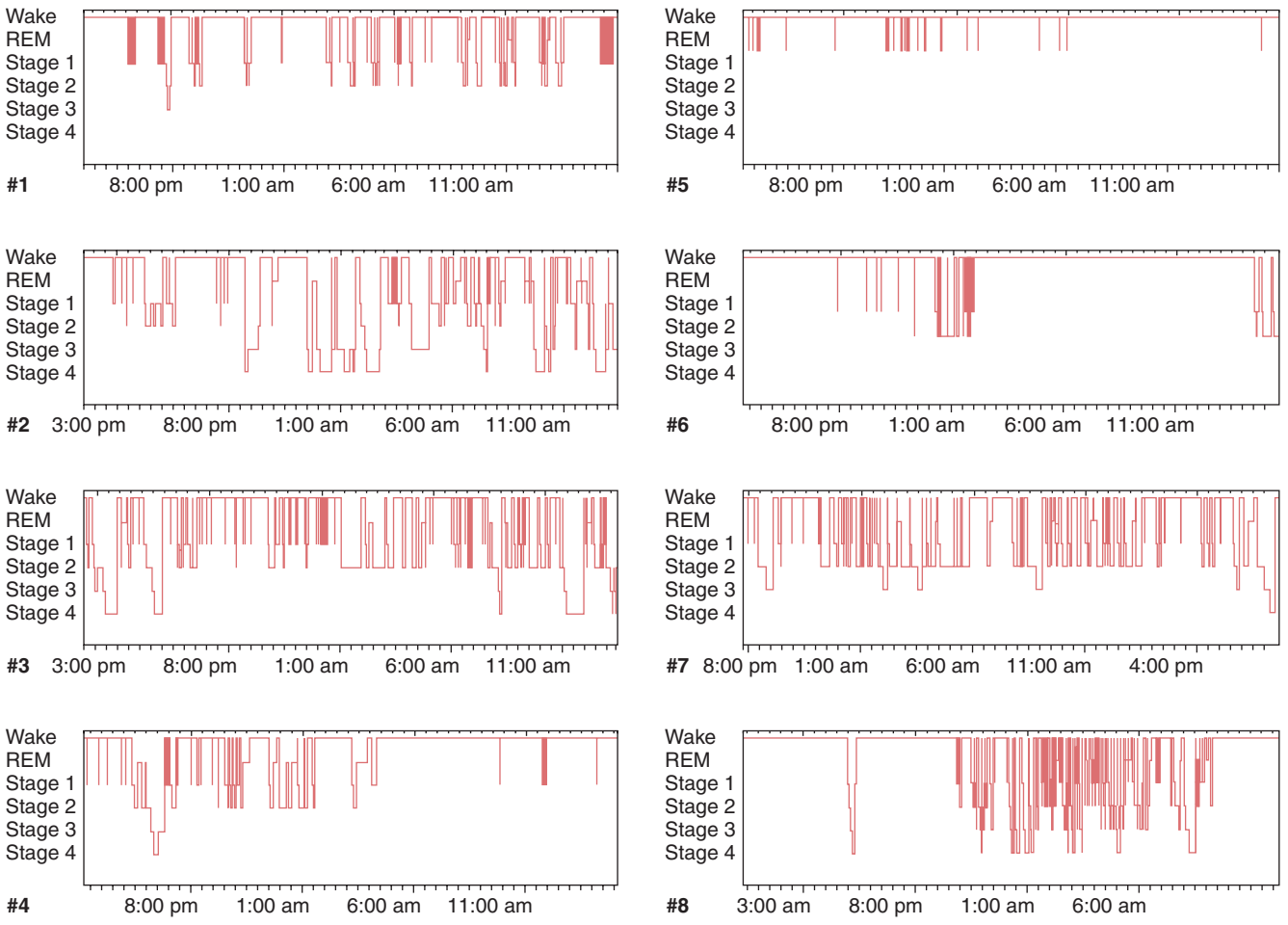

FIGURE 57-2 Disrupted sleep in the ICU (24-hour hypnograms in eight patients). *Vertical axis: REM*, rapid eye movement sleep; *NREM*, non–rapid eye movement sleep stages 1, 2, 3, and 4. *Horizontal axis:* Time in hours. Note (1) sleep was distributed throughout the 24-hour period in all patients except patient 8, in whom sleep was predominantly nocturnal; (2) frequent awakenings; and (3) prolonged wakefulness, especially patients 4, 5, and 6. (Reproduced, with permission, from the American College of Chest Physicians, from Cooper AB, Thornley KS, Young GB, et al. Sleep in critically ill patients requiring mechanical ventilation. *Chest.* 2000;117:809–818.)

and innovative analysis of the EEG holds the best promise for further progress, particularly because less-invasive methodologies to monitor sleep such as assessment by the bedside nurse and actigraphy, are unreliable (Fig. 57-5).[24–26]

CAUSES OF SLEEP DISRUPTION IN THE INTENSIVE CARE UNIT

Medical Disorders

Patients may enter the ICU with preexisting medical or sleep disorders, such as asthma or sleep apnea, which cause disruption of sleep if inadequately controlled. More importantly, the acute illness that precipitated the ICU admission, such as major surgery, can disrupt sleep. A very consistent finding in surgical patients is the reduction or absence of both SWS and REM sleep in the immediate postoperative period. This is characteristically followed by "REM rebound," an increase in both the number of phasic eye movements and the overall amount of REM sleep.[13,15,18,19] REM rebound may result from the withdrawal of REM-suppressing medications, such as narcotics,[18] analgesics, and benzodiazepines,[27] and/or a decrease in illness-related sleep disruptors such as pain.

Medications

Several medications can alter sleep. A comprehensive review of this topic has been published.[27–29] Table 57-1 summarizes the effects of some medications that are commonly used in the ICU. Although benzodiazepines can increase total sleep time, they are known to reduce both SWS and REM sleep and are associated with rebound insomnia once they are stopped.[30] Opiates also decrease SWS and REM sleep, increase the amount of wakefulness after sleep onset, and are associated with withdrawal hypersomnolence.[27,30,31] Glucocorticoids are often associated with insomnia[29] and many selective serotonin reuptake inhibitors increase alertness and restlessness, in addition to exacerbating sleep

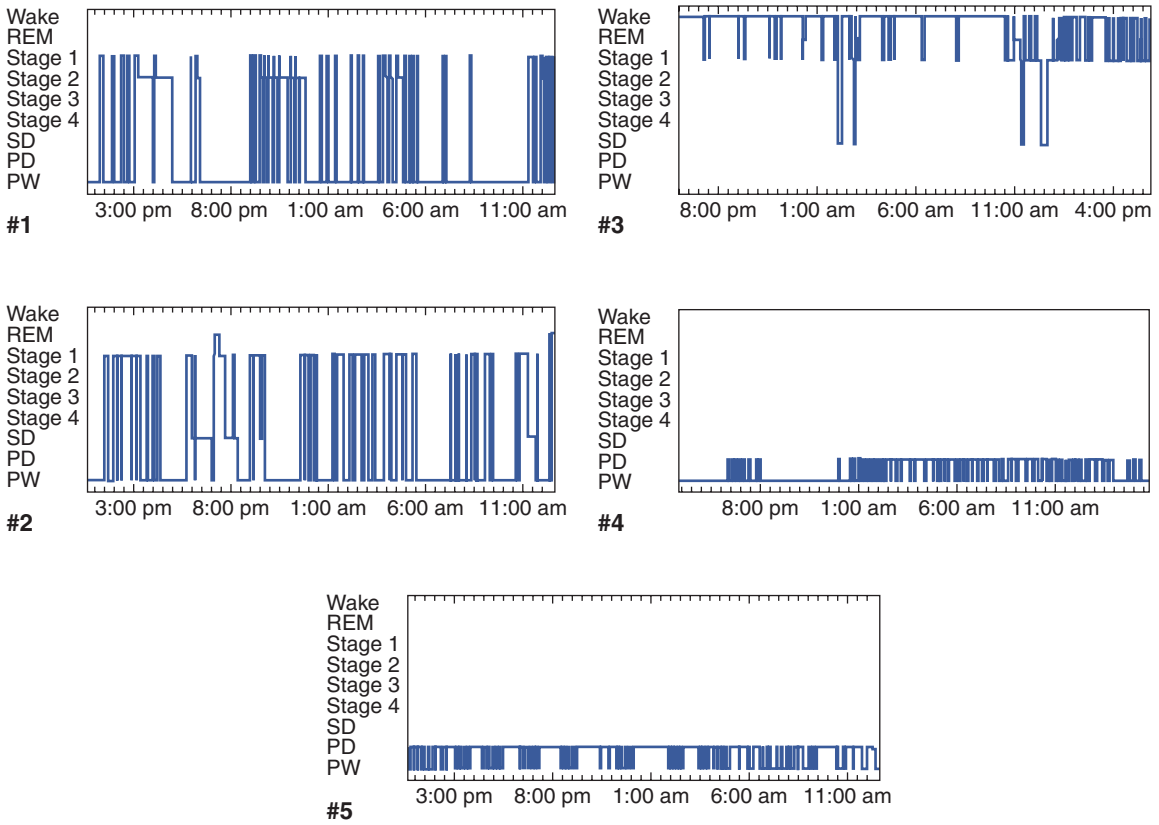

FIGURE 57-3 Atypical sleep in the ICU (24-hour hypnograms in five patients). *Vertical axis: REM*, rapid eye movement sleep; *NREM*, non–rapid eye movement sleep stages 1, 2, 3, and 4; sleep delta (*SD*); pathologic delta (*PD*); and pathologic wakefulness (*PW*). *Horizontal axis:* Time in hours. (Reproduced, with permission, from the American College of Chest Physicians, from Cooper AB, Thornley KS, Young GB, et al. Sleep in critically ill patients requiring mechanical ventilation. *Chest.* 2000;117:809–818.)

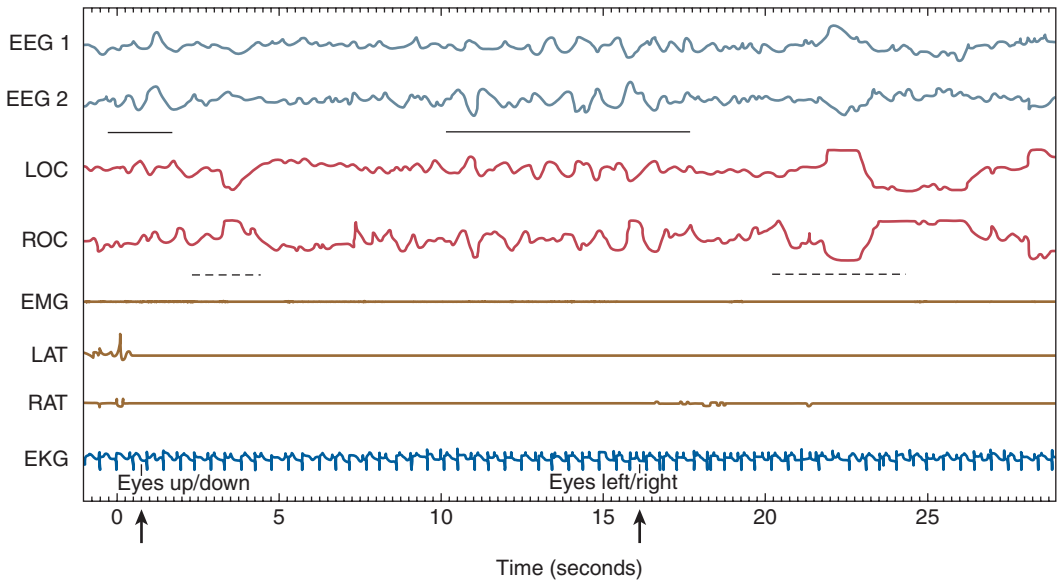

FIGURE 57-4 Pathologic wakefulness during atypical sleep (30-second epoch). *Vertical axis: EEG*, electroencephalogram; *EKG*, electrocardiogram; *EMG*, submental electromyogram; *LAT*, left anterior tibialis EMG; *LOC*, left oculogram; *RAT*, right anterior tibialis EMG; *ROC*, right oculogram. *Horizontal axis:* Time in seconds. Note the slow-wave EEG activity (indicated by the *solid horizontal bar*) during the patient's responses (eye movements, indicated by *broken horizontal lines*) to biocalibration (indicated by a *bold arrow*). (Reproduced, with permission, from the American College of Chest Physicians. Cooper AB, Thornley KS, Young GB, et al. Sleep in critically ill patients requiring mechanical ventilation. *Chest.* 2000;117:809–818.)

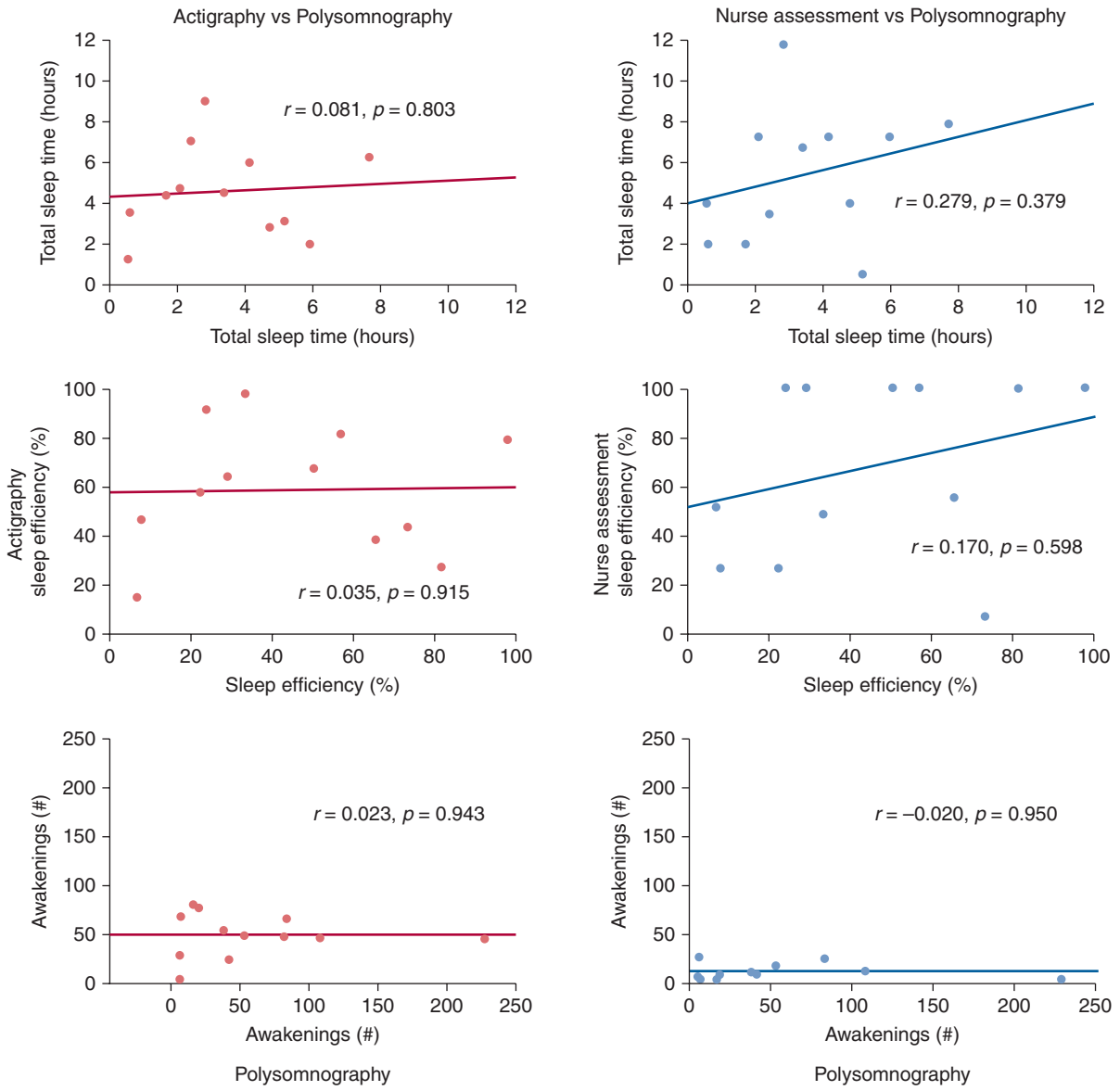

FIGURE 57-5 Total sleep time (total duration of sleep during the recording period), sleep efficiency (total sleep time expressed as a percentage of total recording time), and the number of awakenings during the recording period estimated by actigraphy (customized setting shown) and nurse assessment compared with polysomnographic findings. (Used, with permission, from Beecroft et al.[26])

disorders such as restless leg syndrome and periodic limb movement disorder.[32]

Altered Circadian Rhythm

Almost all biologic functions have a circadian rhythm, which synchronizes interactions both among themselves and with the external environment. Alteration of the circadian rhythm that regulates sleep and wakefulness is a recognized cause of insomnia in patients who are not critically ill[33] and may contribute to sleep disruption in the ICU. The circadian clock has been evaluated in critically ill patients by measuring either core body temperature or melatonin levels in the blood or urine. Two retrospective studies, which measured core body temperature, found that circadian rhythm was absent in 20% to 80% of patients.[34,35] Gazendam et al[36] recorded core body temperature in twenty-one patients and reported that a 24-hour rhythm was detectable in all patients. The rhythm, however, was advanced or delayed by several hours compared with control subjects, and the degree of displacement was correlated with the severity of illness, reflected by Acute Physiology and Chronic Health Evaluation (APACHE) III scores. Several studies have measured melatonin levels in ICU patients.[37–41] Melatonin is secreted by the pineal gland and its release is closely synchronized with sleep in healthy individuals;[42] it starts to rise between 9 and 11 PM, peaks between 1 and 3 AM, and

TABLE 57-1: EFFECTS OF MEDICATIONS ON SLEEP

Medication	Clinical Effects	Changes on Polysomnography
CNS medications		
Narcotics	Varies with agent; withdrawal hypersomnolence	Acute: ↑WASO, ↓SWS, ↓REM
Benzodiazepines	Sedation, withdrawal insomnia	↑TST, ↓SL, ↓W, ↓SWS, ↓REM
Tricyclic antidepressants	Improve sleep; may be sedating	Generally ↑TST, ↓W, ↓REM
Selective serotonin reuptake inhibitors	May worsen sleep; few daytime complaints	Generally ↓TST, ↑W, ↓REM
Barbiturates	Sedation, withdrawal insomnia	↑TST, ↓W, ↑ ↓SWS, ↓REM
Phenytoin	Sedation	↓SL
Carbamazepine	Sedation	↓SL and ↑TST
Cardiac medications		
β-antagonists	Insomnia, nightmares	↑W, ↓REM
α_2-agonists (clonidine, methyldopa)	Insomnia, nightmares, sedation	↑TST, ↑↓REM
αβ-antagonists	Insomnia, fatigue, somnolence	No studies
Diltiazem	Insomnia, abnormal dreams, sleepiness	No studies
Amiodarone	Insomnia, nightmares	No studies
Other medications		
Aspirin	—	Acute: ↓SWS
Glucocorticoids	Insomnia	↑W, ↓REM
Theophylline	Insomnia	↑W, ↓TST

Abbreviations: CNS, central nervous system; *REM,* rapid eye movement sleep; *SL,* sleep latency; *SWS,* slow-wave sleep; *TST,* total sleep time; *W,* wakefulness; *WASO,* wakefulness after sleep onset.

Adapted, with permission, from Wooten[27] and Schweitzer.[29]

falls to low baseline values between 7 and 9 AM. The characteristic nocturnal rise in melatonin is absent in critically ill patients, and this has been correlated with the use of mechanical ventilation,[40,41] sepsis,[39] and the postoperative period.[38] Although altered circadian rhythm may contribute to sleep disruption in the ICU, this has yet to be proven. Moreover, the extent of its role is likely to vary among individual patients depending on factors such as the ICU environment, illness severity, the length of stay, and the impact of competing sources of sleep disruption.

Intensive Care Unit Environment

Several studies have examined the role of light, patient-care activities, and noise in causing sleep disruption in the ICU.[43–49] Meyer et al[47] found that circadian light levels were maintained in the ICU, and modern ICUs minimize light intensity at nighttime. Consequently, light does not appear to be a significant source of sleep disruption. Nursing interventions occur at least hourly in the ICU[47] (Fig. 57-6), and have been associated with arousals.[13] The presence of excessive noise in the ICU has been thoroughly documented.[43,46–49] Aaron et al observed a strong correlation between the number of sound peaks of greater than 80 A-weighted decibels and arousals from sleep in a group of ICU patients.[48] Balogh et al reported that alarms were the most irritating noise, and observed that even during the night, the longest "quiet" interval was only 22 minutes.[46]

Another investigative approach has been to simulate the noisy ICU environment in a controlled setting such as

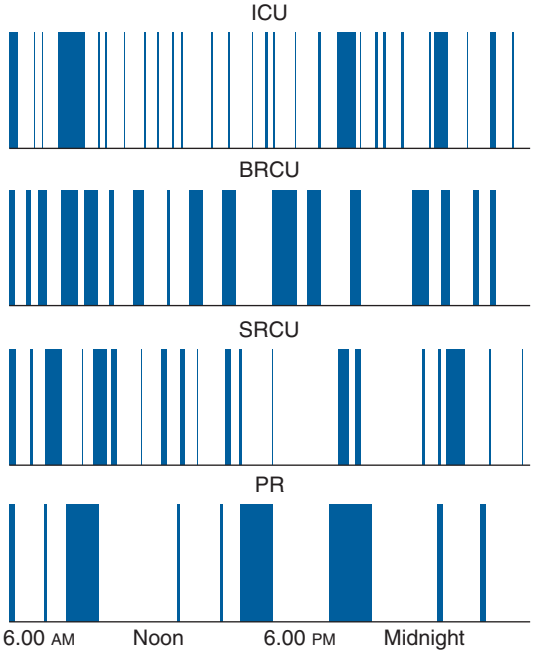

FIGURE 57-6 Patient interruptions by staff over 24 hours in four areas: a three-bed medical ICU, a three-bed respiratory care unit (*BRCU*), a single respiratory care unit room (*SRCU*), and a private room (*PR*) on a general medical floor. The *dark areas* represent interruptions and the *clear areas* represent time available for sleep. (Reproduced, with permission, from the American College of Chest Physicians. Meyer TJ, Eveloff SE, Bauer MS, et al. Adverse environmental conditions in the respiratory and medical ICU settings. *Chest.* 1994;105:1211–1216.)

a sleep laboratory. Exposure of healthy subjects in a sleep laboratory to recorded ICU noise–induced sleep disruption similar to that observed in patients in the ICU.[44,45,49] These studies in the ICU and sleep research laboratory led to the assumption that sleep disruption in the ICU was predominantly caused by noise and patient-care activities. The ICU studies, however, did not include simultaneous monitoring of noise and arousals. Consequently, the association was, at best, indirect. Furthermore, the simulated ICU environment is limited by the fact that it evaluates the impact of noise in isolation without the interaction of other competing sleep disruptors that are found in the ICU. Consequently, the role of the ICU environment, specifically noise and patient-care activities, were reassessed. Freedman et al,[50] using polysomnography and time-synchronized recording of environmental noise, directly linked noise to arousals. They determined that noise was responsible for only 15% of all arousals and awakenings. Although it was the first study to demonstrate that common noise elevations directly cause arousals in ICU patients, other environmental factors such as patient-care activities were not assessed.

Gabor et al subsequently evaluated the contribution of the ICU environment to sleep disruption in both ventilated patients and healthy subjects, and also evaluated the effectiveness of a noise-reduction strategy (moving the subject from the open ICU to a single room).[51] They performed comprehensive, synchronized monitoring of sleep by polysomnography, noise (calibrated sound meter), and all patient-care activities (audiovisual recording) for 24 hours. Although loud noise and frequent patient-care activities were prevalent in the ICU environment, they were responsible for less than 30% of the observed sleep disruption (Fig. 57-7). Healthy individuals slept relatively well in this potentially disruptive environment. Although noise accounted for a significant proportion of sleep disruption in this group, its extent was not pathologic. A quantitative improvement in sleep quality was observed as a result of noise reduction; however, there was no change in sleep architecture. The cause of 68% of arousals and awakenings in these mechanically ventilated patients could not be attributed to noise or any patient-care activity (Table 57-2).

Mechanical Ventilation

In addition to the noise associated with ventilators and their alarms, mechanical ventilation can disrupt sleep by producing periodic breathing with recurrent central apneas, or through the development of patient–ventilator dyssynchrony. Recurrent central apneas occur when the ventilator assist is excessive relative to the patient's ventilatory demand.[52] This is most likely to occur during sleep when demand is lowest and has been observed in critically ill patients.[53]

Dyssynchrony occurs when cycling of the ventilator is not in phase with the patient's efforts. Thus, the ventilator may be delivering gas when the patient wants to exhale, and vice versa. This dyssynchrony is common during conventional mechanical ventilation. Leung et al found that 28% of patients' inspiratory efforts occur during the ventilator's expiratory phase (ineffective efforts).[54] When one considers that ineffective efforts are the most extreme form of dyssynchrony, the incidence of less extreme forms of dyssynchrony (e.g., excessive delay in triggering or in cycling off the

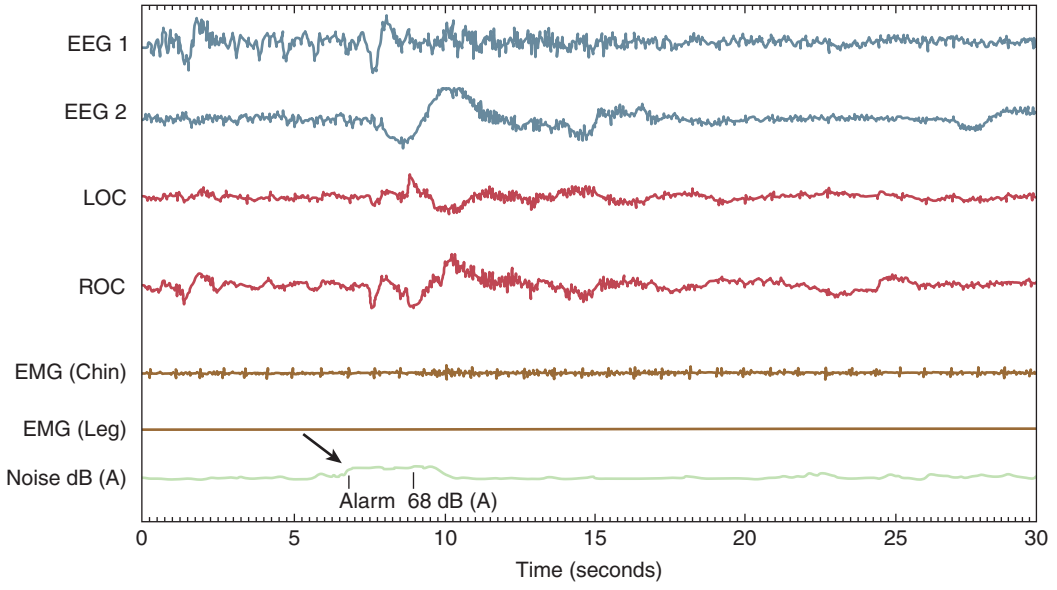

FIGURE 57-7 Polysomnographic example of a noise-induced arousal. *Vertical axis: EEG*, electroencephalogram; *EMG*, electromyogram; *LOC*, left oculogram; *ROC*, right oculogram. *Horizontal axis:* Time in seconds. *Arrow* indicates abrupt increase in noise (68 A-weighted decibels) caused by an alarm, followed by an arousal from stage 2 NREM sleep. (Reprinted with permission of the American Thoracic Society. Copyright © 2012 American Thoracic Society. Gabor JY, Cooper AB, Crombach SA, et al. Contribution of the intensive care unit environment to sleep disruption in mechanically ventilated patients and healthy subjects, *Am J Respir Crit Care Med.* 2003;167:708–715. Offical Journal of the American Thoracic Society.)

TABLE 57-2: IMPACT OF NOISE AND PATIENT-CARE ACTIVITIES ON SLEEP DISRUPTION

Event Type	Number per Hour of Sleep	Percentage Causing Disruption	Percentage of Total Disruption
Sound	36.5 ± 20.1	11.7 ± 8.3	20.9 ± 11.3
Family visits	0.7 ± 0.7	38.6 ± 39.3	1.0 ± 1.3
RT/physio	0.4 ± 0.5	30.7 ± 32.6	0.5 ± 0.7
Suctioning	0.2 ± 0.8	62.5 ± 47.9	0.6 ± 0.8
RN visits	3.5 ± 1.8	21.7 ± 11.6	4.1 ± 3.5
Assess vitals	0.3 ± 0.4	51.4 ± 34.4	0.7 ± 0.9
Med admin	2.7 ± 3.1	49.4 ± 25.6	0.9 ± 1.0
All medical care	7.8 ± 4.2	17.7 ± 5.4	7.1 ± 4.4
Apparatus/tech	1.1 ± 1.0	21.6 ± 26.3	1.4 ± 1.8
Unidentifiable	—	—	68.1 ± 9.7

Abbreviations: Apparatus/tech, noise from the sleep/environmental monitoring equipment or actions by the attending research assistant; *Med admin,* administering medication to a patient; *RT/physio,* any care provided by a respiratory therapist or physiotherapist; *RN visits,* any care provided by a nurse; *Sound,* sound peaks.

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ventilator) may be even more common. In awake individuals, such dyssynchrony is very uncomfortable. Thus, it would seem reasonable to expect dyssynchrony to result in arousals from sleep. Subjectively, 30% of patients in an ICU reported "agony/panic" during mechanical ventilation, which was associated with difficulties to synchronize the patients' breathing with the ventilator.[55]

In one of the first studies that investigated the impact of ventilator mode on sleep in the ICU, Parthasarathy and Tobin[56] reported a higher frequency of arousals and awakenings during pressure-support ventilation versus assist-control ventilation (79 ± 7 vs. 54 ± 7 per hour) in eleven critically ill patients (Fig. 57-8). Six patients, with underlying heart failure, had a high frequency of central apnea (53 ± 8 per hour) during pressure support, which was reduced (to 4 ± 2 per hour) by the addition of dead space (which eliminated the central apneas by increasing ventilatory demand). The decrease in central apneas was accompanied by a fall in the frequency of arousals and awakenings (83 ± 12 to 44 ± 6 per hour). The very high frequency of arousals and awakenings, particularly during pressure support, supports the notion that patient–ventilator dyssynchrony is an important source of sleep disruption in the ICU, and that it can be influenced by the mode of mechanical ventilation.

POTENTIAL CONSEQUENCES OF SLEEP DISRUPTION

Sleep is a biologic requirement for survival, which has been well documented in laboratory animals.[57,58] Prolonged sleep-deprivation experiments (5 to 9 days) in healthy subjects have produced marked cognitive impairment,[59] some objective neurologic signs,[60,61] and collapse requiring hospitalization.[62] In addition, there are five specific areas in which

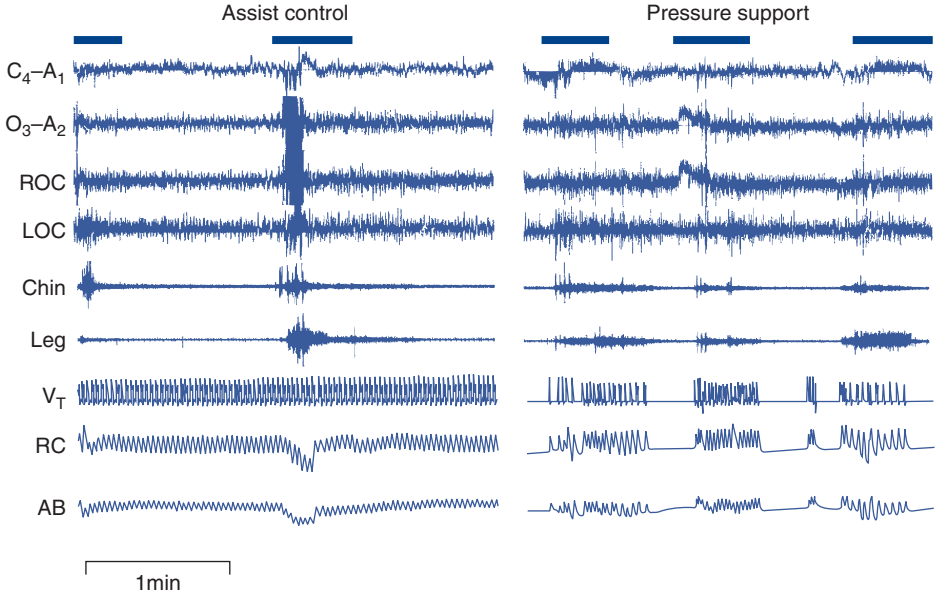

FIGURE 57-8 Sleep disruption during mechanical ventilation. Polysomnographic tracings during assist-control ventilation and pressure-support ventilation in a single patient. Electroencephalogram (*C4 – A1*, *O3 – A2*), electrooculogram (*ROC*, *LOC*), electromyograms (chin and leg), integrated tidal volume (V_T), and rib cage (*RC*) and abdominal (*AB*) excursions on respiratory inductance plethysmography. Arousals and awakenings, indicated by *horizontal bars*, were more numerous during pressure-support than during assist-control ventilation. (Reproduced, with permission, of the American Thoracic Society. Copyright © 2002 American Thoracic Socieity. Parthasarathy S, Tobin MJ, 2002, Effect of ventilator mode on sleep quality in critically ill patients. *Am J Respir Crit Care Med.* 2002;166:1423–1429. Official Journal of the American Thoracic Society.)

sleep disruption can adversely affect the clinical outcome of patients in the ICU.

Intensive Care Unit Psychosis

This refers to a state of delirium that characteristically starts after admission to the ICU.[63,64] Delirium is estimated to occur in 19% to 32% of patients in the ICU.[63,65] The pathogenesis is multifactorial, but includes sleep disruption associated with the patient's acute illness.[66,67] In addition, the rebound of REM sleep referred to earlier can be associated with delirium and nightmares. Persistence of this altered mental state impairs the ability of patients to interact with their caregivers, and can increase morbidity and delay weaning from the ventilator and discharge from the ICU.[64,66,68]

Rebound of Rapid Eye Movement Sleep

During REM sleep, heart rate, respiration, and blood pressure are highly variable[1] and can exhibit transient irregularities, making REM sleep, and more specifically REM rebound, potentially dangerous to a recuperating critically ill patient. It has been hypothesized that REM rebound, with associated episodes of hypoxemia, variable blood pressure, and cardiac arrhythmias, may play a role in the etiology of postoperative myocardial ischemia and infarction.[15,18,19] This is supported by the observation that REM rebound peaks at approximately the same time that these delayed complications of anesthesia and surgery occur most frequently.[18] This cardiovascular instability has particular relevance in patients who have significant vascular comorbidities.

Delayed Weaning from Mechanical Ventilation

Studies in healthy volunteers and animal models show that sleep deprivation can cause negative nitrogen balance,[57,69] decreased respiratory muscle endurance,[70] and a blunted genioglossus electromyogram response to carbon dioxide, which becomes more severe with advancing age.[71] Other investigators report decreased ventilatory responsiveness to hypoxemia and hypercapnia[72–74] and increased upper airway compliance[75] following sleep deprivation. The combination of decreased central drive and reduced respiratory muscle endurance can be further aggravated by the fact that sleep deprivation is associated with increased oxygen consumption and carbon dioxide production.[76] Weaning difficulty is related to inability of respiratory muscles to cope with the demands imposed by ventilatory requirements and mechanical load.[77–79] Accordingly, the consequences of sleep disruption (decreased respiratory muscle endurance and increased metabolic rate, and, hence, ventilatory requirements) may delay weaning, particularly in patients who have limited respiratory reserve.

Host Defense

Studies in animals indicate that sleep deprivation leads to failure of host defense.[80] During 3 weeks of sleep deprivation, rats developed a progressive negative energy balance and sympathetic activation.[58,81] This culminated in host-defense failure manifested by bloodstream infection and a cachectic-like moribund state.[80] Sleep deprivation in rats is also associated with early infection of the mesenteric lymph nodes by both aerobic and facultative anaerobic intestinal bacteria with migration to major organs.[82] The translocation of bacteria and endotoxin from the intestinal mucosa and their dissemination to extraintestinal sites is thought to drive a systemic inflammatory state and multiorgan failure in critically ill patients.[83–86] The contribution of sleep disruption to this syndrome in patients has not been determined, although sleep loss in humans is associated with changes in some parameters of host defense.[87–89]

Chronic Insomnia

Chronic insomnia has been reported in a subset of acute respiratory distress syndrome survivors 6 months or more following discharge from hospital.[90] None of these patients had insomnia before their hospitalization, which raises the possibility that it was related to their acute illness. This hypothesis, however, was not supported by a subsequent study of 497 patients who required admission to the ICU and whose sleep quality was assessed by questionnaire before their hospitalization, and again 6 and 12 months after discharge.[91] Compared to a community-based control group, these patients were more likely to have disturbed sleep (odds ratio [OR] 3.62, 95% confidence interval [CI] 2.93 to 4.47). Disturbed sleep, however, was strongly associated with concurrent illness (OR 3.29, 95% CI 2.80 to 3.88) and not with indices of their ICU admission, such as diagnosis, APACHE, and length of stay. Moreover, in previously healthy patients, sleep improved over 6 to 12 months after discharge from hospital, in contrast to patients with concurrent disease whose sleep quality remained the same. These results imply that the sleep disturbance associated with critical illness resolves over time and whatever remains is predominantly caused by concurrent disease.

STRATEGIES TO IMPROVE SLEEP IN THE INTENSIVE CARE UNIT

No studies have systematically evaluated strategies to improve sleep in the ICU. Nevertheless, several options can be considered based on our current understanding of the pathogenesis of sleep disruption in this patient population and on anecdotal experience.

Treatment of the Underlying Illness

All sources of sleep disruption related to a patient's underlying medical condition should be reduced as much as possible. This includes management of the acute illness, such as optimal control of postoperative pain, as well as maintaining preexisting treatment for chronic medical disorders such as chronic cough associated with chronic obstructive pulmonary disease or restless legs syndrome. Detailed management of all such conditions is beyond the scope of this chapter.

Optimization of the Intensive Care Unit Environment

Although this has the greatest intuitive appeal to improve sleep in the ICU, it has not been shown to have a dramatic effect. Studies that minimized disruption from light, noise, and nursing interventions did not decrease sleep disruption.[16] Successful reduction of ICU noise and light levels was not associated with improved sleep quality as assessed by the nursing staff.[92] The use of earplugs subjectively improved sleep in a group of acutely ill patients compared to a control group.[93] When healthy volunteers were exposed to recorded ICU noise in a sleep laboratory,[94] subjects without earplugs displayed an increased number of awakenings and decreased REM sleep, similar to previous studies.[44,45,49] More recently, white noise has been shown to reduce arousals during exposure to recorded ICU noise in the sleep laboratory;[95] however, this has not been studied in the ICU. Overall, modification of the ICU environment yielded modest improvement in sleep quality, which is consistent with the observation that the ICU environment is not the major source of sleep disruption.[51] Nevertheless, it is important that all reasonable measures be taken to avoid an excessively disruptive ICU environment.

Several nonpharmacologic therapies have been used successfully in the management of chronic insomnia.[96,97] These therapies can be applied to patients in the ICU, despite the fact they have not been evaluated in this population. Reestablishment of a regular sleep schedule and avoidance of excessive sleep during the day may be feasible in ventilated patients once they have recovered from their acute illness and are being weaned from the ventilator.

Medication

Patients in the ICU receive multiple medications that should be reviewed for their potential to cause sleep disruption or sleep loss (see Table 57-1). Medication can also be used to consolidate sleep, either a pure hypnotic, such as zopiclone, or medication that treats the underlying cause of sleep disruption such as anxiety, depression, or delirium. Few studies have addressed the impact of such interventions on sleep in critically ill patients. One study randomized ICU patients to nocturnal infusions of either midazolam or propofol.[98] Although sleep was not assessed objectively by polysomnography, daily self-assessment questionnaires showed improved sleep with both agents. An alternative approach by Shilo et al[37] found that patients on the hospital ward had the typical nocturnal peak in melatonin levels, whereas nocturnal secretion was blunted in ICU patients. Administration of melatonin to nonventilated ICU patients improved the duration and continuity of sleep, as assessed indirectly by actigraphy.[99] It is possible that other strategies to resynchronize circadian rhythm, such as bright-light therapy, which has been used successfully in ambulatory patients,[42] may improve sleep in some ICU patients.

Mode of Mechanical Ventilation

The study by Parthasarathy and Tobin[56] quoted earlier supports the notion that some modes of mechanical ventilation are more "sleep-friendly" than others. Although assist-control ventilation is not free of dyssynchrony,[54] and may contribute to sleep disruption, they found that sleep fragmentation was less during assist-control ventilation than with pressure support, predominantly because of a reduction in the frequency of central apnea. Central apnea may occur either secondary to underlying disease, such as heart failure, excessive ventilator assistance, or both.[53]

In a randomized crossover study of twenty patients with chronic lung disease who were ready for extubation, Toublanc et al[100] compared polysomnography during assist-control ventilation and pressure support. Pressure support was set at a low level, 6 cm H_2O, whereas assist-control ventilation was titrated "until complete disappearance of spontaneous inspiratory efforts." Sleep architecture was superior during assist-control ventilation than with pressure support, as reflected by reduced wakefulness and increased NREM sleep. A further study compared assist-control ventilation, clinically adjusted pressure support, and automatically adjusted pressure support in fifteen mechanically ventilated patients and found no differences in sleep fragmentation across the three modes.[101] This may reflect appropriate adjustment of ventilator settings because minute ventilation was similar in all three groups of patients. Indeed, in patients with neuromuscular disease, Fanfulla et al[102] demonstrated that tailoring pressure support to the patient's respiratory effort resulted in improved sleep architecture by reducing the frequency of ineffective efforts.

Proportional-assist ventilation is a mode of ventilation that provides ventilatory support in proportion to the patient's inspiratory effort,[103] thereby optimizing patient–ventilator synchrony. The impact of pressure support and proportional assist ventilation on sleep was compared in thirteen patients as they were being weaned from mechanical ventilation.[104] Ventilator settings for both modes were titrated during a spontaneous breathing trial to reduce inspiratory work by 50%. The frequency of

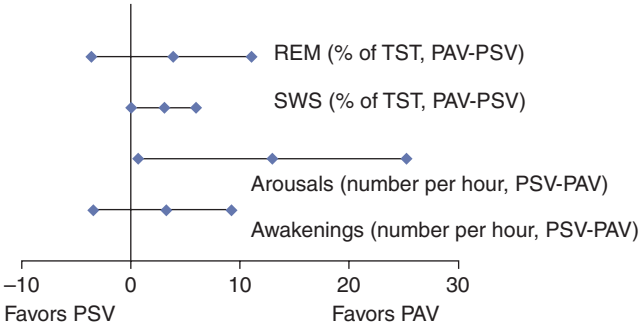

FIGURE 57-9 Multivariate analysis of variance of the effect of modes of ventilation on comprehensive sleep quality. Central diamond indicates the mean absolute difference between proportional-assist ventilation (*PAV*) and pressure-support ventilation (*PSV*); *horizontal bar* indicates the 95% confidence interval. The combined effect of fewer arousals per hour, fewer awakenings per hour, greater rapid eye movement (*REM*) sleep, and greater slow-wave sleep (*SWS*) accounted for the significant ($p < 0.05$) overall improvement in sleep quality with PAV. *TST*, total sleep time. (Used, with permission, from Bosma et al.[104])

patient–ventilator dyssynchrony events was lower with proportional-assist ventilation than with pressure-support ventilation (24 ± 15 vs. 53 ± 59 per hour, $p = 0.02$), which resulted in a lower number of arousals (9, range: 1 to 41 vs. 16, range: 2 to 74) and improved sleep architecture (Fig. 57-9). In summary, the impact of mechanical ventilation on sleep depends upon the underlying disease, the stability of the control of breathing, the mode of mechanical ventilation and the ventilator settings.

IMPORTANT UNKNOWNS

Despite increasing interest and research on sleep disruption in ventilator-supported patients, there is much that we do not know. We do not have a comprehensive understanding of the pathogenesis of sleep disruption in this patient population and the relative contribution of all of the potential sources of sleep disruption discussed above. We also do not know how sleep disruption changes over time in the ICU. Second, we do not know the impact of sleep disruption on outcomes such as weaning, length of stay in the ICU, and hospital morbidity and mortality. Third, it is not clear how much sleep can be improved in ICU patients and what treatment strategies work best.

THE FUTURE

Two issues need to be addressed to facilitate further research on this topic. First, the methodology to monitor sleep in the ventilator-supported patient needs to be addressed. Although attended polysomnography is the reference standard for monitoring sleep, it is labor intensive, costly, cumbersome for staff and patients, and not suited to repeated measurement, especially in the ICU environment. Alternative methodologies that address these limitations and are validated in mechanically ventilated patients are required. Second, larger studies are needed. To date, most studies have consisted of small numbers of patients from a single academic center. Although they have provided new and valuable data, their small sample size limits their applicability to the general ICU population and their ability to measure important clinical outcomes. These concerns could be addressed by multicenter studies that recruit larger numbers of patients.

SUMMARY AND CONCLUSIONS

There is strong evidence that sleep is severely disrupted in mechanically ventilated patients in the ICU, which has the potential to increase their morbidity and mortality through its effect on neurocognitive, cardiorespiratory, and immune function. Although sleep disruption has been attributed predominantly to the ICU environment, noise and patient-care activities account for less than 30% of sleep disruption. Further research is required to provide a comprehensive understanding of the causes of sleep disruption in this patient population, which will form the basis for the evaluation of therapeutic strategies and their impact on both short-term and long-term clinical outcomes.

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WEANING FROM MECHANICAL VENTILATION

Martin J. Tobin
Amal Jubran

Thirty years ago, the weaning of patients from the ventilator was relegated to nurses and respiratory therapists. It aroused little interest among physicians. It certainly wasn't thought worthy of serious scientific inquiry. All this has changed. No other area of critical care has undergone so great a transformation. But the illumination has also cast shadows. In particular, discussion of weaning is now bedeviled by imprecise language. This can be seen as just deserts insofar as few clinicians use the term *weaning* in the strict literal sense—a gradual reduction in the level of ventilator support. Instead, most patients today are taken off the ventilator cold turkey. It would be fine if the confused language stopped there. But this is only one small example of how fundamental scientific misunderstanding has arisen from imprecise word choices.

Under the cloak of imprecise language, much muddled thinking, flawed logic, and misinterpretation has crept into the field. These language problems are not just pedantic quirks. Instead, they impede the rigor of research in this area, as well as interpretation of the findings. Communication is also hindered by the lumping together of many distinct components of this complex process. To enhance clarity, we divide weaning into seven stages.

SEVEN STAGES OF WEANING

We divide weaning into seven stages to draw attention to areas that receive minimal attention (Fig. 58-1). Stage 1 is preweaning, when no attempt at weaning is desirable. For example, when a patient is receiving 80% oxygen and positive end-expiratory pressure (PEEP) of 15 cm H_2O, performing any disconnect from the ventilator (for measurement of

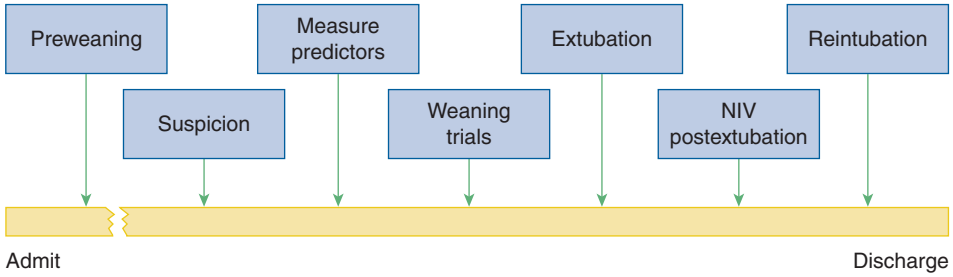


FIGURE 58-1 Seven stages of weaning. Stage 1 is preweaning, a stage that many patients never get beyond. Stage 2 is the period of diagnostic triggering, the time when a physician begins to think that the patient might be ready come off the ventilator. Stage 3 is the time of measuring and interpreting weaning predictors. Stage 4 is the time of decreasing ventilator support (abruptly or gradually). Stage 5 is either extubation (of a weaning-success patient) or reinstitution of mechanical ventilation (in a weaning-failure patient). Stage 6 is use of noninvasive ventilation after extubation. Stage 7 is reintubation. Failure to appreciate stage 2 probably leads to the greatest delays in weaning.

weaning predictors) is inappropriate and may even be dangerous. Every ventilated patient begins at stage 1, and some patients never get beyond that stage. For example, in a prospective study of 249 ventilated patients,[1] sixty-five patients (26%) died during mechanical ventilation without any attempt at weaning. In another report of 357 patients entered into a trial of weaning techniques,[2] 12.9% never reached the stage of any active weaning attempt. We identify this preweaning stage to emphasize the importance of the transition between it and the next stage of a patient's clinical course.

Stage 2 is the period during which the clinician contemplates the possibility that the patient is ready for weaning. This statement may seem obvious to the point of banality. But the point at which this thought first enters the mind of a physician managing a complex patient is not so straightforward. In such a patient, the key act is for a physician to think that the patient just might come off the ventilator successfully. Except for self-extubations, this decision is not made by the patient. The idea has to begin in the doctor's brain. Several large studies have documented that many patients are ventilated for a week or more and the ventilator is then successfully discontinued on the first day that weaning predictor tests are measured.[3,4] A physician has to ask himself or herself whether the patient might have tolerated extubation a day or so earlier. Failure to recognize this second stage may be the greatest obstacle to expeditious weaning.

Psychologists have undertaken extensive research into how probabilistic reasoning is employed in making decisions, investigating how people perceive, process, and evaluate the probabilities of uncertain events.[5–7] Studies have clarified how interactions between the demands of a task and the limitations of a thinker negatively impact cognitive processes. Research on inferences that involve a sequence of steps has revealed that people make wrong decisions because they are more confident in their judgments (such as deciding that a patient is not ready for a T-tube trial) than is validly justified by the data on which the decisions are based.[5]

In his recently published book, *Thinking, Fast and Slow,* the Nobel laureate, Daniel Kahneman, brings together the voluminous research conducted by his group and other investigators on human decision making over the past five decades.[7] Kahneman presents human thinking as involving two independent systems. System One is amazingly fast, intuitive, and effort-free—but prone to error. System Two is the slow process of forming judgments based on conscious thinking and deductive reasoning. To activate System Two requires mental effort and hard work. Consequently, people turn to System One for most decisions. One of the discoveries cited by the Nobel committee was Kahneman's demonstration that overreliance on simple "seat-of-the-pants" decisions (characteristic of System One) can lead to large systematic errors, which have serious and persistent consequences.[6,7] An example of a System One error in ventilator weaning is a clinician's intuition that a patient is not ready for a T-tube trial. Another System One error pertinent to weaning, and highlighted by Kahneman's research, is a clinician's failure to pay close attention to prior probability (Bayesian reasoning)—a failure that leads to major errors in decision making.[6] When taking care of a ventilator-supported patient, physicians should be mindful of these cognitive processes and employ compensatory tactics such as the use of screening tests to spot a patient's readiness for weaning. By alerting an unsuspecting physician to a patient's readiness to tolerate unassisted ventilation—hours or days before he or she would otherwise order a spontaneous breathing trial—weaning-predictor tests circumvent the cognitive errors inherent in clinical decision making.[8]

Stage 3 is the time of obtaining physiologic measurements that serve as predictors, and interpreting the data appropriately in the context of each patient's unique clinical condition. The critical word here is *interpretation*. It is imperative to be clear about why these predictor tests are being performed, the influence of a patient's preexisting condition on the interpretation of the results, what action to take based on the results, and when it is prudent to adjust the thresholds for taking action. These points may seem self-evident, but the literature is replete with evidence of cloudy thinking on each point.

Stage 4 is to decrease ventilator support. Support is either removed abruptly and completely (T-tube trial) or gradually decreased over hours or days. Stage 5 is extubation of a patient who tolerated stage 4 or reinstitution of mechanical

ventilation in a patient who failed the weaning trial. Stage 6 is continued ventilator support after extubation using noninvasive ventilation; this stage applies to only a minority of patients. Stage 7 is reintubation, usually accompanied by the reinstitution of mechanical ventilation.

PATHOPHYSIOLOGY OF WEANING FAILURE

Over the last 20 years, understanding of the mechanisms that cause patients to fail their first attempt to recommence spontaneous breathing has increased considerably. Advances in this aspect of weaning research have been enormously greater than change in clinical management. Greater understanding of pathophysiology has led to new approaches to the timing of the weaning process, prediction of outcome, and techniques used for weaning. Delineation of pathophysiologic principles led to the undertaking of clinical trials. The trials, in contrast, have contributed little to our understanding of the pathophysiology of weaning failure.

Research on pathophysiology has been limited to failure of attempts at spontaneous breathing when a still-intubated patient is first disconnected from the ventilator. Virtually no pathophysiologic research has been conducted in patients who develop acute respiratory failure in the hours immediately after extubation. Likewise, very little research has been conducted in patients who fail repeated weaning attempts, and, as a consequence, may be transferred to centers that specialize in the delivery of mechanical ventilation in the post–intensive care setting.

When intubated patients are disconnected from the ventilator and left to breathe on their own, about a fifth are unable to sustain spontaneous ventilation. If the trial is extended, these weaning failure patients will develop hypercapnia unless severe hypoxemia first intervenes. The pathophysiologic mechanisms that cause weaning failure can be divided into those occurring at the level of control of breathing, mechanics of the lung and chest wall, the respiratory muscles, the cardiovascular system, and gas-exchange properties of the lung.

Control of Breathing

The physiologic processes that fall under the heading of control of breathing primarily include afferent and efferent signals, and the processing of these signals in the brainstem. Clinical research on control of breathing has primarily focused on the overall level of respiratory motor output, termed respiratory drive. In human research, it is not realistic to obtain electrode recordings from the respiratory centers, and it is extremely difficult to measure phrenic nerve traffic. Consequently, a number of indirect methods have been used to assess respiratory drive. Measurement of the ventilatory response to hypercapnia or hypoxia is used in ambulatory patients, but difficult to apply in weaning failure patients. Electromyographic (EMG) recordings from the diaphragm reflect phrenic nerve traffic, but are difficult to standardize among patients.

Most data on respiratory drive in weaning failure patients has been obtained with two techniques: the airway occlusion method ($P_{0.1}$) and mean inspiratory flow (V_T/T_I) of breathing pattern analysis. In a spontaneously breathing patient, it is not possible to measure $P_{0.1}$ on every breath or even at frequent intervals. If $P_{0.1}$ is measured repeatedly, the act of measurement will alter respiratory drive.[9] As such, continuous measurements of respiratory drive over the evolution of weaning failure have been limited to V_T/T_I. V_T/T_I suffers from the limitation that oral airflow is far removed from the brainstem. Any intervening impediment, such as abnormal lung mechanics, can cause a decrease in V_T/T_I. Thus, there is always the possibility that V_T/T_I is providing an underestimate of respiratory drive. An advantage, however, of breathing pattern analysis over other methods of measuring respiratory drive is that it also provides information on respiratory timing.

Tobin et al[10] studied seventeen patients who underwent a T-tube trial of weaning. Seven patients developed severe distress, and arterial carbon dioxide tension (Pa_{CO_2}) rose from 42 to 56 mm Hg, and pH fell from 7.43 to 7.35. Between the beginning and end of the trial, which lasted 40 ± 11 minutes, the patients developed an increase in V_T/T_I: 265 ± 27 to 328 ± 32 mL/s. These findings were surprising. At that time, it was expected that acute hypoventilation—the physiologic terminology for an increase in Pa_{CO_2}—would have been accompanied by a decrease in drive. Yet, not one patient had a value of V_T/T_I below the 95% confidence limits of normal subjects. Although V_T/T_I was not depressed in the weaning failure patients, it was not higher than in the weaning success patients. Subsequent studies, using $P_{0.1}$, revealed that respiratory drive is higher in weaning failure patients than in weaning success patients.[11–15]

The patients also showed marked changes in respiratory timing (Fig. 58-2). Upon resumption of spontaneous breathing, the weaning-failure patients exhibited immediate and marked shortening of inspiratory time (T_I): 0.81 ± 0.11 versus 1.41 ± 0.27 seconds in weaning-success patients. Within the respiratory centers, expiratory time (T_E) is strongly coupled to T_I. Consequently, T_E was also shorter in the weaning-failure patients than in the weaning-success patients: 1.24 ± 0.27 versus 2.48 ± 0.47 seconds. The combined changes in T_I and T_E led to a marked increase in respiratory frequency (f): 32.3 ± 2.3 versus 20.9 ± 2.8 breaths/min. Because the rate of inspiratory flow (V_T/T_I) was equivalent in the two patient groups, the short T_I resulted in a lower tidal volume (V_T) in the weaning-failure patients: 194 ± 23 versus 398 ± 56 mL. The decrease in V_T was balanced by the increase in f, and thus minute ventilation ($\dot{V}_E$) was equivalent in the two groups. A decrease in V_T without an increase in $\dot{V}_E$ must result in higher overall dead space ventilation (V_D/V_T). Indeed, the combined changes in V_T and f accounted for 81% of the increase in Pa_{CO_2} observed in the weaning-failure patients. From the above discussion, it is evident that the

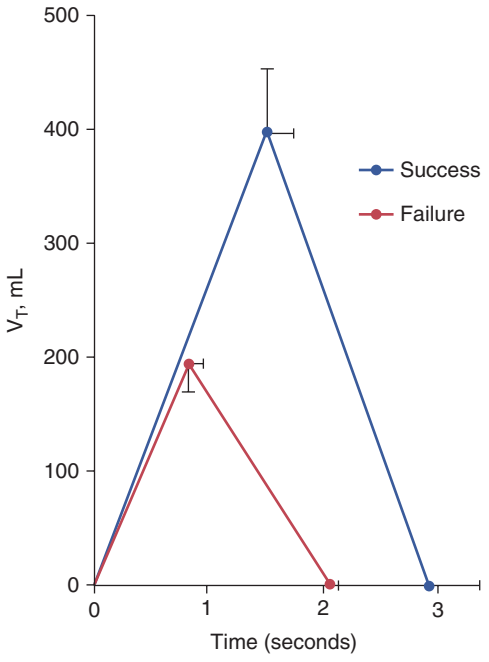


FIGURE 58-2 The mean respiratory cycle during spontaneous breathing in seven weaning-failure and ten weaning-success patients. The early termination of inspiratory time in the weaning-failure patients leads to a decrease in tidal volume (V_T). The decrease in inspiratory time, coupled with a decrease in expiratory time, results in a faster respiratory frequency. Bars represent 1 standard error (SE). (Used, with permission, from Tobin et al.[10])

fundamental abnormality in control of breathing in weaning failure is a shortening of T_I.

Several groups of investigators have shown that the combination of increased f and low V_T is a characteristic abnormality in weaning-failure patients. Vassilakopoulos et al[16] studied thirty patients at two points in time. Measurements were first obtained shortly after the patients failed a T-tube trial. Measurements were repeated approximately 9 days later, shortly before the patients were successfully extubated. The investigators found that an index of rapid shallow breathing, frequency-to-tidal-volume ratio (f/V_T), was lower in weaning failure than in weaning-success patients: 62 ± 21 versus 98 ± 38. They obtained additional detailed measurements of lung mechanics and respiratory muscle function, and found that only two variables, tension–time index and f/V_T, were significant determinants of weaning failure.

Research indicates that most weaning-failure patients develop an increase in respiratory drive as they experience progressive ventilatory failure. Clinical experience, however, suggests that at least some patients have depressed respiratory drive. Jubran and Tobin[15] observed that two of seventeen (11.8%) weaning-failure patients developed Pa_{CO_2} values of greater than 70 mm Hg during a T-tube trial, and yet detailed measurements of their lung mechanics and respiratory muscle function were within the range of the weaning-success patients. These limited data suggest that perhaps 10% of patients who develop hypercapnia during a failed weaning trial may do so primarily because of respiratory center depression.

Respiratory Mechanics

Physiologic variables for quantifying lung mechanics can be grouped under three major headings: resistance, elastance, and gas trapping. The most detailed data on respiratory mechanics in patients being weaned from mechanical ventilation comes from a study by Jubran and Tobin of thirty-one patients with chronic obstructive pulmonary disease (COPD) undergoing a weaning trial.[17] Over the course of a trial of spontaneous breathing lasting 45 ± 8 minutes, seventeen patients developed acute distress and an increase in Pa_{CO_2} (from 45 to 58 mm Hg), requiring the reinstitution of mechanical ventilation. The remaining fourteen patients tolerated the trial and were successfully extubated; these served as a control group.

At the start of the trial, inspiratory lung resistance was equivalent in the weaning-failure and weaning-success patients: 9.0 ± 1.7 versus 5.3 ± 1.1 cm H_2O/L/s (Fig. 58-3).[17]

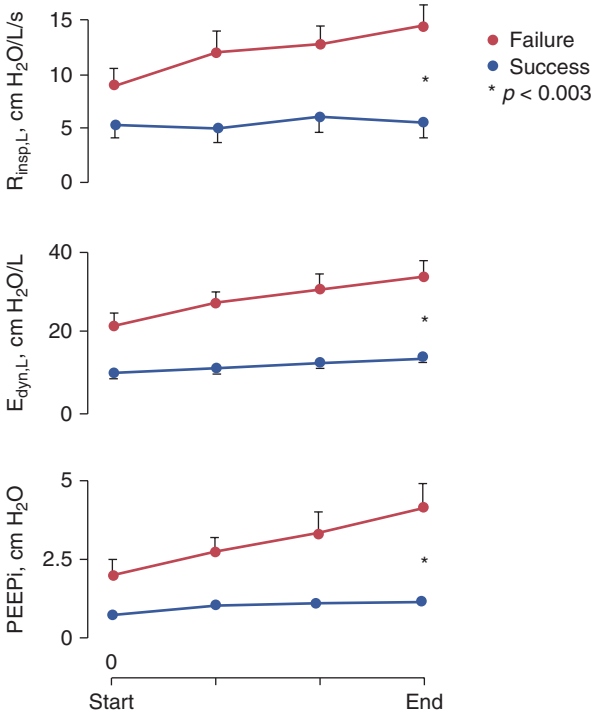


FIGURE 58-3 Inspiratory resistance of the lung ($R_{insp,L}$), dynamic lung elastance ($E_{dyn,L}$), and intrinsic positive end-expiratory pressure (*PEEPi*) in seventeen weaning-failure patients and fourteen weaning-success patients. Data displayed were obtained during the second and last minute of a T-tube trial, and at one-third and two-thirds of the trial duration. Between the onset and end of the trial, the failure group developed increases in $R_{insp,L}$ (p <0.009), $E_{dyn,L}$ (p <0.0001), and PEEPi (p <0.0001) and the success group developed increases in $E_{dyn,L}$ (p <0.006) and PEEPi (p <0.02). Over the course of the trial, the failure group had higher values of $R_{insp,L}$ (p <0.003), $E_{dyn,L}$ (p <0.006), and PEEPi (p <0.009) than the success group. (Used, with permission, from Jubran and Tobin.[17])

By the end of the trial, resistance increased to 14.8 ± 2.0 cm H_2O/L/s in the failure patients, but it did not change in the success patients. Four factors may account for the increase in resistance: (a) an increase in inspiratory flow (unlikely because the increase in flow was no higher in failure patients than in success patients); (b) a decrease in lung volume (unlikely because most patients also develop gas trapping); (c) accumulation of secretions (unlikely because all patients had been suctioned before the trial, and secretions were no different in the two groups); and (d) bronchoconstriction. Bronchoconstriction appears to be the most likely explanation in that patients with COPD have heightened airway reactivity—although it is not clear why this should be greater in weaning-failure than in weaning-success patients.

Dynamic lung elastance was higher in weaning-failure patients than in weaning-success patients at the start of the trial: 21.2 ± 3.4 versus 9.9 ± 1.7 cm H_2O/L (see Fig. 58-3).[17] At the end of the trial, elastance increased to 34.1 ± 4.0 cm H_2O/L in the failure patients and to 14.0 ± 2.0 cm H_2O/L in the success patients. The elevated elastance at the start of the trial was probably secondary to frequency dependence of elastance. Three factors may account for the increase in elastance over the course of the trial: (a) dynamic hyperinflation (this possibility is supported by a twofold increase in intrinsic PEEP [PEEPi] by the end of the trial); (b) development of subclinical pulmonary edema secondary to increased left ventricular afterload; and (c) microatelectasis (a possibility supported by the marked decrease in V_T).

PEEPi, an indirect measure of gas trapping, was higher in the failure patients than in the success patients at the onset of the trial: 2.0 ± 0.5 versus 0.7 ± 0.1 cm H_2O. By the end of the trial, PEEPi increased to 4.1 ± 0.8 cm H_2O in the failure patients and to 1.1 ± 0.2 cm H_2O in the success patients (see Fig. 58-3).[17]

Jubran and Tobin did not partition total PEEPi into the component resulting from expiratory muscle contraction and that resulting from an increase in end-expiratory lung volume. This information was subsequently obtained by the same group of investigators,[18] who partitioned total PEEPi into that resulting from expiratory muscle contraction (abdominal muscles, expiratory rib cage muscles, or both) by calculating the rise in gastric pressure (Pga) between the onset of expiratory flow and the point of rapid decline in esophageal pressure (Pes), and the remaining portion, suggesting an increase in end-expiratory lung volume. After correcting for expiratory-muscle contribution, the remaining portion of total PEEPi increased between the start and end of the weaning trial in seven of the ten patients.[18] These data suggest that many weaning-failure patients develop dynamic hyperinflation. Expiratory flow limitation[19] and tachypnea, through a decrease in time available of exhalation,[10] are the most likely determinants of dynamic hyperinflation. It should be recognized that it has not been possible to obtain direct measurements of end-expiratory lung volume in patients experiencing acute respiratory failure, and the use of esophageal pressure to estimate this entity is based on many assumptions.[20]

Other investigators have also reported a worsening of lung mechanics in weaning-failure patients. An innovative approach was employed by Vassilakopoulos et al.[16] They first studied patients at the end of a T-tube trial. Then they reinstituted ventilation in the assist-control mode, sedated the patients, and hyperventilated them to abolish spontaneous respiratory muscle activity. Next they adjusted the ventilator settings to simulate a patient's pattern of spontaneous breathing, and measured lung mechanics under passive conditions. The investigators studied the patients at two points in time: shortly after they first failed a T-tube trial, and approximately 9 days later, shortly before they were successfully extubated. Between the time of weaning failure and weaning success, airway resistance decreased from 9.6 ± 3.4 to 7.9 ± 3.3 cm H_2O/L/s, static PEEPi decreased from 6.1 ± 2.5 to 3.8 ± 2.7 cm H_2O, and static respiratory compliance did not change. The investigators also disconnected the patients from the ventilator (after first delivering some breaths simulating spontaneous breathing), and allowed them to exhale freely until zero expiratory flow was reached. This point was taken as the elastic equilibrium volume of the respiratory system, and the increase in functional residual capacity secondary to gas trapping (PEEPi) was taken as the difference between inspired and expired volume. This volume was 327 ± 180 mL during weaning failure, and it fell to 213 ± 175 at the time of weaning success.

The observation that weaning-failure patients display more severely deranged lung mechanics than do weaning-success patients raises the question of whether the derangements might be detectable ever before patients reattempt spontaneous breathing (i.e., while patients are still receiving full ventilator support). Jubran and Tobin[21] studied lung and chest wall mechanics of patients before the onset of a weaning trial. Inspiratory resistance was about fourteen times higher than that in healthy subjects but it was equivalent in the failure and success patients: 13.9 and 13.0 cm H_2O/L/s, respectively. Static elastance of the lung and the chest wall were similar in the two groups.[21] Dynamic elastance of the lung was higher in the failure patients than in the success patients, 28 ± 3 versus 17.8 ± 2 cm H_2O/L, and this was the only measurement of passive mechanics that differentiated the two groups. Dynamic PEEPi during passive ventilation was equivalent in the groups. This picture contrasts with the more severely deranged mechanics in failure patients than in success patients during a weaning trial.[17] The difference indicates that something in the act of spontaneous breathing, rather than an intrinsic abnormality in respiratory mechanics, is responsible for the marked difference between failure and success patients during a weaning trial.

Patient Effort

The deterioration in lung mechanics during a failed weaning trial leads to increased work of breathing. The increased respiratory work is made manifest by greater swings in esophageal pressure (Fig. 58-4). In the study of

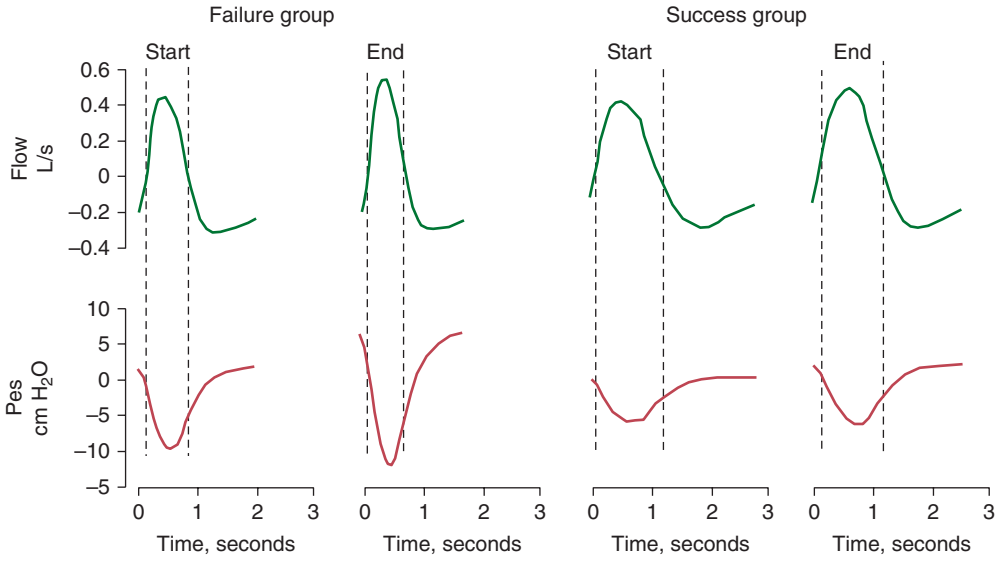


FIGURE 58-4 Ensemble average plots of flow and esophageal pressure (*Pes*) at the start and end of a T-tube trial in seventeen weaning-failure patients and fourteen weaning-success patients. At the start of the trial, the inspiratory excursion in Pes was greater in the failure patients, and it increased further by the end of the trial. To generate these plots, flow and Pes tracings were divided into twenty-five equal time intervals over a single respiratory cycle for each of the 5 breaths for each patient in the two groups. For a given patient, the 5 breaths from the start of the trial were then superimposed and aligned with respect to time, and the average at each time point was calculated. The group mean tracings were then generated by ensemble averaging of the individual mean from each patient. The same procedure was performed for breaths at the end of the trial. (Used, with permission, from Jubran and Tobin.[17])

Jubran and Tobin, pressure-time product was not different in the weaning-failure and weaning-success patients at the onset of a spontaneous breathing trial: 255 ± 59 and 158 ± 23 cm H_2O*s/min (normal: 94 ± 12).[17] At the end of the trial, pressure-time product increased more in the failure patients than in the success patients: 388 ± 68 versus 205 ± 25 cm H_2O*s/min. The increase in effort in the failure patients resulted from worsening of all elements of respiratory mechanics. Partitioning of the increase in pressure-time product at end of the trial revealed that the fraction caused by PEEPi increased by 111%, that caused by the non-PEEPi elastic component increased by 33%, and the fraction caused by the resistive component increased by 42%.[17]

In sixty patients being weaned from mechanical ventilation, Jubran et al[22] characterized the changes in esophageal-pressure swings over the course of a trial of spontaneous breathing (Fig. 58-5). The median time to reach ±10% of the average value of esophageal pressure during the last minute of the trial was 7.5 (interquartile range [IQR]: 4.2 to 14.8) minutes in the weaning-failure patients and 5 (IQR: 2 to 8.5) minutes in the weaning-success patients (Fig. 58-6). In contrast, f/V_T, a measure of rapid shallow breathing, reached ±10% of its final average value at 2 (IQR: 1 to 2) minutes in both the weaning-success and weaning-failure patients. The more gradual and progressive increase in esophageal pressure over time may have resulted from a slow increase in partial pressure of carbon dioxide (P_{CO_2}), as commonly occurs in weaning-failure patients.[10,17] The relative constancy in f/V_T may be related to the increases in both inspiratory resistive and inspiratory elastic loads that occur in weaning-failure patients. These loads have opposing effects on breathing pattern. A resistive load slows respiratory frequency while preserving tidal volume, thereby producing a decrease in f/V_T.[23,24] In contrast, an elastic load increases respiratory frequency accompanied by a decrease in tidal volume, both of which will produce an increase in f/V_T.[25,26]

Respiratory Muscles

Research into the mechanisms whereby abnormalities of the respiratory muscles might contribute to weaning failure has focused on inspiratory muscle strength and respiratory muscle fatigue. Muscle strength has been assessed by measuring the pressure generated during a maximal inspiratory effort against an occluded airway.[27] Early investigators reported that maximal inspiratory pressure ($P_I$max) was lower in weaning-failure patients than in weaning-success patients, but later investigators reported no difference between the two groups.[14,28–31] The pattern of reporting suggests the possibility of test-referral bias, whereby patients with the lowest values of $P_I$max were deliberately excluded from the subsequently conducted studies.[32] Another consideration is the well-recognized difficulty of ensuring reliable measurements of $P_I$max, given its total dependence on patient motivation and cooperation—an even greater challenge in critically ill patients.[27] Studies using phrenic nerve stimulation, and specifically the technique of twitch interpolation, revealed that patients being weaned from mechanical ventilation typically make submaximal efforts when $P_I$max is being measured. Moreover, Laghi et al[29] found that six of nine weaning-failure patients

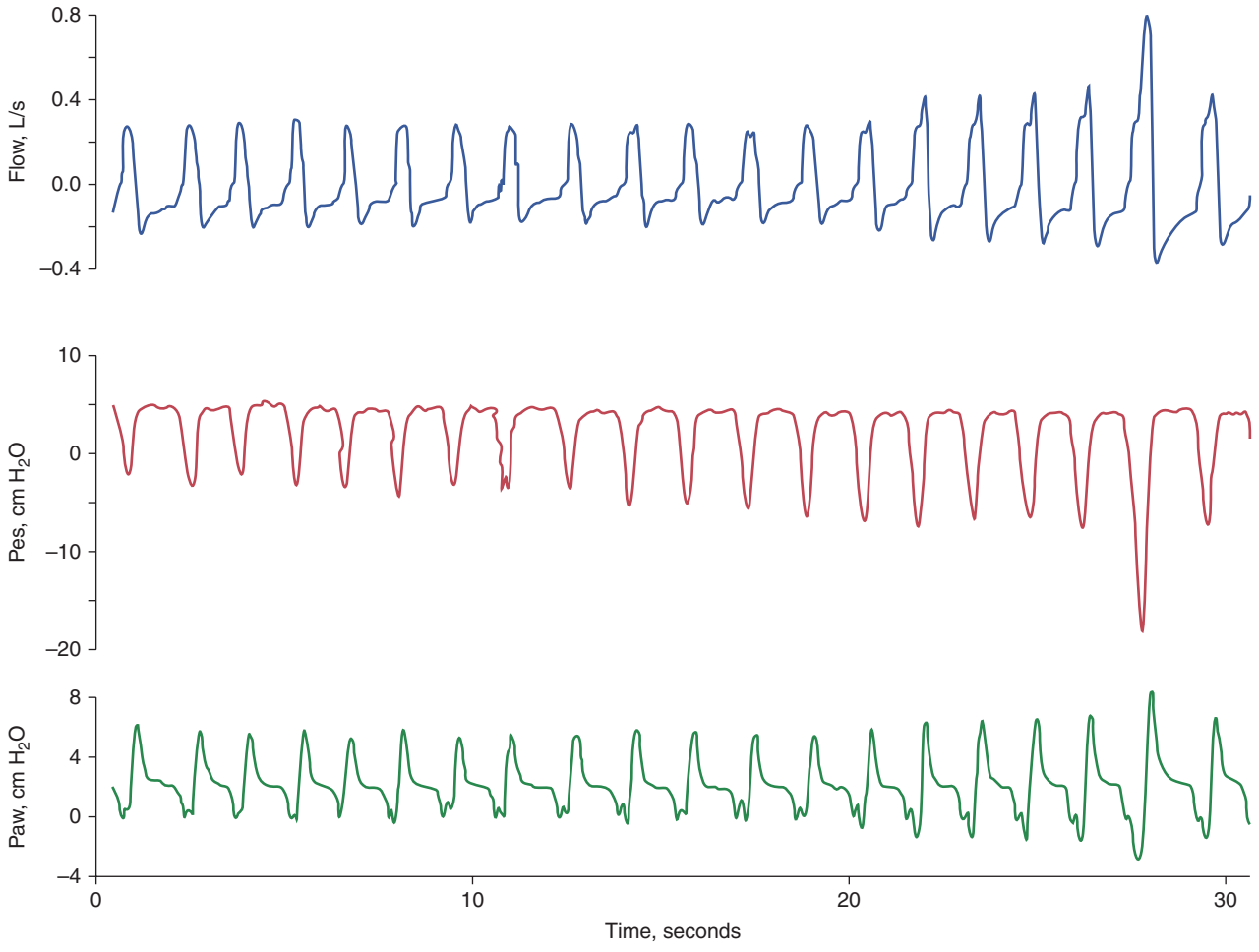


FIGURE 58-5 Progressive increase in inspiratory effort in a weaning-failure patient. Flow (*top panel*), esophageal pressure (Pes, *middle panel*), and airway pressure (Paw, *bottom panel*) in a patient who developed severe respiratory distress while receiving continuous positive airway pressure of 5 cm H_2O. The patient had developed respiratory failure (requiring mechanical ventilation) after developing a pulmonary embolus subsequent to undergoing lobectomy for lung cancer. The swings in esophageal pressure became progressively more negative over the first 30 seconds of the trial.

had twitch transdiaphragmatic pressure (Pdi) values below 10 cm H_2O. Healthy subjects have twitch Pdi values of 35 to 39 cm H_2O, and stable patients with COPD have values of 17 to 20 cm H_2O. Contrary to previous thinking, these data indicate that weaning-failure patients may have considerable muscle weakness.

For years, researchers and clinicians have believed that most if not all weaning-failure patients develop respiratory muscle fatigue by the time a failed weaning trial is stopped. This belief has been largely based on observations made by Cohen et al.[33] These investigators studied twelve patients who exhibited difficulties during weaning. Seven patients developed a shift in the power spectrum of the EMG signal recorded from the diaphragm, a finding judged to signify muscle fatigue. Six of the seven patients also exhibited paradoxical motion of the abdomen (inward displacement of the abdomen during inspiration) and four exhibited respiratory alternans (phasic alternation between the contribution of the rib cage and abdominal compartments to V_T). The changes in rib cage–abdominal motion were not observed in the five patients who did not develop EMG changes. The investigators concluded that respiratory muscle fatigue was a common cause of weaning failure, and that its presence could be detected by finding paradoxical motion of the abdomen.

Subsequent detailed recordings of rib cage–abdominal motion revealed that when paradoxical motion of the abdomen occurs in weaning-failure patients, it occurs immediately upon discontinuation of the ventilator and displays no progression over time.[34] When quantified objectively, the extent of abdominal paradox was no greater in weaning-failure patients than in weaning-success patients. In studies of healthy volunteers, fatigue was found to be neither necessary nor sufficient to induce abnormal rib cage–abdominal motion.[35] These data indicated that rib cage–abdominal motion could not be used for detecting respiratory muscle fatigue. The studies, however, did not exclude the possibility that fatigue is common in weaning-failure patients.

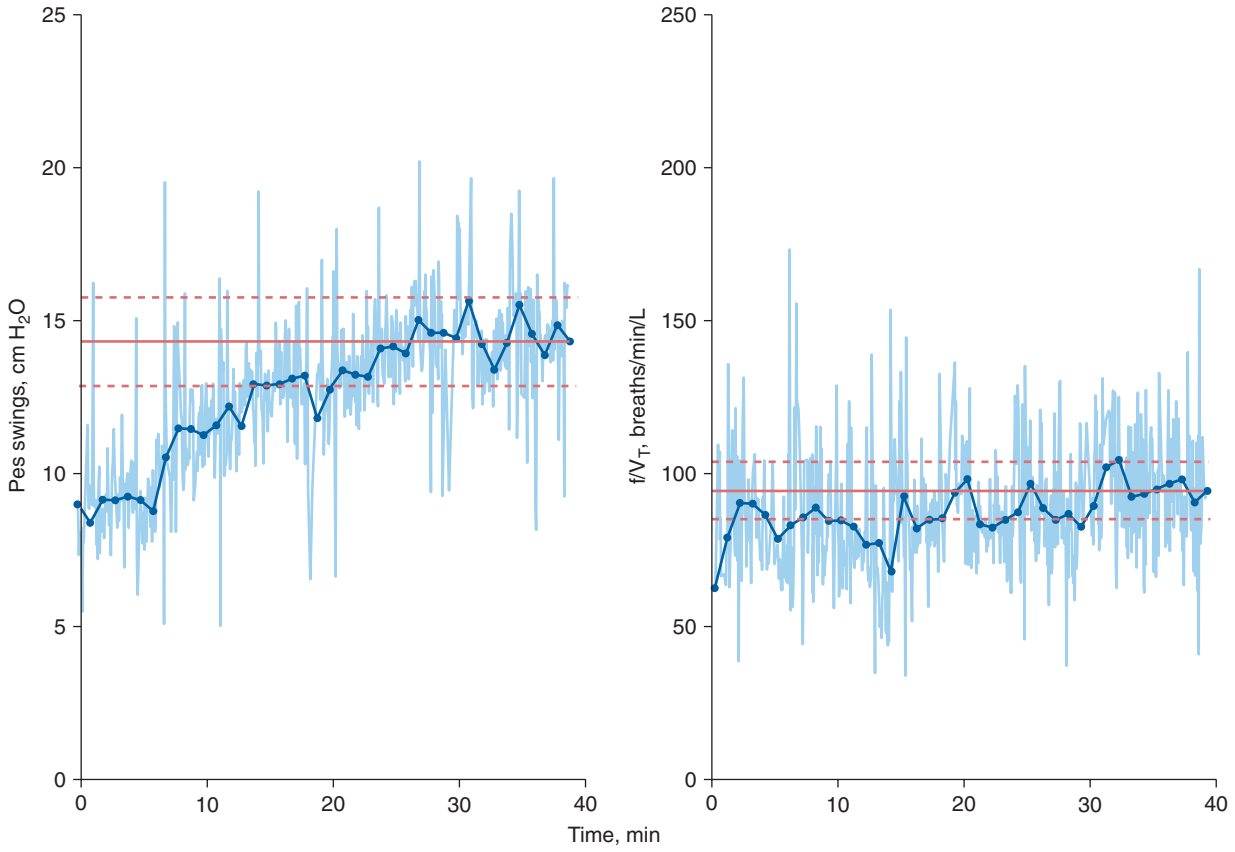


FIGURE 58-6 Time-series plot of swings in esophageal pressure (*Pes*; *left panel*) and frequency-to-tidal-volume ratio (f/V_T; *right panel*) during a trial of spontaneous breathing in a weaning-failure patient. *Dots* represent 1-minute averages. The *solid horizontal line* indicates the average value of Pes swings and f/V_T during the final minute of the trial. The *dashed lines* indicate ±10% of the final minute values for Pes swings and f/V_T. The time taken to reach ±10% of the final value was 14 minutes for Pes swings and 2 minutes for f/V_T. (Used, with permission, from Jubran et al.[22])

Investigators also evaluated a more complex measure of fatigability, tension–time index. Tension–time index is the product of two fractions:

$$(\text{mean pressure per breath}/P_I\text{max}) \times (T_I/T_{TOT})$$

Studies in healthy volunteers show that respiratory muscle fatigue becomes inevitable when subjects breathe against an inspiratory load that causes tension–time index to rise above a threshold of 0.15. In a number of studies,[16,17,36] many more weaning-failure patients than weaning-success patients were found to exhibit tension–time index values above 0.15. As such, weaning-failure patients experience workloads that are sufficient to induce respiratory muscle fatigue.

The EMG power spectrum and tension–time index provide only indirect evidence of fatigue, and do not provide direct proof of its occurrence. In neurophysiologic terms, fatigue means that a muscle is generating less force in response to a given neural stimulus than it had generated in the past. The most direct method for detecting fatigue in patients is to stimulate the phrenic nerves in the neck and measure the resulting change in Pdi. The challenge with use of phrenic nerve stimulation in critically ill patients is to ensure that successive twitches are all generated at the same end-expiratory lung volume, a constant degree of neural depolarization is achieved by the stimulator, and twitch potentiation (the increase in pressure that occurs with a recent forceful contraction) is avoided. Laghi et al[29] measured twitch Pdi using phrenic stimulation in eleven weaning-failure patients and eight weaning-success patients before and after a T-tube trial. Twitch Pdi was 8.9 ± 2.2 cm H_2O before the trial and 9.4 ± 2.4 cm H_2O after the trial in the weaning-failure patients (Fig. 58-7). The respective values in the weaning-success patients were 10.3 ± 1.5 and 11.2 ± 1.8 cm H_2O. No patient in either group exhibited a fall in twitch Pdi. The failure to develop fatigue was surprising because seven of the eight weaning-failure patients had a tension–time index above 0.15.

The most likely reason that patients did not develop fatigue is because physicians reinstituted mechanical ventilation before there was enough time for its development. The relationship between tension–time index and the length of time that a load can be sustained until task failure follows an inverse-power function. Bellemare and Grassino[37] expressed the relationship as: time to task failure = 0.1 (tension–time index).$^{-3.6}$ Figure 58-8 shows the increase in tension–time index over the course of the weaning trial[29] and predicted time to task failure.[37] At the point that the physician reinstituted mechanical ventilation, patients were predicted to

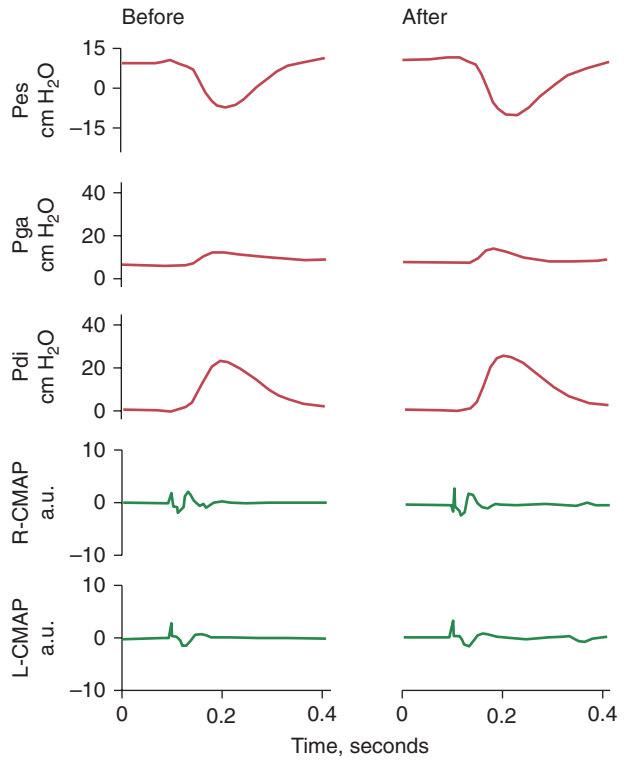


FIGURE 58-7 Esophageal pressure (*Pes*), gastric pressure (*Pga*), transdiaphragmatic pressure (*Pdi*), and compound motor action potentials (*CAMP*) of the right and left hemidiaphragms after phrenic nerve stimulation before (*left*) and after (*right*) a T-tube trial in a weaning-failure patient. The end-expiratory value of Pes and the amplitude of the right and left CAMPs were the same before and after the trial, indicating that the stimulations were delivered at the same lung volume and that the stimulations achieved the same extent of diaphragmatic recruitment. The amplitude of twitch Pdi elicited by phrenic nerve stimulation was the same before and after weaning. (Used, with permission, from Laghi et al.[29])

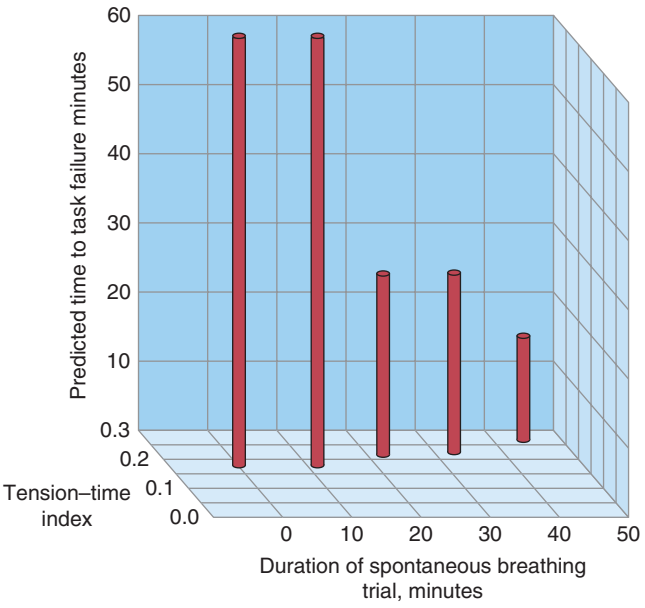


FIGURE 58-8 Interrelationship between the duration of a spontaneous breathing trial, tension–time index of the diaphragm, and predicted time to task failure in nine patients who failed a trial of weaning from mechanical ventilation. The patients breathed spontaneously for an average of 44 minutes before a physician terminated the trial. At the start of the trial, the tension–time index was 0.17, and the formula of Bellemare and Grassino[37] (see text for details) predicted that patients could sustain spontaneous breathing for another 59 minutes before developing task failure. As the trial progressed, the tension–time index increased and the predicted time to development of task failure decreased. At the end of the trial, the tension–time index reached 0.26. That patients were predicted to sustain spontaneous breathing for another 13 minutes before developing task failure clarifies why patients did not develop a decrease in diaphragmatic twitch pressure. In other words, physicians interrupted the trial on the basis of clinical manifestations of respiratory distress, before patients had sufficient time to develop contractile fatigue. (Used, with permission, from Laghi and Tobin.[27])

be able to sustain an additional 13 minutes of spontaneous breathing before developing task failure. In other words, clinical manifestations of severe respiratory distress were evident for a substantial time before the patients were predicted to develop fatigue. In an intensive care setting, these clinical signs will lead attendants to reinstitute mechanical ventilation before fatigue has time to develop.

In a study of nineteen patients being weaned from mechanical ventilation,[18] all but one of the eleven weaning-failure patients exhibited expiratory muscle activity (the exception being a patient with paraplegia). Expiratory muscle activity—as quantified by the expiratory rise in Pga—was absent in all but three of eight weaning-success patients, and its magnitude was trivial in the remainder (Fig. 58-9). At the onset of the trial, the expiratory rise in Pga was equivalent in the failure and success groups, 0.9 ± 0.5 and 0.1 ± 0.1 cm H_2O, respectively. At the end of the trial, the expiratory rise in Pga increased to 4.4 ± 1.1 cm H_2O in the failure group ($p = 0.0005$), whereas it did not change, 0.1 ± 0.1 cm H_2O, in the success group. Compared with the success group, the failure group exhibited larger increases in expiratory rise in Pga ($p = 0.004$). In the failure group, expiratory muscle activity accounted for 53 ± 4% of total PEEPi throughout the weaning trial.

In the study of Parthasarathy et al,[18] sternomastoid EMG activity, measured with fine-wire electrodes, was evident in 83 ± 9% of all the breaths in the weaning-failure group and in 19 ± 10% of all breaths in the weaning-success group ($p = 0.002$) (Fig. 58-10). Sternomastoid activity became evident within the first minute of the trial in eight of the eleven failure patients and in one of the eight success patients. By the end of the trial, sternomastoid activity was noted in all failure patients but in only three of the success patients, and this activity was modest. The immediate increase in sternomastoid activity in the failure patients probably results from increased respiratory motor output in response to a combination of decreased capacity of the respiratory muscles to generate pressure[29] and an increase in mechanical load that occurs early during the weaning trial. In addition to increased sternomastoid activity, weaning-failure patients

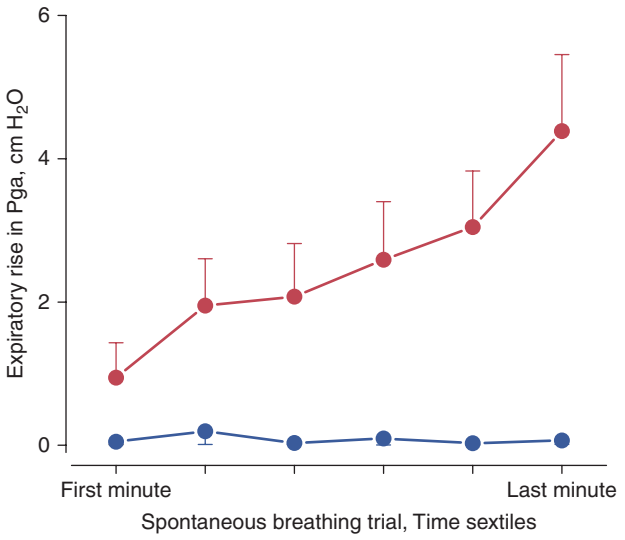


FIGURE 58-9 Expiratory rise in gastric pressure (*Pga*) during the course of a weaning trial in failure (•) and success patients (•). Between the onset and the end of the trial, failure patients developed an increase in the expiratory rise in Pga ($p = 0.0005$) whereas success patients did not. Over the course of the trial, failure patients had higher values of expiratory rise in Pga ($p = 0.004$) than did success patients. Bars represent ± standard error (SE). (Modified, with permission, from Parthasarathy et al.[18])

displayed greater inspiratory rib cage muscle contribution to tidal breathing throughout the trial than did the success patients (Fig. 58-11).

A striking feature of the weaning-failure patients is the timing at which different muscle groups become active.[18] The sequence begins with activity of the diaphragm and with greater activity of inspiratory rib cage muscles than is the case in the success patients; recruitment of sternomastoids and rib cage muscles is near maximum within 4 minutes of trial commencement, whereas the expiratory muscles are not recruited until quite late in the trial (at 17 to 20 minutes).[18] The existence of a hierarchy of respiratory muscle activation is supported by the known delayed activation of the sternomastoid muscles[38] and expiratory muscles in healthy volunteers[39,40] and in ambulatory patients with COPD.[41]

Cardiovascular Performance

Although the respiratory muscles do not develop fatigue, they perform a huge workload. Thus, they depend on an efficient transport of oxygen by the cardiovascular system. Aware of this fact, several researchers have examined cardiovascular performance during weaning. Lemaire et al[42]

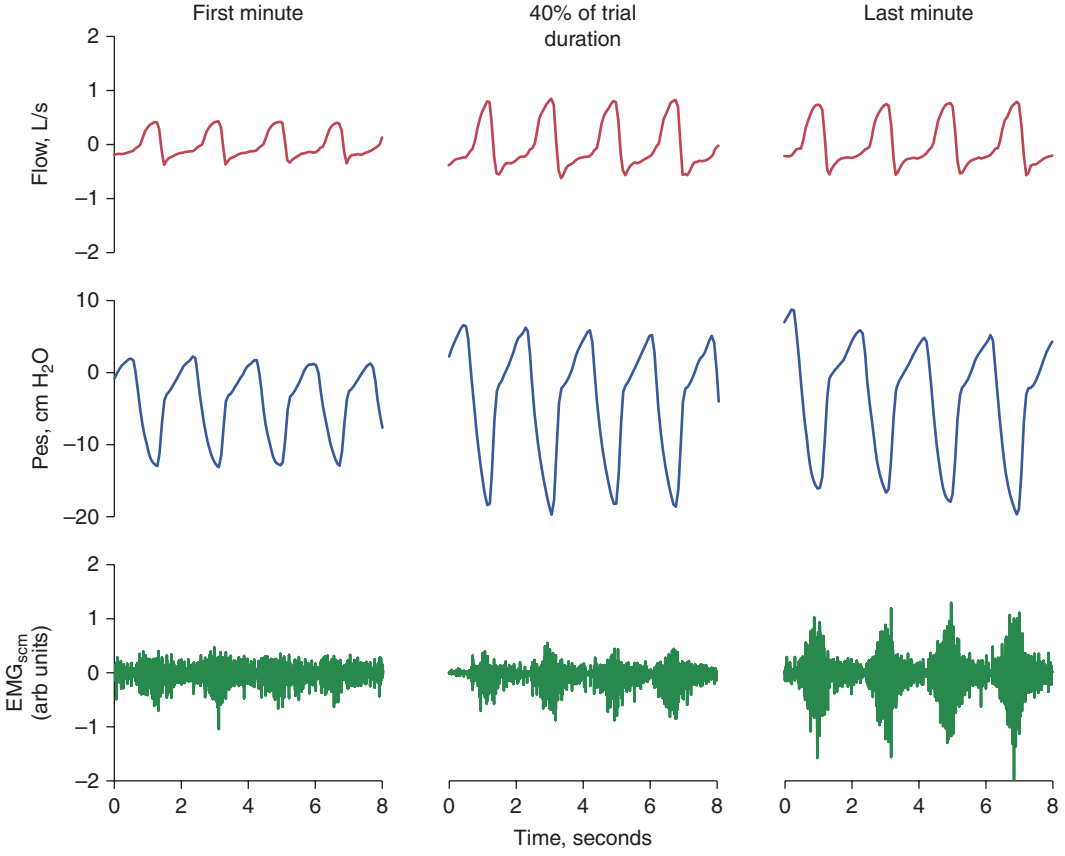


FIGURE 58-10 Representative tracings of flow, esophageal pressure (Pes), and electromyogram of the sternomastoids (EMG_{scm}) in a weaning-failure patient. Recordings were obtained during the first minute of the weaning trial, 40% of trial duration, and last minute of the trial. Phasic inspiratory activity of the sternomastoid muscle was evident within the first minute of the trial, and it increased progressively over the course of the trial. Note that phasic activity of the sternomastoids persists into expiration. (Used, with permission, from Parthasarathy et al.[18])

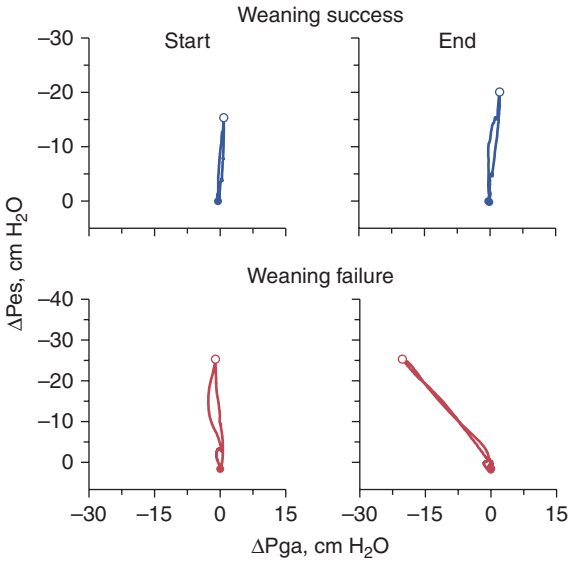


FIGURE 58-11 Plots of tidal changes in esophageal pressure (*ΔPes*) against tidal changes in gastric pressure (*ΔPga*) in a weaning-success patient and a weaning-failure patient. At the start of a weaning trial, the success patient (*top left panel*) exhibited swings in esophageal pressure that became markedly more negative between the onset (*closed symbol*) and the end of inspiration (*open symbol*); in contrast, gastric pressure increased only slightly. Therefore, the slope of the Pes–Pga plot at the onset of weaning (*top left panel*) was much greater than the slope recorded in healthy subjects during resting breathing, where the tidal change in gastric pressure is often greater than the tidal change in esophageal pressure. The steep Pes–Pga plot (*top left panel*) indicates a greater-than-usual contribution of the rib cage muscles to tidal breathing than that of the diaphragm. Between the onset (*top left panel*) and the end of weaning (*top right panel*), the slope of the Pes–Pga plot changed very little, indicating a constant contribution of the diaphragm and rib cage muscles to tidal breathing over the course of the weaning trial. In the case of the weaning-failure patient, the inspiratory swings in esophageal pressure and gastric pressure had a similar pattern at the start of the trial to that in the success patient (*bottom left panel*). At the end of the trial, the failure patient exhibited a markedly negative slope in the Pes–Pga plot, signifying a further increase in inspiratory rib cage muscle recruitment that was out of proportion to diaphragmatic recruitment.

studied fifteen patients with COPD, seven of whom had documented ischemic heart disease. After 10 minutes of breathing (through the ventilator without PEEP), the patients developed increases in transmural pulmonary artery occlusion pressure (PAOP) (8 to 25 mm Hg), cardiac index (3.2 to 4.3 L/min/m^2), left ventricular end-diastolic volume index (65 to 83 mL/m^2), and right ventricular end-diastolic volume index (83 to 103 mL/m^2). The investigators attributed the increase in left ventricular end-diastolic volume to augmentation of venous return (secondary to low pleural pressure during spontaneous breathing and central translocation of blood volume secondary to peripheral vasoconstriction) and increased left ventricular afterload (secondary to markedly negative pleural pressure swings and increased catecholamine release). Nine of the fifteen patients were weaned after 10 days of diuretic therapy, at which time PAOP had fallen to 9 mm Hg.

Although a particular PAOP has not been rigorously linked with the inevitable onset of cardiogenic pulmonary edema, an increase in PAOP above 18 mm Hg during a weaning trial is widely considered to indicate the onset of weaning-induced pulmonary edema.[43,44] Several research groups have reported increases in PAOP in patients as they failed a weaning trial, although these researchers did not detect a concomitant decrease in cardiac output.[42,45–47] As such, the cardiorespiratory stress posed by the resumption of spontaneous breathing after a period of mechanical ventilation resembles the challenges posed by whole-body exercise, which also results in increases in cardiac output and work of breathing.[48] Increases in adrenergic tone that accompany increased cardiorespiratory stress can produce increases in venous return, left-ventricular afterload, cardiac work, and myocardial oxygen demand—all of which may precipitate myocardial ischemia in predisposed patients.[42,43]

Richard et al[49] studied a group of twelve patients with COPD who did not have documented coronary artery disease. All of the patients tolerated at least two 30-minute T-tube trials. (This finding suggests that they were weaning-success patients, although it is not stated that they tolerated extubation.) Ejection fraction, measured by technetium^{99m} radionuclide angiography, was 54.5 ± 12.4% during mechanical ventilation. Spontaneous breathing resulted in a fall in ejection fraction to 47 ± 13%. The fall was homogenous and not accompanied by regional wall abnormalities that occur with myocardial ischemia. Moreover, thallium imaging performed 15 minutes after the weaning trial revealed normal myocardial perfusion. The investigators attributed the decrease in ejection fraction to increased left ventricular afterload.

The increases in oxygen consumption during a weaning trial means that patients who are unable to achieve sufficient increases in cardiac output are at risk of experiencing a decrease in oxygen transport. To investigate these considerations, Jubran et al[39] continuously recorded mixed venous oxygen saturation ($S\bar{v}_{O_2}$) in eight weaning-failure and eleven weaning-success patients over the course of T-tube trials that lasted about 40 minutes. Immediately before the trial, $S\bar{v}_{O_2}$ was equivalent in the two groups. On discontinuation of the ventilator, $S\bar{v}_{O_2}$ fell progressively in the failure patients (to 51.5 ± 7.9% at the end of the trial), whereas it did not change in the success patients (Fig. 58-12). Oxygen demand ($\dot{V}_{O_2}$) was similar in the two groups during the weaning trial, although it differed in the manner with which it was met.

The success patients demonstrated an increase in cardiac index between mechanical ventilation and the end of the trial, 3.07 to 3.51 L/m/m^2, which was accompanied by an increase in oxygen transport (Fig. 58-13). The failure group did not experience an increase in oxygen transport (partly because of elevations in right and left ventricular afterload); instead, they experienced an increase in oxygen extraction ratio, which, in turn, contributed to the fall in $S\bar{v}_{O_2}$. The failure patients also had more impaired pulmonary gas exchange ($\dot{Q}_{VA}/\dot{Q}_T$ was 0.32 at the start of the trial). The combination of greater venous admixture and low $S\bar{v}_{O_2}$

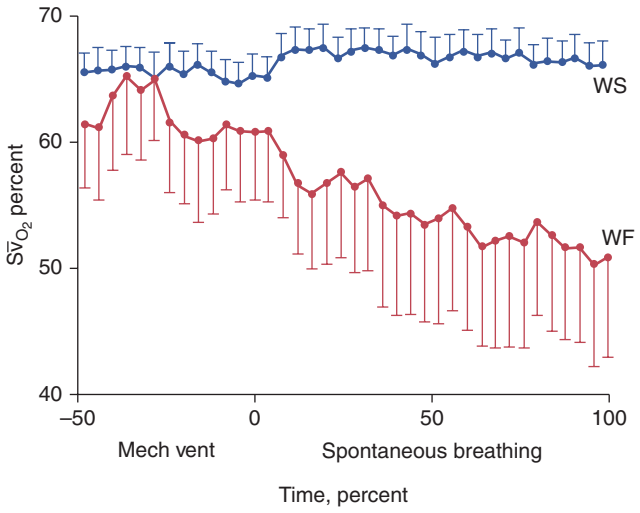


FIGURE 58-12 Ensemble averages of the interpolated values of mixed venous oxygen saturation ($S\bar{v}_{O_2}$) during mechanical ventilation (Mech Vent) and a trial of spontaneous breathing in weaning-success patients (*blue symbols*) and weaning-failure patients (*red symbols*). During mechanical ventilation, $S\bar{v}_{O_2}$ was similar in the two groups ($p = 0.28$). Between the onset and the end of the trial, $S\bar{v}_{O_2}$ decreased in the failure patients ($p < 0.01$), whereas it did not change in the success patients ($p = 0.48$). Over the course of the trial, $S\bar{v}_{O_2}$ was lower in the failure patients than in the success patients ($p < 0.02$). (Bars represent standard error [SE].) (Used, with permission, from Jubran et al.[45])

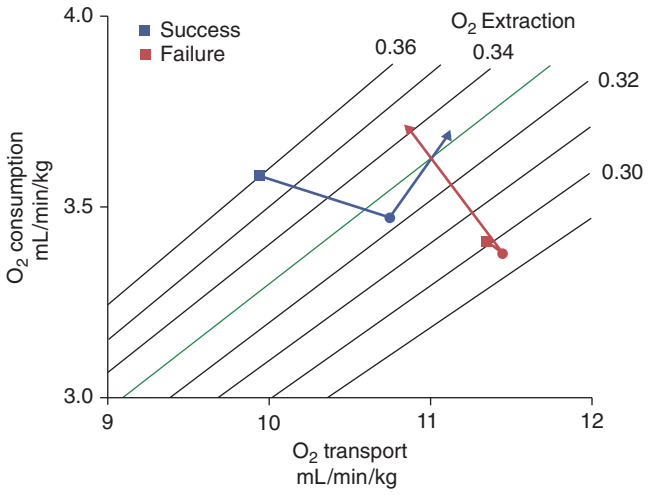


FIGURE 58-13 Oxygen transport, oxygen consumption, and isopleths of oxygen extraction ratio in weaning-success (*blue symbols*) and weaning-failure patients (*red symbols*) during mechanical ventilation (*squares*) and at the onset (*circles*) and end (*triangles*) of a T-tube trial. (Used, with permission, from Jubran et al.[45])

led to rapid arterial desaturation and a relative decrease in oxygen being supplied to the tissues.

Mean pulmonary artery pressure was higher in the failure patients than in the success patients during mechanical ventilation (Fig. 58-14). The pressure increased further over the course of the trial in the failure patients, whereas the success patients showed no change. Several factors account for the increase in pulmonary artery pressure. Hypoxemia and acidosis are potent vasoconstrictors. Pulmonary artery pressure can also be increased by alveolar vessel compression secondary to the increase in alveolar pressure that accompanies the dynamic hyperinflation and deterioration in pulmonary mechanics in weaning failure. During mechanical ventilation, the two groups had an equivalent mean arterial pressure, which increased in the failure patients by the end of the trial. The increase in mean arterial pressure combined with no change in cardiac index indicates an increase in left ventricular afterload.

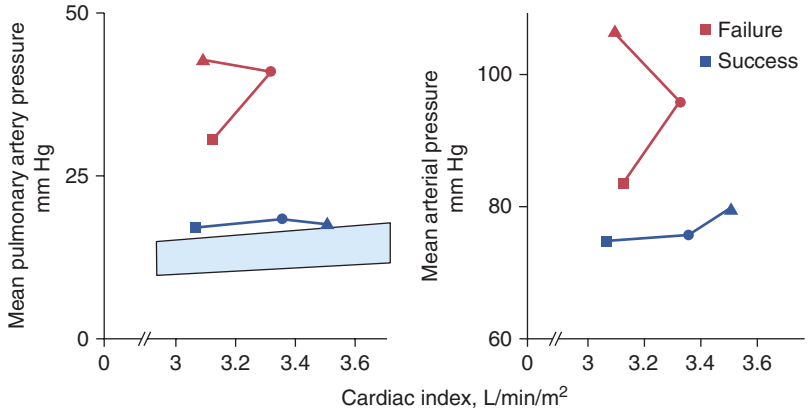


FIGURE 58-14 Mean pulmonary artery pressure and mean arterial pressure versus cardiac index during mechanical ventilation (*squares*) and at the onset (*circles*) and end (*triangles*) of a T-tube trial in weaning success (*blue symbols*) and weaning-failure patients (*red symbols*). The *blue shaded area* represents the normal range of increase in mean pulmonary artery pressure with cardiac index. In the success patients, cardiac index increased between mechanical ventilation and the end of the trial, mean pulmonary artery pressure remained slightly above the normal range, and mean arterial pressure did not change. Conversely, in the failure patients, cardiac index was similar during mechanical ventilation and at the end of the T-tube trial, but both mean pulmonary artery pressure and mean arterial pressure were higher by the end of the trial ($p < 0.025$ and $p < 0.05$, respectively). The increases in these vascular pressures, together with the lack of change in cardiac index, indicate increases in right and left ventricular afterload in the failure patients. (Used, with permission, from Jubran et al.[45])

In an investigation of similar design, Zakynthinos et al[31] studied twelve weaning-success and eighteen weaning-failure patients during a spontaneous breathing trial. Half of the failure patients increased their oxygen consumption and this increase was met mainly by an increase in oxygen extraction. The remaining half of the failure patients did not exhibit an increase in oxygen consumption; instead, increase in oxygen delivery was accompanied by a decrease in oxygen extraction. These studies[31,42,45] demonstrate variability in circulatory and global tissue oxygenation responses during weaning failure.

Gas Exchange

A primary goal of mechanical ventilation is to improve gas exchange, and accordingly one expects some deterioration in gas exchange with the resumption of spontaneous breathing. The most detailed study of gas exchange during weaning is that conducted by Beydon et al.[50] They studied eight patients with COPD who were considered ventilator dependent (although the patients were able to sustain at least 1- to 3-hour periods of spontaneous breathing). When switched from controlled ventilation, patients developed an increase in frequency, fall in V_T (without change in $\dot{V}_E$), and an increase in P_{CO_2} (41 to 49 mm Hg). Using the multiple inert gas technique, the investigators found that the distribution of ventilation to regions of ventilation–perfusion ($\dot{V}_A/\dot{Q}$) relationships above 100 (i.e., V_D/V_T) increased from 39 ± 8% during controlled ventilation to 46 ± 7% during spontaneous breathing. Perfusion of low $\dot{V}_A/\dot{Q}$ regions was higher during spontaneous breathing than during controlled ventilation (15 ± 11 vs. 6 ± 8%). The investigators also performed isotope scans, which revealed a decrease in $\dot{V}_A/\dot{Q}$ ratios between the apex and the base of the lungs. This observation indicated that the low $\dot{V}_A/\dot{Q}$ units identified by the inert gas technique were located at the lung bases. The major determinant of the $\dot{V}_A/\dot{Q}$ abnormalities was the size of V_T: It correlated with perfusion in the low $\dot{V}_A/\dot{Q}$ range, the decrease of $\dot{V}_A/\dot{Q}$ ratios in the bases, and widening of the isotopic craniocaudal gradient. The maldistribution of $\dot{V}_A/\dot{Q}$ ratios during spontaneous breathing were improved by controlled ventilation but not by pressure support of 10 cm H_2O.

Torres et al[51] used the multiple inert gas technique to study eight patients with COPD who were apparently successfully weaned. Measurements were first obtained during assist-control ventilation (V_T 700 mL, rate 12 breaths/min, and FI_{O_2} ≤0.40). On discontinuation of the ventilator, the patients developed rapid shallow breathing (relative to ventilator settings) and acute respiratory acidosis (increase in P_{CO_2} from 49 to 59 mm Hg, decrease in pH from 7.42 to 7.36). Spontaneous breathing caused an overall worsening of ventilation–perfusion inequality: The fraction of cardiac output distributed to low $\dot{V}_A/\dot{Q}$ (<0.1) areas increased from 9.4% to 19.6%, and the dispersion of ventilation distribution increased. Despite the deterioration in P_{CO_2} relationships, the expected fall in partial pressure of oxygen (P_{O_2}) was prevented by an increase in cardiac output (4.7 to 6.7 L/min) and increase in mixed venous P_{O_2} (37 to 42 mm Hg). A largely similar pattern of gas exchange was reported by Ferrer et al,[52] who studied seven patients with COPD who were not yet ready to tolerate complete discontinuation of mechanical ventilation.

PREDICTING OUTCOMES

General Principles of Medical Decision Analysis

When talking about weaning indices or weaning predictors, many clinicians overlook the fact that these measurements constitute a form of diagnostic testing. Accordingly, evaluation of the reliability of weaning-predictor tests must comply with the canons developed for evaluating diagnostic tests.[53–55] To understand the literature on medical diagnostic testing, the reader has to cope with a huge number of specialized terms, many of which have meanings that contradict the meaning of the same words in everyday speech. Specificity, for example, measures the fraction of patients who are correctly identified as not having the disease under consideration. In regular everyday speech, specificity means that something that "possesses properties that characterize a species" or that is "clearly defined and definite." These ideas are the opposite of the absence of a property (disease). The terms are also duplicative. Specificity is also known as true-negative rate and as 1 minus false-positive rate. All of the specialized expressions are simply different ways of combining true-positive, true-negative, false-positive, and false-negative results. Life would be easier if research on weaning predictors were solely communicated using these four test characteristics, and terms such as specificity were avoided. The reader, however, cannot adopt this minimalist approach and must instead grapple with the many terms because of their widespread use.

A second problem arises when a reader desires a more fundamental understanding and consults a textbook on medical decision analysis. Diagnostic test results are called "positive" (or abnormal) when they diagnose a "disease" (or undesirable condition), and "negative" when they indicate a normal or desirable condition.[45] When applying these concepts to weaning, the reader must think of "disease" as "weaning success" and a positive or abnormal test result as one that predicts weaning success. This orientation may seem counterintuitive. But too large a body of research already exists to make a fundamental change.

A third problem for the reader of a textbook on decision analysis is that the discussion is usually in generic terms, covering all possible disease states and all forms of diagnostic testing. This generic or abstract approach makes the discussion long-winded. The reader has to relate abstract concepts to the particular clinical situation that the reader is interested in. To ease discussion, we discuss the fundamental principles

of decision analysis in terms of a single diagnostic test. We select a test used for predicting weaning outcome, the f/V_T, because it has been subjected to the most investigation. And we focus on a single outcome: a patient's ability to tolerate a 30-minute T-tube trial without distress that is followed by extubation. This outcome is weaning success. Thus, a positive diagnostic test result is a recording that predicts actual successful weaning outcome without the need for reintubation. The development of distress during a T-tube trial that leads to the reinstitution of mechanical ventilation is weaning failure; extubation followed by reintubation is not a necessary requirement to satisfy the definition of weaning failure. Thus, a negative diagnostic test result is a reading that predicts either the development of distress during a T-tube trial (leading to the reinstitution of mechanical ventilation) or the need for reintubation after extubation. The reader can apply the same framework to other diagnostic tests (such as maximum inspiratory pressure) and to other outcomes (such as the prediction of reintubation in a patient who is extubated after a successful weaning trial).

The data generated by most diagnostic tests, including f/V_T, are reported as continuous variables. It is common, however, to focus on a threshold and view the data in dichotomous terms: An f/V_T value equal to or less than 100 (breaths/min/L) is referred to as a positive result (indicating a high likelihood of weaning success). All tests are inaccurate to varying degrees: No diagnostic test has a one-to-one correspondence with a disease state. The degree of error is assessed by comparing a test's performance against a reference test. For weaning predictors, the reference standard is a patient's ability to tolerate a weaning trial that leads to extubation. This reference standard gives rise to significant difficulties in interpreting research findings (see below). Its lack of concreteness (necessary if a disorder is to fit an ontologic model of disease) contrasts with more rigorous reference standards available for other diagnostic tests (histologic findings for evaluating a cancer marker).

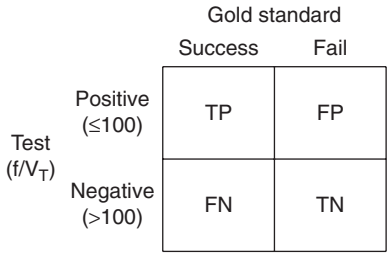
The characteristics of test results are most easily displayed by a fourfold table, often referred to as a "2 × 2" table (Fig. 58-15). For f/V_T, a true-positive result is a reading of equal to or less than 100 (the test predicts weaning success) in a patient who actually tolerates a T-tube trial that leads to extubation (weaning success). A true-negative result is an f/V_T reading greater than 100 (the test predicts weaning failure) in a patient who actually develops distress during a T-tube trial and requires the reinstitution of mechanical ventilation (weaning failure). A false-positive result is an f/V_T reading equal to or less than 100 (the test predicts weaning success) in a patient who actually fails a weaning trial. A false-negative result is an f/V_T reading equal to or less than 100 (the test predicts weaning failure) in a patient who actually tolerates a weaning trial and is extubated.

Each cell in Figure 58-15 represents one of the four unique characteristics of a test (true-positive, true-negative, false-positive, and false-negative results). When developing a new weaning predictor, researchers need to undertake the initial evaluation in roughly equal numbers of weaning-success and weaning-failure patients if the predictor is to prove reliable under future testing.[46] Once the four test characteristics have been determined in a broad spectrum of weaning-success and weaning-failure patients, the test characteristics are considered constant and the test can be applied to the evaluation of any given patient. There is, however, one major assumption, which is all too often ignored. The formulae assume that the prevalence of weaning success and weaning failure in the new groups in which the test is being applied is the same as in the sample from which the four test characteristics were originally developed.[53,56,57] If researchers are mindful of this fundamental requirement, much confusion can be avoided.

Sensitivity (also known by the more intuitive term, true-positive rate) answers the question: "In a weaning-success patient, what is the likelihood that the predictor test will be positive ($f/V_T \leq 100$)?" Thus, sensitivity measures the proportion of weaning-success patients in whom the predictive test is positive ($f/V_T \leq 100$). When clinicians are primarily interested in screening, they employ diagnostic tests that have a high sensitivity.[53] The purpose of a screening test is to pick up as many cases of a disease as possible out of the population being tested; screening can also be viewed as an exercise in ruling out disease, and a test for this purpose should have a low number of false-negative results (thus, a high sensitivity).[58] (Mnemonics have been proposed to remember these relationships. SnNout: If a test has a sufficiently high Sensitivity, a Negative result rules out the target disorder.) In the weaning context, this step is equivalent to using a predictor that will identify as many patients as possible who will actually pass a T-tube trial. Screening tests are typically performed in situations in which the pretest probability of the disease in question is low.[55] Because results are most often negative, the test should be easy to perform. As such, a test that takes 30 minutes or more to conduct, such as a T-tube trial, is not a satisfactory screening test.

Specificity (also known as true-negative rate) answers: "In a weaning-failure patient, what is the likelihood that the predictor test will be negative (f/V_T 100)?" Thus, specificity measures the proportion of weaning-failure patients in whom the predictive test is negative ($f/V_T > 100$). When clinicians are primarily interested in confirming (or ruling in) the presence of a disease, they employ diagnostic tests that have a low number of false-positive results and, thus, a high specificity.[53,58] (A mnemonic to remember this relationship is SpPin: If a test has a sufficiently high Specificity, a Positive result rules in the target disorder.) Because f/V_T has a relatively low specificity (0.64 in the original study,[59] it alone is not sufficient to confirm the presence of weaning failure. Instead, clinicians should undertake additional diagnostic testing, such as with a T-tube trial.

What are the characteristics of an ideal weaning-predictor test? Consider the following three diagnostic tests which differ in sensitivity and specificity. Test A has a sensitivity of 0.96 and specificity of 0.70; test B has a sensitivity of 0.70 and specificity of 0.96; and test C has a sensitivity of 0.83 and specificity of 0.83. Which test is best? The question cannot be answered until you are informed for what purpose



TP = Test predicts weaning success and patient actually succeeds

TN = Test predicts weaning failure and patient actually fails

FP = Test predicts weaning success and patient actually fails

FN = Test predicts weaning failure and patient actually succeeds

$$\text{Sensitivity} = \frac{TP}{TP + FN} = TPR = [1 - FNR]$$

$$\text{Specificity} = \frac{TN}{TN + FP} = TNR = [1 - FPR]$$

$$PPV = \frac{TP}{TP + FP}$$

$$NPV = \frac{TN}{TN + FN}$$

FN rate = 1 – sensitivity

FP rate = 1 – specificity

Likelihood ratio for a positive test = TPR / FPR = sensitivity / (1 – specificity)

Likelihood ratio for a negative test = FNR / TNR = (1 – sensitivity) / specificity

Prevalence = TP + FN / (TP + TN + FP + FN)

Diagnostic accuracy = [TP + TN] / [TP + TN + FP + FN]

FIGURE 58-15 A 2 × 2 tabular display of the characteristics of diagnostic tests. The vertical columns represent the results of the reference standard test. The horizontal rows represent the results of the index test. Readings of f/V_T equal to or less than 100 are classified as positive test results and readings greater than 100 are classified as negative test results. The relationship of these binary results to the outcome of a T-tube weaning trial forms a decision matrix that has four possible combinations.

the diagnostic test will be used. Many clinicians look on diagnostic testing from a monolithic perspective—a test is a test is a test. In reality, diagnostic testing is expected to fulfill two very different demands.[53–55] The first is screening, that is, to pick up cases of a condition at the earliest possible time. This demand requires a test with high sensitivity.[53–55] The second is confirmation of a condition for which there is already a strong suspicion. This demand requires a test with high specificity.[53–55] "A single test can seldom be excellent for the goals of both discovery [screening] and confirmation," Alvan Feinstein emphasized. "With rare exceptions, the same procedure cannot be sensitive enough to find all cases of the disease while simultaneously being specific enough to avoid false-positive identifications."[54] For example, chest radiography is reasonably sensitive (but nonspecific) in detecting lung cancer. Almost all patients with lung cancer will have an abnormal chest radiograph. (A normal chest radiograph is good in ruling out lung cancer.) But not everyone with an abnormal chest radiograph has lung cancer (high false-positive rate). Conversely, a positive histology result on bronchoscopic biopsy is a reasonably specific diagnostic method (false-positive results are uncommon). But it

is insensitive (often failing to capture cancers at inaccessible sites). For these reasons, clinicians commonly use diagnostic tests in combination.

A weaning-predictor test is used to spot the earliest point in time that a patient might tolerate a weaning trial. It serves solely as a screening test. On its own a positive predictor-test result is not used as justification for extubation. Before that step, a confirmatory test, such as with a T-tube trial, is undertaken. The ideal time to undertake a screening test is when the pretest probability of weaning success is 20% or less.[53] In contrast, weaning trials are commonly performed when the pretest probability of success is 75% or more.

The development of a reliable screening test hinges on avoiding false-negative results (a test predicting failure, but the patient actually succeeds).[53,54] Simultaneously the test needs to pick up every possible true-positive result—the mindset is to miss no patient who can breathe without the ventilator. To capture the maximum meaningful number of true-positive results, the threshold for defining a positive screening test may be set deliberately high.[53,54] This necessarily increases the number of false-positive results, producing a proportional decrease in specificity. Sensitivity captures exactly the components that define the reliability of a screening test because it contains only true-positive and false-negative rate. Likewise, specificity captures exactly the constituents of a reliable confirmatory test: avoidance of false-positive results (a test predicting success, but the patient actually fails) and maximizing true-negative rate.[53,54]

Sensitivity and specificity are often regarded as constant properties of a diagnostic test. The characteristics, however, for any diagnostic test are derived from data collected in a selected group of patients. Consequently, sensitivity and specificity of diagnostic tests vary across different parts of the clinical spectrum of the disease they are attempting to identify or exclude.[57,60] Both sensitivity and specificity also perform differently in populations with different distributions of disease severity. For example, the sensitivity and specificity of electrocardiographic stress testing differs between patients with triple-vessel coronary artery disease and patients with mild single-vessel disease.[61]

False-positive rate answers: "What is the likelihood that a weaning-failure patient will have a positive test result ($f/V_T \leq 100$)?" Thus, the false-positive rate measures the proportion of positive test results ($f/V_T \leq 100$) in all weaning-failure patients. In a weaning-failure patient, test results are only true-negatives or false-positives. Thus, false-positive rate is the complement of true-negative rate (false-positive rate = 1 minus true-negative rate).

False-negative rate answers: "What is the likelihood that a weaning-success patient will have a negative test result ($f/V_T > 100$)?" Thus, false-negative rate measures the proportion of negative test results ($f/V_T > 100$) in all weaning-success patients. In a weaning-success patient, test results are only true-positives or false-negatives. Thus, false-negative rate is the complement of true-positive rate (false-negative rate = 1 minus true-positive rate).

Sensitivity and specificity are calculated in patients in whom a diagnosis is already known. Clinicians, however, are faced with positive and negative results in patients whose diagnosis is not yet established. When contemplating a diagnosis, a clinician is not oriented down the vertical columns of the 2 × 2 table, but across the horizontal rows (see Fig. 58-15). Thus, clinicians think more in terms of positive-predictive and negative-predictive values than in terms of sensitivity and specificity.[52] Positive-predictive value answers: "What is the likelihood of weaning success in a patient who has an f/V_T equal to or less than 100?" Thus, positive-predictive value measures the fraction of patients with positive test results ($f/V_T \leq 100$) who are successfully weaned. Negative-predictive value answers: "What is the likelihood of weaning failure in a patient who has an f/V_T greater than 100?" Thus, negative-predictive value measures the fraction of patients with negative test results ($f/V_T > 100$) who fail a weaning trial. The positive- and negative-predictive values of a diagnostic test are particularly susceptible to variation in the prevalence of the condition under consideration (see below).

Likelihood ratio combines sensitivity and specificity into a single number. The likelihood ratio for a positive test relates the likelihood that a weaning-success patient will have a positive test result ($f/V_T \leq 100$) to the likelihood that a weaning-failure patient will have a positive test result. In other words, it is the probability of a positive test result ($f/V_T \leq 100$) in weaning-success patients divided by probability of the same test result in weaning-failure patients. It is calculated as true-positive rate/false-positive rate (or: sensitivity/[1 minus specificity]). The likelihood ratio for a negative test relates the likelihood that a weaning-success patient will have a negative test result ($f/V_T > 100$) to the likelihood that a weaning-failure patient will have a negative test result. In other words, it is the probability of a negative test result ($f/V_T > 100$) in weaning-success patients divided by probability of the same test result in weaning-failure patients. It is calculated as false-negative rate/true-negative rate (or: [1 minus sensitivity]/specificity).

Evidence-Based Medicine Task Force on Weaning

An Evidence-Based Medicine (EBM) Task Force of the American College of Chest Physicians[62,63] evaluated the usefulness of weaning-predictor tests. Employing a meta-analysis, the Task Force calculated pooled likelihood ratios for several predictors. They concluded that all weaning-predictor tests have low power, and recommended that clinicians should start the weaning process with a spontaneous breathing trial (a confirmatory test), and use the initial few minutes of the trial as a screening test.[62] This reverses the logic axiomatic to diagnostic testing. It is analogous to saying that when you suspect diabetes, start with a glucose-tolerance test and then, as the test gets underway, ask the patient for a urine sample in order to do a dipstick.[8]

The Task Force's meta-analysis contained more than fifteen methodologic errors, including several examples of the three main types of systematic error—selection bias (test-referral bias, spectrum bias), misclassification bias (categorizing reintubation as weaning failure), and confounding (considering pressure support to represent a form of unassisted breathing)—as well as several errors of interpretation.[64,65] Any one of the systematic errors would be sufficient to scupper the conclusions of the meta-analysis; yet when these flaws were subsequently identified and reported, the EBM Task Force did not contend a single one of them.[65–68] Instead, the Task Force viewed the errors as side issues that did not detract from their recommendations.[65,67] To ignore test-referral bias in the evaluation of a diagnostic test is analogous to a physiologist who claims that a partial pressure of arterial oxygen (Pa_{O_2}) of 80 mm Hg is always better than a Pa_{O_2} of 60 mm Hg, and the fact that the measurements were made at inspired oxygen concentrations of 50% and 21%, respectively, is an academic distraction best ignored.

Physicians recognize that writing an order for a T-tube trial constitutes a clinical decision. A corollary might be proffered that not writing an order means that no decision has been made. That interpretation would be wrong. Whenever a physician looks at a ventilated patient and does not order a T-tube trial (or weaning-predictor test), the physician is deciding that the patient is not weanable at this time (stage 2 of weaning; see Seven Stages of Weaning above). This subtle distinction is missed by the recommendation of the EBM Task Force to dispense with screening and commence the weaning process with a confirmatory test (a spontaneous breathing trial). They are thus encouraging physicians not to test for weanability until a patient looks ready for a T-tube trial. Their recommendation betrays a failure to comprehend the very purpose of weaning predictors. The sole purpose of a screening test (weaning predictors) is to alert a physician to consider doing a T-tube trial sooner than is the physician's custom—for the trial to occur earlier than would otherwise happen.[8] A positive result on a weaning-predictor test acts as a "physician alert," and aids in the cognitive process known as diagnostic triggering.[69]

The Bayes' Theorem

Before clinicians perform a diagnostic test, they formulate a pretest (or prior) probability of disease. In the context of weaning, clinicians form an initial gestalt of a patient's likelihood of passing a T-tube trial based on their previous experience of patients with similar clinical characteristics. After measuring a weaning predictor test, and knowing its test characteristics (sensitivity and specificity), the clinician formulates a new probability statement (of whether the patient is likely to pass the T-tube trial). The new statement is the posttest (or posterior) probability. The Bayes' theorem is an equation that describes the relationship between pretest probability and posttest probability. It is used to estimate how much the uncertainty of weaning outcome changes from before measurement of a predictor test (the pretest probability) to after obtaining the new information (the conditional probability). In particular, the Bayes' theorem is used to transform the information contained in sensitivity and specificity into a format that can be employed in diagnostic testing (calculation of posttest probability, in the format of positive-predictive and negative-predictive value).[54]

Conditional probability refers to the probability that a particular event will occur given that some other condition has been met.[57] In the weaning context, it addresses, "What is the probability of a positive f/V_T result (<100) conditional upon the patient's passing (or failing) a weaning trial?" A clinician can calculate the posttest probability of weaning success if the clinician has three pieces of information: (a) the pretest probability of weaning success (typically, the prevalence); (b) the probability of a positive f/V_T result (≤100) conditional upon the patient's passing a weaning trial (true-positive rate, or sensitivity); and (c) the probability of a positive f/V_T result (≤100) conditional upon the patient's failing a weaning trial (false-positive rate, or 1 minus specificity). A useful weaning predictor test has a high conditional probability (a high likelihood ratio), and thus markedly alters the posttest probability of weaning success. The Bayes' theorem is employed to convert the vertical indices in the 2×2 table (sensitivity and specificity) into the desired horizontal indices of disease prediction, which indicate posttest probability.[54] The posttest probability of weaning success after obtaining a positive test result (f/V_T ≤100) is the positive-predictive value. The posttest probability of weaning failure after obtaining a negative test result (f/V_T >100) is the negative-predictive value.

The Bayes' theorem operates on the assumption that the sensitivity and specificity of a test are constant irrespective of the pretest probability of disease. But "[i]n the few instances in which this assumption has been checked," notes Feinstein,[54] "it was found to be erroneous." In a study of exercise electrocardiography for the diagnosis of coronary artery disease, Hlatky et al[70] found sensitivity was 0.80 in patients with typical angina and 0.53 in patients with atypical chest pain; sensitivity was 0.85 in patients with triple-vessel disease and 0.48 in patients with single-vessel disease. Specificity was 0.85 when left-ventricular ejection fraction was equal to or greater than 50% and 0.73 when ejection fraction was 30% to 49%. In a study of patients being evaluated for urinary tract infection, Lachs et al[60] found that sensitivity of the dipstick test was 0.92 in patients with a high (>0.50) pretest probability of infection (patients with dysuria, urgency, and hematuria), and sensitivity was 0.56 in patients with a low pretest probability (≤0.50). Conversely, specificity was 0.42 in patients with a high pretest probability for infection, and 0.78 in patients with a low pretest probability. Indeed, for any condition, history and physical examination is likely to be more abnormal when a disease is extensive, and thus, the clinician will assign a high pretest probability.[71] In many studies of weaning predictors, researchers have assumed that reported values for sensitivity and specificity apply in all

circumstances. This assumption can give rise to errors when Bayes' theorem is applied.[54,57,72]

Pretest Probability of Successful Outcome

In evaluating the performance of weaning predictors, probably no aspect is ignored more often—and the source of greater confusion—than recognizing the fundamental importance of pretest probability (the anticipated prevalence of a disorder). The pretest probability is the fraction of weaning-success patients out of an entire weaning population (both success and failure patients). This pretest probability markedly affects the interpretation of new test information. In their book on medical decision analysis, Sox et al[55] state, "Perhaps the most important idea in this book is the following: The interpretation of a test result depends on the pretest probability of disease." That is, a clinician's interpretation of new diagnostic information depends on what the clinician believed before doing the test. As a clinician's estimate of pretest probability of weaning success increases, so also does the posttest probability of weaning success.

The pretest probability has an enormous influence over the ability of the results of any diagnostic test to alter the posttest probability of disease. When the pretest probability of weaning success is high, a positive test result ($f/V_T \leq 100$) has little effect. (The probability cannot increase much after a positive test because of a ceiling effect.) A negative test result ($f/V_T > 100$) will drop the probability considerably, but only into the large middle range of probability that is diagnostically inconclusive.[72] Conversely, when the pretest probability of weaning success is low, a negative test result ($f/V_T > 100$) has little effect. (The probability does not have anywhere to drop after a negative test. A positive test result [$f/V_T \leq 100$] has a large effect, but it only brings the clinician into the large middle range of probability.) Thus, when the pretest probability is already close to diagnostic certainty (high or low), a test that does not confirm the diagnostic suspicion can produce substantial changes in posttest probability. The above description is not unique to weaning predictors, but applies to all diagnostic tests in medicine. The only exception to this relationship between pretest probability and postprobability is an imaginary test with 100% sensitivity and 100% specificity.

A clinician gains the maximum increase in posttest probability for a positive test when pretest probability is 40%, and gains the maximum increase for a negative test when the pretest probability is 60%.[53] That is, physicians have most to gain from diagnostic testing when the pretest probability of a condition is close to 50%.[53] For a weaning predictor test to influence decision making, it needs to be measured early in a patient's course (expediting the transition between weaning stage 2 and stage 3). If a clinician observes that half or more of the clinician's measurements of weaning predictors generate positive results (indicating that a patient is ready for a weaning trial), that clinician is not measuring the predictor test early enough in his or her patient's course. A clinician who is measuring predictor tests early in a patient's course will obtain negative test results (indicating that a patient is not ready for a weaning trial) at least as often as positive results. Measuring weaning predictors in patients who have already passed a weaning trial is a futile undertaking. Unfortunately, most studies of weaning predictors have been conducted in patients who had a pretest probability of weaning success of 75% or higher (Table 58-1). Such a high pretest probability markedly decreases the apparent reliability of a weaning-predictor test (Fig. 58-16).

Sequential Diagnostic Testing

The implications of pretest probability are greater for weaning than for many clinical situations because weaning involves a sequence of three diagnostic tests: measurement of predictors, followed by a weaning trial, followed by an extubation trial. The Bayes' theorem assumes that the conditional probability of a test result is independent of pretest (prior) information—the assumption of conditional independence. The idea of independence is one of the most important concepts in probability theory.[73]

Two events are judged independent if the knowledge that one event has occurred tells you nothing about whether the second event will occur. The events "the patient has a skull fracture" and "the patient has cholecystitis" are independent. That is, conditioning on one event does not change

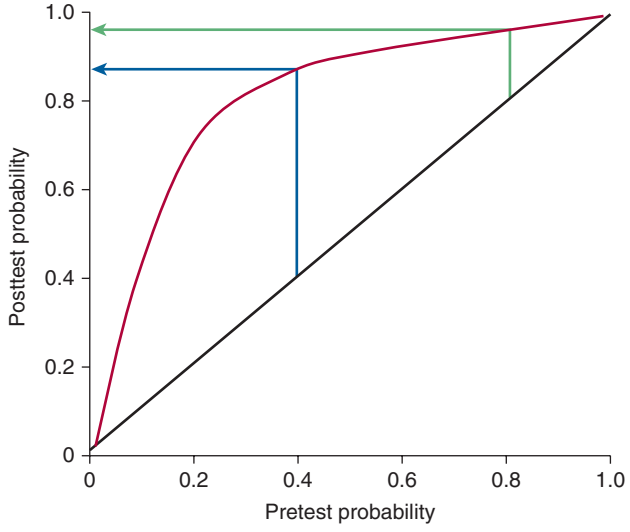


FIGURE 58-16 Relationship between pretest probability and posttest probability for a good weaning-predictor test, sensitivity of 0.9 and specificity of 0.9, is characterized by the red curve. If pretest probability of weaning success is 0.40, the Bayes' theorem dictates that a positive result on the weaning-predictor test will yield a posttest probability of 0.86. If pretest probability is 0.80, posttest probability will be 0.97. The increase between pretest and posttest probability in the second instance (21%, 0.17/0.80) is only a fraction of that in the first instance (115%, 0.46/0.40) despite the sensitivity and specificity being identical. Thus, a high pretest probability markedly decreases the apparent reliability of a weaning-predictor test.

TABLE 58-1: ACCURACY OF f/V_T IN PREDICTING WEANING OR EXTUBATION OUTCOME

Author	No. Patients	Outcome End Point	Threshold	Sensitivity	Specificity	PPV	NPV	Positive Likelihood Ratio	Negative Likelihood Ratio	Pretest Prob of Success	Data Available to Primary	Location
1. Yang & Tobin[59]	64	WF or EF	≤105	0.97	0.64	0.78	0.95	2.69	0.05	0.56	No	MICU
2. Gandia & Blanco[13]	40	WF or EF	<96	0.89	0.83	0.93	0.77	5.24	0.13	0.7	No	NS
3. Sassoon & Mahutte[14]	45	WF or EF	≤100	0.97	0.40	0.85	0.80	1.62	0.08	0.78	No	NS
4. Yang[128]	31	WF or EF	≤100	0.94	0.73	0.79	0.92	3.48	0.08	0.1352	No	MICU
5. Mohsenifar[117]	29	WF or EF	≤105 (PS 7 to 8)	1.00	0.27	0.69	1.00	1.37	0.00	0.62	Not clear	RICU
6. Lee[133]	52	EF only	≤105 (PS ?)	0.72	0.11	0.79	0.08	0.81	2.55	0.83	Yes	MICU
7. Capdevila[15]	67	EF only	60	0.73	0.75	0.92	0.36	2.92	0.36	0.82	Yes	Multidisc ICU
8. Epstein[1]	94	EF only	<100	0.92	0.22	0.83	0.40	1.18	0.36	0.81	Yes	MICU
9a. Chatila[108]	100	WF or EF	≤100	0.89	0.41	0.72	0.68	1.51	0.27	0.63	Yes	MICU, CCU
9b. Chatila[108]	100	WF or EF	≤100	0.98	0.59	0.83	0.94	2.39	0.03	0.63	Yes	MICU, CCU
10. Dojat[129]	38	WF or EF	<100	0.94	0.81	0.80	0.94	4.95	0.07	0.45	No	MICU, SICU
11. Leitch[75]	163	EF only	≤100 (PS 7)	0.96	0.00	0.98	0.00	0.96	> 2.55	0.982	Yes	M-SICU
12. Mergoni[181]	75	WF or EF	<105	0.65	0.58	0.60	0.63	1.54	0.61	0.49	Yes	M-SICU
13. Bouachour[120]	15	WF only	≤105	1.00	0.40	0.77	1.00	1.67	0.00	0.67	Not clear	NS
14. Baumeister[182]	47 Ped	EF only	≤11 breaths/min/mL/kg	0.79	0.78	0.94	0.47	3.59	0.27	0.81	No	PICU
15. Гологорский[183]	127	Not Defined	Not stated	0.84	0.83	0.80	0.86	—	—	—	Not clear	SICU
16a. Jacob[109]	183	WF or EF	100	0.97	0.33	0.94	0.50	1.45	0.09	0.92	Yes	SICU
16b. Jacob[109]	183	WF or EF	100	0.96	0.31	0.94	0.40	1.39	0.13	0.92	Yes	SICU
17a. Kreiger[130]	49	WF	≤105	0.74	0.73	0.90	0.44	2.74	0.36	0.78	Yes	MICU
17b. Kreiger[130]	49	WF	≤130 at 3 hours	0.93	0.89	0.97	0.80	8.45	0.08	0.78	Yes	MICU
18a. Rivera & Weissman[132]	40	WF only	65 (PS 5)	0.90	0.80	0.90	0.70	4.50	0.13	0.7	Yes	SICU
18b. Rivera & Weissman[132]	40	WF only	65 (PS + IMV)	1.00	0.82	0.84	1.00	5.56	0.00	0.7	Yes	SICU
19. Farias[184]	84 Ped	WF	≤11 breaths/min/mL/kg	0.48	0.86	0.53	0.83	3.43	0.60	0.75	No	PICU
20. Vallverdu[77]	217	WF or EF	≤100	0.90	0.36	0.66	0.73	1.41	0.28	0.58	Yes	M-SICU
21. Thiagarajan[185]	227 Ped	EF only	≤8 breaths/min/mL /kg	0.74	0.74	0.97	0.22	2.85	0.35	0.89	No	PICU
22. Zeggwagh[127]	101	EF only	<88	0.77	0.79	0.68	0.86	3.67	0.29	0.63	No	MICU
23. Maldonado[118]	27	WF only	≤105	0.93	0.75	0.83	0.89	3.72	0.09	0.56	Yes	RICU
24. Uusaro[78]	68	EF only	<100 (PS 5)	0.96	0.18	0.78	0.60	1.17	0.22	0.75	Yes	M-SICU
25. Khamiees[79]	100	EF only	≤105	0.84	0.17	0.82	0.19	1.01	0.94	0.82	Yes	MICU, CCU
26. Smina[81]	115	EF only	<100	0.90	0.42	0.92	0.36	1.55	0.24	0.89	Yes	MICU, CCU
27. Conti[131]	51	WF or EF	≤100	0.81	0.14	0.71	0.22	0.94	1.36	0.73	No	MICU, SICU
28. Fernandez[82]	57	WF; EF	<50	0.35	0.56	0.81	0.14	0.80	1.16	0.84	Yes	MICU, SICU
29. Jiang[186]	55	EF only	≤105	0.81	0.57	NR	NR	1.88	0.33	0.58	Yes	MICU

Abbreviations: CCU, cardiac care unit; *EF,* extubation failure; *f/V_T,* frequency-to-tidal-volume ration; *IMV,* intermittent mandatory ventilation; *MICU,* medical intensive care unit (ICU); *M-SICU,* medical-surgical ICU; *Multidisc ICU,* multidisciplinary ICU; *NPV,* negative-predictive value; *NS,* nonstated location; *PICU,* pediatric ICU; *PPV,* positive-predictive value; *PS,* pressure support; *RICU,* respiratory ICU; *SICU,* surgical ICU; *WF,* weaning failure.

The listed studies are those that reported data on the accuracy of f/V_T as a predictor of weaning outcome. Four groups of investigators, Chatila et al, Jacob et al, Krieger et al, and Rivera and Weissman (studies 9, 16, 17, and 18 in the table), report data under two different conditions in their articles; both sets of data are presented. Pretest probability of success in a study is the fraction of patients with a successful outcome out of the total population (both success and failure patients) included in the study.

the probability of the other event. In contrast, the events "the patient has cholecystitis" and "the patient has abdominal pain" are not independent. The conditioning probability of abdominal pain, given cholecystitis, is much higher than the nonconditional probability of abdominal pain (the proportion of all patients in the world with abdominal pain). When both an exercise electrocardiogram and a radionuclide myocardial scan are performed before coronary arteriography, the false-positive rate of each test depends on the results of the other test.[55] That is, the assumption of conditional independence of the two tests is invalid. Likewise, the conditioning probability that a T-tube trial will be successful and lead to extubation is much higher given a positive f/V_T test result (≤100). The two events, a positive f/V_T test result (≤100) and a successful T-tube trial, are not conditionally independent.

Because the assumption of conditional independence has not been verified for most combinations of two or more tests, experts recommend that the posttest probability of the first test be used as the pretest probability of the second test.[55] Figure 58-17 shows typical changes in pretest probability of successful extubation and posttest probability of successful extubation with the sequential performance of f/V_T measurement, a T-tube trial, and a trial of extubation.

Spectrum Bias and Test-Referral Bias

The term *spectrum* denotes the range of disease presentation and severity found in patients used to challenge the sensitivity and specificity of a diagnostic test.[58] Spectrum bias occurs when a diagnostic test performs differently in different groups of patients, as occurs when the new study population contains more sick (or less sick) patients than the population in which the diagnostic test was originally developed.[60] Another form of bias, test-referral bias, occurs when the results of a test under evaluation (f/V_T) are used to select patients for the reference-standard test (T-tube trial).

To illustrate spectrum bias, we discuss the introduction of a hypothetical new weaning-predictor test. To make our account easy to understand, we use f/V_T as the previously unevaluated weaning-predictor test. To determine if the new test is reliable in predicting extubation outcome, the investigators study 100 patients. The average value of f/V_T in these patients is 111. Because the investigators do not know whether f/V_T is reliable or not, all patients proceed to a T-tube trial; and if they pass that, the patients continue to a trial of extubation. The investigators report that an f/V_T value of less than 100 is reliable in predicting a successful outcome. Subsequently, another group of investigators decide to reevaluate the usefulness of the weaning-predictor test. They also study 100 patients, and the average value of f/V_T is again 111. Of the study population, seventy patients have positive f/V_T results (values <100), and thirty have negative f/V_T results (values >100). The seventy patients with positive f/V_T results proceed to a T-tube trial. Because the initial study revealed that negative f/V_T results were reliable in predicting weaning failure, the clinicians refuse to undertake a T-tube trial in the thirty patients with negative f/V_T results. These are thus excluded in the second study. The exclusion of patients with negative results skews the study population toward less severely ill patients, an effect termed *spectrum bias*. The patients in the first study, who had an average f/V_T

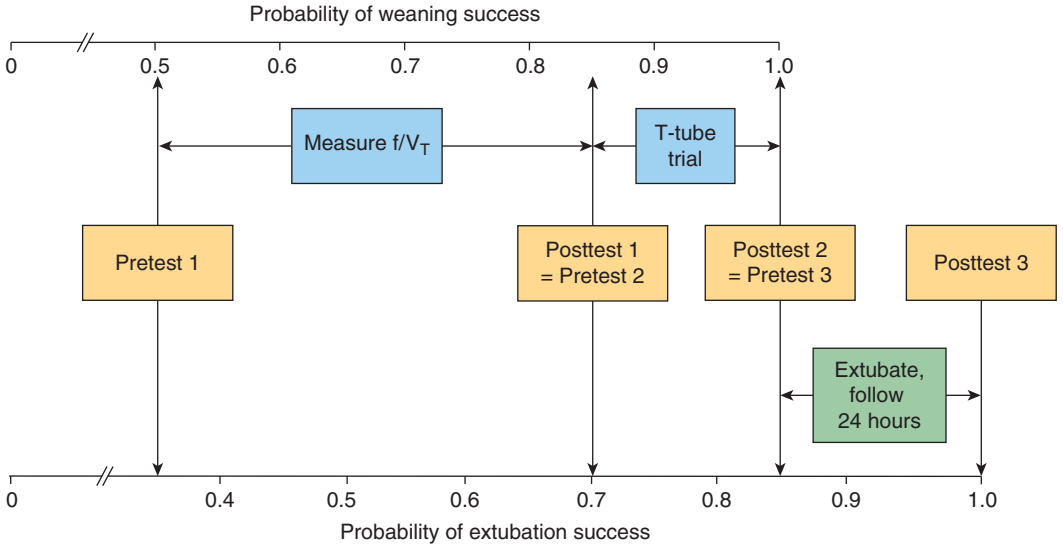


FIGURE 58-17 Interpreting the sequence of diagnostic testing in a patient who is weaned from mechanical ventilation and then extubated, with successful outcome defined as the ability to breathe spontaneously without ventilator assistance for 24 hours after extubation. Pretest 1 is the pretest probability of extubation success before measurement of f/V_T. The f/V_T reading constitutes the posttest results of the first diagnostic test, and also pretest probability of extubation success for the second diagnostic test, a T-tube trial. The outcome of the T-tube trial constitutes the posttest result of the second diagnostic test, and also the pretest probability of extubation success for the third diagnostic test, a trial of extubation. The outcome of the trial of extubation constitutes the posttest result of the third diagnostic test. In this hypothetical example, pretest probability of weaning success for the first diagnostic test is set arbitrarily at 0.50; the extent of the change for each subsequent step is based on average changes reported in published studies.

of 111, were more severely ill than the patients in the second study who had an average f/V_T of ninety. The selection of less severely ill patients in the second study produces an increase in the pretest probability of success; it also alters the sensitivity and specificity of the test.[54,55]

A second form of bias, test-referral bias, occurs when the results of a test under evaluation are used to select patients for the reference-standard test.[54,55] Consider a weaning-predictor test where its reliability is evaluated in terms of its ability to predict the successful toleration of extubation. If patients are required to pass a weaning trial before extubation, this study-entry requirement necessarily excludes all patients who fail. This step has three effects on the study population: first, fewer patients with negative results (of the weaning-predictor test) are included; second, relatively more patients with positive results are included; third, pretest probability of success is increased.[54,55] The first consequence produces a decrease in the specificity of the weaning-predictor test in this population compared with the population in which the test was originally developed. The second consequence increases the sensitivity of the test. Figure 58-18 provides a hypothetical example of how test-referral bias leads to changes in pretest probability, sensitivity, and specificity. The risk for the occurrence of test-referral bias is enormous when three diagnostic tests are undertaken in a sequential manner, as is the case with weaning and extubation.

Spectrum bias and test-referral bias accounts for much confusion in the interpretation of studies of weaning predictor tests. A skilled clinician who measures f/V_T will obtain on average at least as many (if not more) negative test results as positive test results (if the clinician is trying to move the transition between stage 2 and stage 3 of weaning [see Fig. 58-1] to an earlier time in a patient's course). Thus, pretest probability of weaning success is 50% or lower. Clinicians commonly use the f/V_T result to decide which patients will progress that day to a weaning trial. They subsequently use the results of the weaning trial to decide which patients will undergo a trial of extubation. If tolerance of extubation is used as the reference gold standard for evaluating the accuracy of f/V_T, the requirement to pass a weaning trial before extubation (as a criterion for entry into a study) will lead to fewer patients with negative test results (f/V_T >100) and relatively more patients with positive test results (f/V_T ≤100) in the study population (test-referral bias). Thus, the patients in the new study population will have a lower f/V_T on average than the population in which the weaning predictor was originally developed (spectrum bias). Test-referral bias leads to an increase in both true-positive rate and false-positive rate.

Several studies of weaning predictors suffer from the flaws of spectrum bias and test-referral bias.[15,74–82] The misinformation that has resulted from failure to take into account test-referral and other forms of bias brings to mind the comment of the late Alvan Feinstein, the founding father of clinical epidemiology:[56] "The most important issues in biostatistics are not expressed with statistical procedures. The issues are inherently scientific, rather than purely statistical, and relate to the architectural design of research, not to the numbers with which the data are cited and interpreted."

The extreme case of test-referral bias is the situation in which investigators require a positive f/V_T result (value ≤100) before subjecting a patient to a T-tube trial. By design, no patient with a negative f/V_T result (value >100) would undergo a T-tube trial. In that instance, all failed T-tube trials

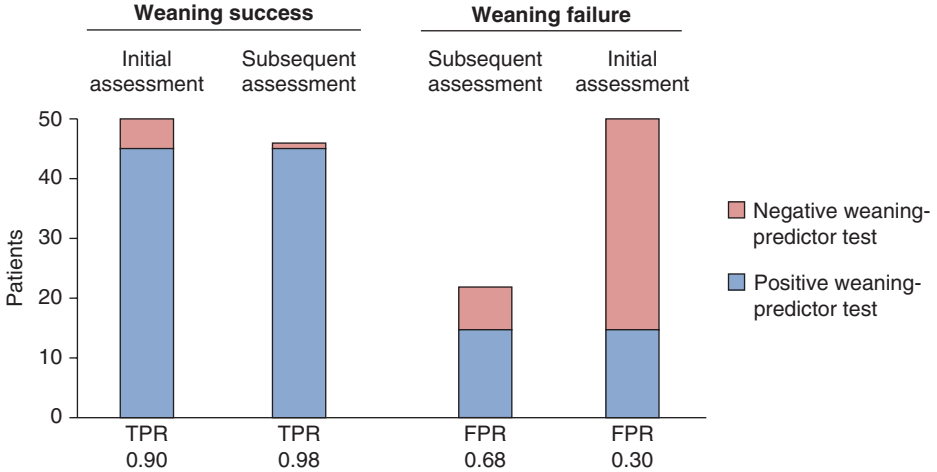


FIGURE 58-18 Test-referral bias. An initial study population (*outer two columns*) for the development of a new weaning predictor consists of fifty weaning-success patients and fifty weaning-failure patients. Of the fifty success patients, forty-five have a positive-test result (true-positive rate [*TPR*] or sensitivity of 0.90) (*first column*). Of the fifty failure patients, thirty-five have a negative-test result (false-positive rate [*FPR*] of 0.30 or specificity of 0.70) (*fourth column*). In a subsequent study (*second and third columns*), clinicians decide not to refer 80% of patients with negative test results (that predict weaning failure) for a T-tube trial. The 80% decrease in negative-test results in the success arm causes a decrease in false-negative results (true-positive results do not change); thus, the true-positive rate (sensitivity) increases to 0.98 (*second column*). The 80% decrease in negative-test results (twenty-eight fewer patients with negative-test results) in the failure arm causes a decrease in true-negative results (false-positive results do not change); thus, the false-positive rate increases to 0.68 (specificity decreases to 0.32) (*third column*).

would be in patients who had positive f/V_T results. Thus, the false-positive rate of f/V_T equal to or less than 100 would tend toward 1.0, and specificity toward 0. Investigators who have evaluated the accuracy of f/V_T have not required an f/V_T equal to or less than 100 per se before referring patients for a weaning trial (the reference gold standard test). Vallverdu et al[77]and Fernandez et al,[82] however, did require patients to have a frequency equal to or less than 35 breaths/min and V_T equal to or greater than 5 mL/kg; for an average 70-kg patient, these criteria result in f/V_T less than 100. Khamiees et al[79] required f/V_T less than 125 for entry. Not surprisingly, these three groups reported very low specificities for f/V_T (see Table 58-1). (Specificity in the study of Fernandez et al[82] is inflated through use of an f/V_T threshold of 50.)

Bayesian Analysis of Reported Performance of f/V_T

Motivated by the meta-analysis undertaken by the EBM Task Force[62,63] and cognizant of the group's failure to employ Bayesian principles in their pooled calculation, Tobin and Jubran[32] examined whether variation in reported reliability of f/V_T in predicting weaning success might be explained by spectrum and test-referral bias, as reflected by variation in pretest probability of success. They took data from the twenty studies included in the EBM Task Force's meta-analysis and nine additional studies published after the meta-analysis. Table 58-1 lists the evaluated studies.

Pretest probability of successful outcome varied from 0.45 to 0.98; reported sensitivity ranged from 0.35 to 1.00, with a mean of 0.87 ± 0.14; and specificity ranged from 0.00 to 0.89 (Table 58-1). The data were entered into a Bayesian model with pretest probability (prevalence of success) as the operating point. A weighted Pearson correlation analysis, which adjusts for the number of patients contained in a study, was used to compare the relationship between pretest probability and the reported values of positive- and negative-predictive value.

Figures 58-19 and 58-20 show that most of the positive-predictive and negative-predictive values in the studies fall close to or above the lower 95% confidence interval (CI) of the values predicted by the Bayes' theorem for pretest probability, using the sensitivity and specificity originally reported by Yang and Tobin.[59] Figure 58-21 shows that reported positive-predictive values were significantly correlated with the values of positive-predictive values predicted on the basis of the sensitivity and specificity originally reported by Yang and Tobin: $r = 0.86$, $p < 0.0001$. The correlation between reported and predicted negative-predictive values was $r = 0.82$, $p < 0.0001$. These correlations provide de facto confirmation of the sensitivity and specificity reported in the original 1991 study.

Also evident in Table 58-1 is the high rate of successful outcome, 75% or higher in more than half the studies. The high success rate reflects occurrence of spectrum bias, and the lower value of f/V_T in subsequent studies than in the original report (77.4 vs. 89.1) provides further evidence of spectrum bias. The high occurrence of test-referral bias is suggested by the high success rate together with the lower specificity of f/V_T in subsequent studies than in the original report (0.52 vs. 0.64). These analyses indicate that the low values of likelihood ratio for f/V_T reported by the Task Force are largely explained by their failure to correct for the occurrence of spectrum bias and test-referral bias.

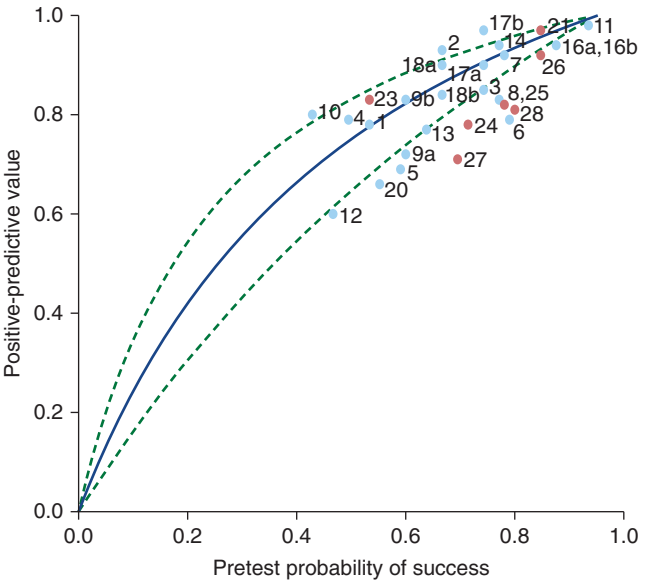


FIGURE 58-19 Positive-predictive value (posttest probability of successful outcome) for f/V_T plotted against pretest probability of successful outcome. Studies included in EBM Task Force meta-analysis are indicated by *blue symbols*; additional studies are indicated by *red symbols*. The curve is based on the sensitivity and specificity originally reported by Yang and Tobin[59] and the Bayes' formula for 0.01-unit increments in pretest probability between 0.00 and 1.00.[55] The lines represent the upper and lower 95% CIs for the predicted relationship of the positive-predictive values against pretest probability. The observed positive-predictive value in a study is plotted against the pretest probability of weaning success. The numbering of a study corresponds to its numbering in Table 58-1, and not to the numbering of the references. (Used, with permission, from Tobin and Jubran.[32])

A key requirement in establishing a scientific fact is to test a hypothesis under various settings and see if a finding is reproducible. The data from the twenty-nine studies in Table 58-1 are aggregated data from thousands of patients, in various settings, collected by investigator groups who varied widely in research skills. When these data were entered into a Bayesian model with pretest probability as the operating point, the observed posttest probabilities were closely correlated with the values predicted by the original study on f/V_T ($p < 0.0001$).

A further limitation in the Task Force's analysis was their failure to focus on the goal of a weaning-predictor test: to screen for weanability. Their use of likelihood ratio represents conflation of screening and confirmation. Likelihood ratio is not precisely suited to the evaluation of a screening test because it includes test components vital for screening (true-positive and false-negative rates) but

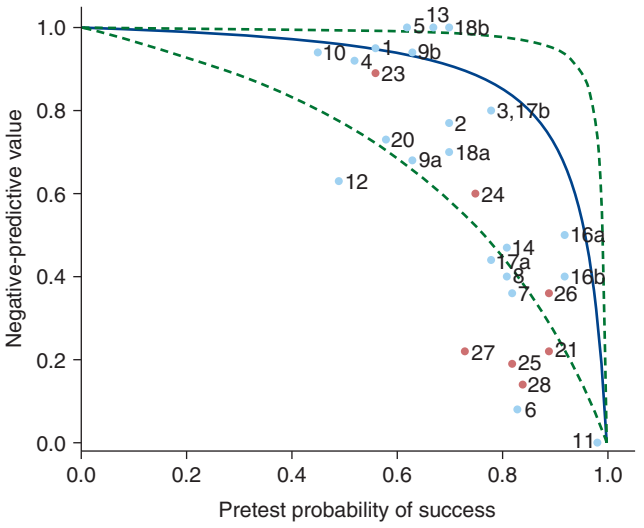


FIGURE 58-20 Negative-predictive value (posttest probability of unsuccessful outcome) for f/V_T. Studies included in EBM Task Force metaanalysis are indicated by *blue symbols*; additional studies are indicated by *red symbols*. The curve, its 95% CIs, and placement of a study on the plot are described in the legend to Figure 58-19. The observed negative-predictive value in a study is plotted against the pretest probability of weaning success (prevalence of successful outcome). The numbering of a study corresponds to its numbering in Table 58-1, and not to the numbering of the references. (Used, with permission, from Tobin and Jubran.[32])

also components not directly focused on screening (true-negative and false-positive rates); the latter cloud the contribution of the vital components.[54] In contrast, sensitivity captures exactly the components that define the reliability of a screening test because it contains only true-positive and false-negative rate. The average reported sensitivity of f/V_T was 0.87 (Table 58-1). Thus, contrary to the conclusion reached by the EBM Task Force, the facts included in the aggregated studies show that f/V_T is a reliable predictor of weaning success.

Tailoring a Predictor to Patient Needs

The threshold value of a test (the single value that separates positive from negative results) is determined by conducting research in a large number of patients. When applying the test to an individual patient, however, clinicians may decide to raise or lower the threshold value, taking into account unique aspects of a particular patient's condition.

Consider a severely immunocompromised patient in whom the physician believes that the risk of complications with continued ventilation far outweigh the risk of weaning failure or reintubation. With that mindset, the physician wants a weaning predictor test that has a very low rate of false-negative results. (A false-negative result is a test that predicts failure, f/V_T >100, but the patient succeeds.) False-negative results are reflected in sensitivity (for f/V_T, 0.97)[59] and negative-predictive value (for f/V_T, 0.95.)[59] To minimize the likelihood of a false-negative result in this patient, the physician may decide to undertake a T-tube trial even when f/V_T is higher than the usual threshold of 100 (say, 115 or 125). Use of a higher threshold moves borderline patients away from being kept on the ventilator and pushes them toward a weaning attempt. The clinician must recognize that a lower false-negative likelihood can only be achieved by also accepting a higher false-positive likelihood for the test result.

The second example relates to a patient with a neck deformity who the physician is leaning toward keeping on the ventilator for an additional day or longer rather than taking a risk of weaning failure and reintubation. The physician wants a weaning predictor test that has a very low rate of false-positive results. (A false-positive is a test that predicts

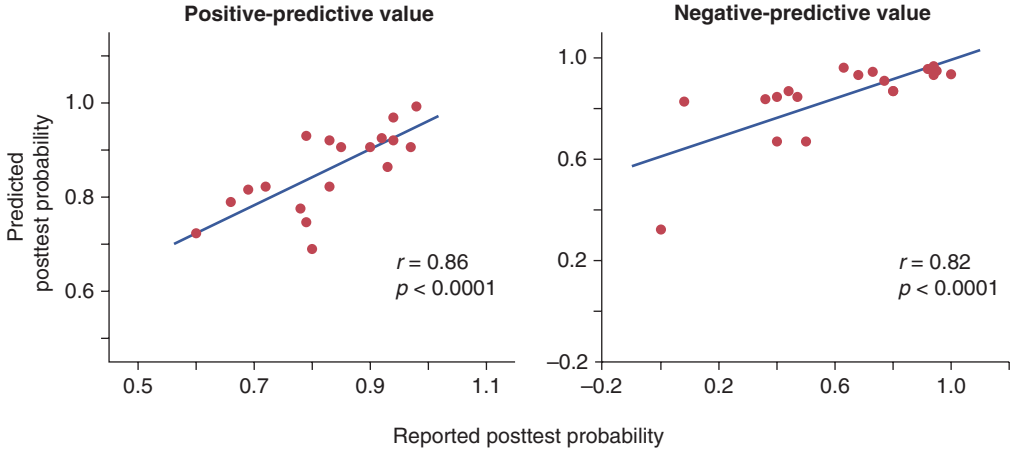


FIGURE 58-21 The relationship between the reported posttest probabilities for f/V_T (among the studies included in the EBM Task Force's meta-analysis) and the values predicted by observed pretest probability together with the sensitivity and specificity originally reported by Yang and Tobin.[59] The weighted Pearson correlation for positive-predictive value was $r = 0.86$, $p < 0.0001$ (*left panel*), and for negative-predictive value the correlation was $r = 0.82$, $p < 0.0001$ (*right panel*). (Used, with permission, from Tobin and Jubran.[32])

success, f/V_T <100, but the patient will fail a weaning trial.) False-positive results are reflected in specificity (for f/V_T, 0.64)[59] and positive-predictive value (for f/V_T, 0.78).[59] To minimize the likelihood of a false-positive result in this patient, the physician may decide to undertake a T-tube trial only if the f/V_T threshold is lower than the usual 100 (say, 90 or 80). But, again, the lower false-positive likelihood can be achieved only by accepting a higher false-negative likelihood for the test result.

If the particular group of patients that a clinician manages usually have a high likelihood of weaning success (high prevalence, or pretest probability, of success), the clinician should use an f/V_T threshold higher than 105, and thus accept a higher false-positive rate so as to maintain a high true-positive rate.[83] This new threshold will result in a higher sensitivity and lower specificity.

How much to adjust thresholds in an attempt to minimize false-negative results and false-positive results is an area of active decision-analysis research. In population studies, the threshold of a test is set such that the burden of false-positive results multiplied by the number of false-positive results balances the burden of false-negative results multiplied by the number of false-negative results. When adjusting the threshold value for an individual patient, the clinician needs to do an analogous computation. Reducing the occurrence of one undesirable test result can only be achieved by simultaneously increasing the occurrence of the other undesirable result. In the language of game theory, this balancing action is a zero-sum game (one goal is achieved at the expense of another).

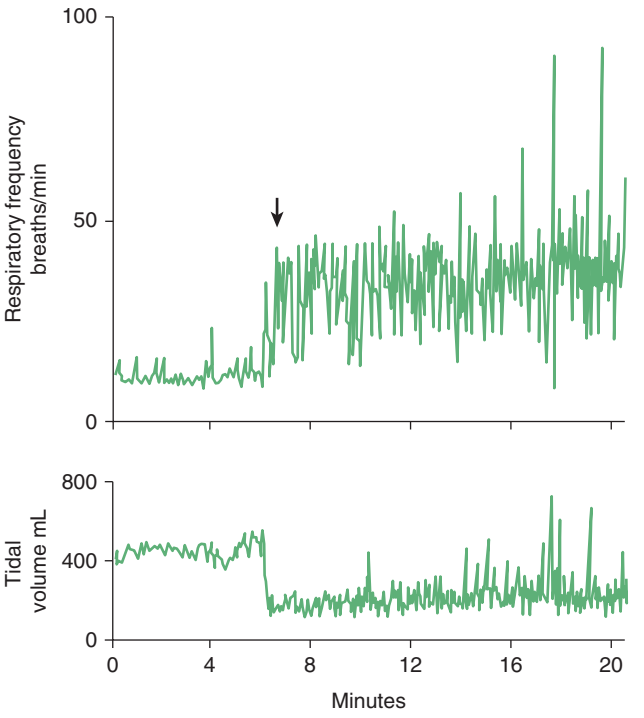


FIGURE 58-22 A time-series, breath-by-breath plot of respiratory frequency and tidal volume in a patient who failed a weaning trial. The *arrow* indicates the point of resuming spontaneous breathing. Rapid, shallow breathing developed almost immediately after discontinuation of the ventilator. (Used, with permission, from Tobin et al.[10])

PREDICTION OF WEANING OUTCOME

Frequency-to-Tidal-Volume Ratio

TECHNICAL DETAILS

The introduction of f/V_T as a weaning predictor stemmed from research into the pathophysiology of weaning failure. In 1986, Tobin et al[10] showed that patients who failed a T-tube trial exhibited an increase in frequency and a fall in V_T in the first few minutes after removal of ventilator support (Fig. 58-22).[10] In 1991, Yang and Tobin[59] reported that f/V_T was superior to nine other weaning predictors. In that study, sensitivity was 0.97, specificity 0.64, positive-predictive value 0.78, and negative-predictive value 0.95. Since the initial study, f/V_T has been employed in hundreds of studies, not all of them related to weaning. The manner of making the measurement and the use of f/V_T in decision making has varied considerably. The key steps that should be followed in order to obtain a reliable measurement of f/V_T are discussed in the following paragraphs.

The measurement should be performed relatively early in the patient's course. In the original study, Yang and Tobin[59] pointed out that the measurement was aimed at detecting "the earliest time that a patient might resume spontaneous breathing." That is, f/V_T functions solely as a screening test. The intent is to move the transition between stage 2 and stage 3 of weaning (see Fig. 58-1) to an earlier time in a patient's course. It makes no sense to make the measurement after the performance of a trial of spontaneous breathing, as many researchers have done.[15,84]

In the original study, the measurement of f/V_T was made with a handheld spirometer after disconnecting the patient's endotracheal tube from the ventilator circuit. That is, the measurement was made while the patient breathed room air, as that was the custom when obtaining weaning predictors in the 1980s. This is the approach we still employ (Fig. 58-23). (Some patients exhibit oxygen desaturation during the measurement, which indicates that they are not ready to proceed to a weaning trial.)

To measure f/V_T, some researchers use the pneumotachograph within the ventilator, taking care to place the patient in the "flow-by" mode and ensure that pressure support (PS) and continuous positive airway pressure (CPAP) are both set at zero. Patel et al[85] recently reported that such use of the pneumotachograph within an Evita ventilator (Evita 4 or Evita XL, Dräger, Telford, PA) yielded equivalent values of f/V_T to those obtained manually with a Wright spirometer.[85]

The measurement should be obtained over a full minute of unassisted breathing. Some clinicians employ a shorter duration, but this is unreliable because of variability in breathing. It is also important that the patient's breathing

FIGURE 58-23 Measurement of f/V_T. The patient's endotracheal tube is disconnected from the ventilator circuit and from supplemental oxygen, and the patient breathes room air. A handheld spirometer (with a filter) is attached to the end of the endotracheal tube. After the patient has established a regular respiratory rhythm (which may take about 1 minute), cumulative ventilation is measured for exactly 1 minute while respiratory frequency is simultaneously counted. The average tidal volume is calculated as minute ventilation divided by respiratory frequency. f/V_T is calculated as respiratory frequency divided by the average tidal volume.

pattern achieves equilibrium before starting the measurement. Mechanical ventilation can depress respiratory motor output through several mechanisms,[86] and shallow breaths and apneic pauses are common during the first minute after disconnecting a patient from the ventilator. We wait until we see that the patient has established a regular respiratory rhythm, which generally occurs by the end of the first minute of unassisted breathing. We then make the measurement of f/V_T over the subsequent minute (see Fig. 58-23).

A common mistake is to measure f/V_T while the patient is receiving ventilator assistance, either in the form of PS or CPAP. The goal of recording a patient's respiratory frequency and tidal volume is to forecast the values of these variables following removal of the endotracheal tube—when a patient will be breathing without PS or CPAP. Thus, it is irrational to measure f/V_T while the patient is receiving ventilator assistance. Moreover, the numbers themselves are drastically different. Values of f/V_T during unassisted breathing are 23% to 52% higher than during PS of 5 cm H_2O; values during unassisted breathing are 46% to 82% higher than during PS of 10 cm H_2O(Fig. 58-24).[87–90] Some clinicians assert that a PS of 5 to 10 cm H_2O simply overcomes the resistance posed by an endotracheal tube. This claim ignores the inflammation and edema that develops in the upper airways after an endotracheal tube has been in place for some time. After the endotracheal tube has been removed, the mucosal swelling produces an increase in upper airway resistance. Straus et al[91] demonstrated experimentally that the respiratory work dissipated against the supraglottic airway after extubation is almost identical to the work dissipated against the endotracheal tube before extubation (see Techniques of Weaning below).

The measurement of f/V_T while a patient is receiving CPAP also suffers from flawed thinking. In healthy subjects, CPAP 5 cm H_2O caused f/V_T to decrease by 38% as compared with unassisted breathing.[92] In thirty-three patients recovering from coronary bypass surgery, f/V_T was 49% lower when measured in the presence of CPAP 5 cm H_2O than during unassisted breathing: f/V_T 36 ± 14 and 71 ± 23 (standard deviation [SD]), respectively (see Fig. 58-24).[93] In sixty ventilated patients, f/V_T was 21% lower when measured in the presence of CPAP 5 cm H_2O (delivered through the ventilator circuit) than when patients breathed through a T-piece circuit without CPAP: median values of 71 (IQR: 52 to 88) and 90 (IQR: 59 to 137), respectively (p <0.001).[85] In the latter study, 89% of patients satisfied the threshold f/V_T for weaning success, equal to or less than 105, while receiving CPAP 5 cm H_2O, but only 65% satisfied it while breathing through a T-piece circuit. The ability of CPAP to alter the distribution of patients on each side of the threshold is sufficient to account for much of the variation in performance of f/V_T in research studies.

Some authors claim that use of CPAP 5 cm H_2O simply replaces the loss of "physiologic PEEP," which results from the presence of an endotracheal tube.[63] Physiologic PEEP, however, is a myth. Static recoil pressure of the respiratory system is zero at end-expiration. The addition of external PEEP while a patient is still intubated confounds clinicians in their ability to assess the challenges the patient will have to face following extubation.

In the original study on f/V_T, the value that best discriminated weaning-success patients from weaning-failure patients was equal to or less than 105.[59] This threshold is commonly rounded to 100 because sensitivity was the same for both f/V_T equal to or less than105 and f/V_T equal to or less than 100. Although it is crucial for investigators to adhere meticulously to a threshold of 105 (or 100) when conducting a research study, clinicians should not feel tethered to such a threshold in every patient (see "Tailoring a Predictor to Patient Needs" above). Dichotomizing the readings of a diagnostic test on the basis of a single cutoff value inevitably means that much information is discarded; an f/V_T reading of 106 does not carry the same clinical significance as an f/V_T of 136 (despite being handled identically in a research study). Physicians should use their judgment in making decisions based on the actual

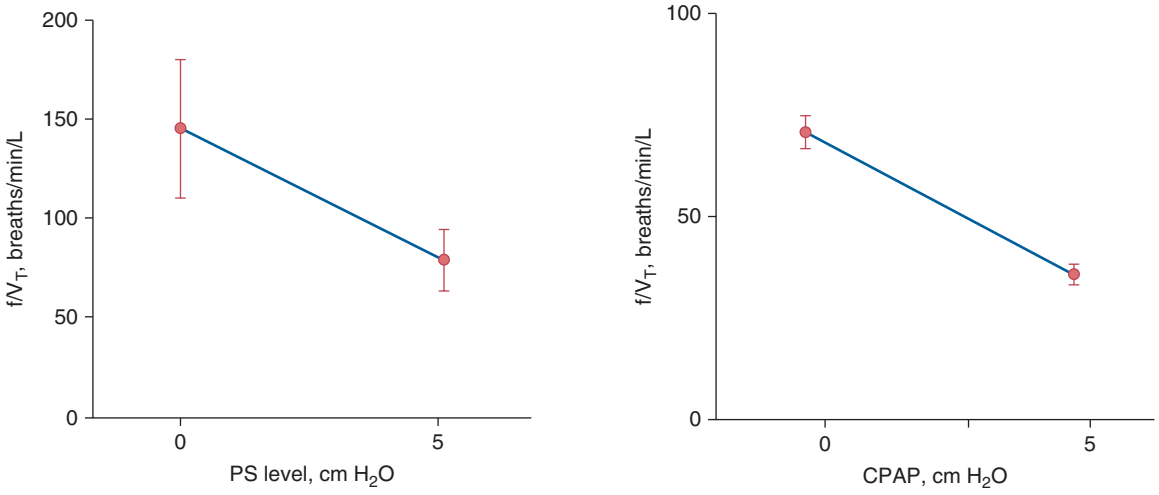


FIGURE 58-24 Effect of pressure support (*PS*) and continuous positive airway pressure (*CPAP*) on frequency-to-tidal volume ratio (f/V_T). *Left panel:* In twelve patients with COPD, f/V_T was 145 ± 121 (standard deviation [SD]) while patients received no ventilator assistance; the addition of PS 5 cm H_2O caused f/V_T to decrease to 79 ± 53 (45% decrease).[90,138,139] *Right panel:* In thirty-three postoperative patients, f/V_T was 71 ± 23 (SD) during unassisted breathing; the addition of CPAP 5 cm H_2O caused f/V_T to decrease to 36 ± 14 (49% decrease).[93]

reading of f/V_T and the characteristics of the patients rather than feeling constrained by a single cutoff value.

COMPARISON OF FREQUENCY-TO-TIDAL-VOLUME RATIO WITH OTHER DIAGNOSTIC TESTS

A detailed evaluation of a diagnostic test, when confined to that test alone, leaves a reader with an incomplete understanding of its usefulness. It is helpful for a reader to compare the performance of the test against other tests in common use. Table 58-2 provides a listing of true-positive rate (sensitivity), false-positive rate (1 minus specificity), and likelihood ratios for f/V_T as a weaning predictor and a number of other tests in common use, as reported by Sox et al.[55]

RANDOMIZED, CONTROLLED TRIAL

Tanios et al[94] undertook a randomized, controlled trial (RCT) to determine whether the inclusion of f/V_T in a weaning protocol influenced weaning time. They studied 304 patients: 153 in the f/V_T-protocol group and 151 in the nonprotocol group. Patients in the f/V_T-protocol group could proceed to a weaning trial (CPAP 5 cm H_2O and PS 7 cm H_2O or less) if—and only if—they had an f/V_T of less than 106. In the second study arm, clinicians did not follow the protocolized approach to weaning. The rate of extubation was the same in both groups: 82%. The duration of weaning was longer in the f/V_T-protocol group than in the nonprotocol group: median 3 (IQR: 1, 5) versus 2 (2, 6) days ($p = 0.04$). The authors concluded that including a weaning predictor (f/V_T) in a protocol prolonged weaning time.

The study has three major problems. The first arises with clinical management of patients in the control group. It is assumed that physicians managing patients in this group did not calculate f/V_T. Physicians are highly aware that respiratory frequency and tidal volume are key variables in deciding whether a patient will tolerate weaning and extubation. Once this knowledge has crept into a physician's brain, it cannot be surgically extirpated at the point of commencing an RCT. To ensure that physicians did not employ breathing pattern in their decision making, Tanios et al[94] would have had to have taken steps to hide or occlude the display of frequency and tidal volume on the bedside monitor and ventilator screen. Alternatively, Tanios et al[94] would have had to compare their usual care group with matched patients weaned in their unit before the late 1980s—before research studies began emphasizing the importance of respiratory frequency and tidal volume in clinical decision making on weaning.[10,59,95]

A second problem is the pretest probability of weaning/extubation success, 82%, in the patients of Tanios et al.[94] At a pretest probability of weaning success of 82%, the posttest probability for a positive f/V_T result, as calculated by the Bayes' theorem, is 93%. The benefit that accrues from such a small increment (from 82% to 93%) is extremely difficult to detect by means of an RCT.

The third problem is that f/V_T was one of several components in a weaning protocol. It is important to make a distinction between the use of a protocol in conducting a research study and its use in everyday clinical practice. In the research protocol of Tanios et al,[94] patients who had an f/V_T of 105 or less progressed to a weaning trial whereas patients with an f/V_T of 106 or higher were returned to the ventilator. When conducting research, this is exactly how a protocol must be specified and followed. No flexibility was permitted. A competent clinician, however, would think it daft to slavishly comply with a protocol that decided an entire day of ventilator management on a one-unit difference in a single measurement of f/V_T. Rather, intelligent physicians customize knowledge to the particulars of each

TABLE 58-2: TEST CHARACTERISTICS OF SOME COMMON DIAGNOSTIC TESTS

Test	TPR	FPR	Positive LR	Negative LR
f/V_T ≤105	0.97	0.36	2.72	0.04
f/V_T 100	0.97	0.32	3.03	0.04
f/V_T 80	0.81	0.11	7.52	0.22
Acid phosphatase for prostatic metastases	0.83	0.01–.003	42	0.17
Angiography in abdominal aortic aneurysm	0.70	0.05	14	0.32
Chest X-ray in lung cancer	0.60	0.04	15	0.42
CPK-MB in acute myocardial infarction	0.94	0.10	9.4	0.07
Ventilation–perfusion scan (segmental/larger) in PE	0.76	0.20	3.8	0.30
Pa_{O_2} <90 mm Hg in pulmonary embolism	0.95	0.50	1.9	0.10
FEV_1 <80% for COPD				
Young, minimal symptoms, nonsmoker	0.07	0.05	1.4	0.98
Middle age, moderate symptoms, smoker	0.27	0.10	2.7	0.81
Stress ECG for coronary artery disease	0.60	0.17	3.5	0.45
Theophylline >20 mcg/mL for toxicity	0.60	0.10	6.0	0.44
Ultrasound for endocarditis	0.37	0.04	9.3	0.66
WBC indium scan for abdominal abscess	0.86	0.05	17.2	0.15

Abbreviations: COPD, chronic obstructive pulmonary disease; *CPK-MB,* creatine phosphokinase-myocardial band; *ECG,* electrocardiogram; *FEV_1,* forced expiratory volume in 1 second; FPR, false-positive rate (1 – specificity); *f/V_T,* frequency-to-tidal-volume ratio; *LR,* likelihood ratio; *Pa_{O_2},* partial arterial oxygen pressure; *PE,* pulmonary embolism; *TPR,* true-positive rate; *WBC,* white blood cell count.

LR >10 or <0.1 = generates large and often conclusive changes in pretest to posttest probability;
LR 5 to 10 or 0.1 to 0.2 = generates moderate and usually useful shift in pretest to posttest probability;
LR 2 to 5 or 0.5 to 0.2 = generates a small and sometimes important change in pretest probability;
LR 1 to 2 or 0.5 to 1.0 = generates a small and rarely important change in pretest probability.

Source: Modified, with permission, from Sox et al.[55]

patient and are expected to outperform the inflexible application of a protocol—as has been shown in numerous studies of weaning protocols (see Weaning by Protocol versus Usual Care below).

Tanios et al[94] concluded that the inclusion of f/V_T in a protocol results in prolonged weaning time, and also that "f/V_T should not be used routinely in weaning decision making." The latter, however, is a non sequitur. The authors are conflating the use of f/V_T as one component of an inflexible protocol and its use in clinical decision making. The authors' experimental design did not test the use of f/V_T in decision making per se; rather, the design tested whether the use of a protocol that keeps a patient ventilated for an additional day when f/V_T is 106 as opposed to 105 increases the time required for weaning.

Arterial Blood-Gas Values

Other than in the course of withdrawing life support, mechanical ventilation is virtually never discontinued in a patient who has severe hypoxemia, such as a Pa_{O_2} less than 55 mm Hg with fractional inspired oxygen concentration (FI_{O_2}) greater than 0.40. Computations such as the Pa_{O_2}/FI_{O_2} ratio or alveolar-arterial P_{O_2} gradient are often used to quantify gas-exchange function. The relationship of these variables to more direct measurements of ventilation–perfusion relationships and shunt is based on many assumptions, and the relationship is variably affected by changes in the concentration of inhaled oxygen.[96] Few of these measurements have been rigorously evaluated as predictors of weaning outcome.

Krieger et al[97] found that a Pa_{O_2}/FI_{O_2} ratio of 238 (equivalent to a Pa_{O_2} of 50 with an FI_{O_2} of 0.21) had a positive-predictive value of 90% and a negative-predictive value of 10%. Yang and Tobin[59] found that a Pa_{O_2}-to-alveolar partial pressure of oxygen (PA_{O_2}) ratio of 0.35 provided the best separation between weaning-success and weaning-failure patients in an initial training data set. When that threshold was evaluated in a subsequent validation data set, the positive-predictive value was 0.59 and negative-predictive value was 0.53. These poor test performances do not mean that measurement of gas exchange is of no value in predicting weaning outcome. All such studies suffer from test-referral bias and patients with severe hypoxia were excluded from the study population. Although threshold values of the efficiency of gas exchange cannot be recommended for weaning prediction, weaning attempts are not recommended in patients with borderline hypoxemia.

Minute Ventilation

Normal minute ventilation ($\dot{V}_E$) is approximately 6 L/min.[98,99] Based on an initial report of Sahn and Lakshminarayan,[100] $\dot{V}_E$ of less than 10 L/min became one of the standard weaning predictors. Table 58-3 summarizes the subsequent studies with accessible data on the accuracy

TABLE 58-3: ACCURACY OF MINUTE VENTILATION IN PREDICTING WEANING OUTCOME

Threshold L/min	Sensitivity	Specificity	Positive-Predictive Value	Negative-Predictive Value	Number of Patients	Probability of Weaning Success	Authors
<9.9	1.00	0.32	0.46	1.00	101	0.63	Zeggwagh et al[127]
10	0.45	0.78	0.89	0.25	47	0.81	Tahvanainen et al[187]
<10	0.79	0.32	0.67	0.48	100	0.63	Chatila et al[108]
	0.50	0.67	0.98	0.20	163	0.988	Leitch et al[75]
	0.31	0.61	0.50	0.40	64	0.56	Yang and Tobin[59]
≤10	0.76	0.07	0.92	0.14	183	0.92	Jacob et al[109]
	0.96	0.47	0.90	0.73	100	0.83	Sahn and Lakshminarayan[100]
<12	0.40	0.50	0.74	0.19	45	0.78	Sassoon and Mahutte[14]
≤12	0.86	0.14	0.72	0.31	92	0.73	Conti et al[131]
>12.5	0.75	0.64	0.45	0.86	40	0.70	Gandia and Blanco[13]
<15	0.97	0.11	0.65	0.67	100	0.63	Chatila et al[108]
	0.78	0.18	0.55	0.38	64	0.56	Yang and Tobin[59]
≤15	0.81	0.20	0.52	0.50	31	0.52	Yang[128]

of $\dot{V}_E$ as a predictor of weaning outcome. When interpreting these data, it is essential to recognize the influence of test-referral bias, because clinicians are reluctant to initiate weaning attempts in patients with a high $\dot{V}_E$.

Maximum Inspiratory Pressure

The airway pressure during a maximum inspiratory effort, maximum inspiratory pressure ($P_I$max), provides a global measure of inspiratory muscle strength. The measurement is usually made at the opening of the endotracheal tube with an aneroid manometer while the patient makes a maximum effort against a closed airway.[101] The use of $P_I$max as a weaning predictor stems from a study by Sahn and Lakshminarayan.[100] They found that all patients with a $P_I$max value more negative than −30 cm H_2O were successfully weaned, whereas all patients with a $P_I$max less negative than −20 cm H_2O failed a weaning trial. Table 58-4 summarizes subsequent studies with accessible data on the accuracy of $P_I$max as a predictor of weaning outcome.

Vital Capacity

The normal vital capacity is usually between 65 and 75 mL/kg, and a value of 10 mL/kg or more has been suggested to predict a successful weaning outcome. Many investigators have found that vital capacity is often

TABLE 58-4: ACCURACY OF MAXIMAL INSPIRATORY PRESSURE IN PREDICTING WEANING OUTCOME

PImax Threshold cm H_2O	Sensitivity	Specificity	Positive-Predictive Value	Negative-Predictive Value	Number of Patients	Probability of Weaning Success	Authors
≤−30	0.68	0	0.74	0	42	0.81	Tahvanainen et al[187]
≤−30	0.57	0	0.44	0	12	0.58	Sassoon et al[11]
	1	0	0.67	0	17	0.65	Fiastro et al[30]
	NR	NR	0.92	0.21	269	0.9	Krieger et al[130]
	0.67	0.69	0.78	0.55	100	0.63	Chatila et al[108]
	0.86	0.21	0.58	0.55	100	0.56	Yang and Tobin[59]
≤−25	0.59	0.75	0.59	0.79	101	0.63	Zeggwagh et al[127]
≤−20	NR	NR	0.91	0.22	269	0.93	Krieger et al[97]
	1	0.14	0.6	1	100	0.56	Yang and Tobin[59]
	0.91	0.3	0.82	0.55	45	0.78	Sassoon and Mahutte[14]
	0.9	0.26	0.67	0.6	100	0.63	Chatila et al[108]
	0.96	0.07	0.92	0.14	183	0.92	Jacob et al[109]
<−16	0.92	0.07	0.72	0.36	92	0.73	Conti et al[131]
<−15	1	0.11	0.59	1	100	0.56	Yang and Tobin[59]

Abbreviation: NR, not reported.

unreliable. For example, Milbern et al[102] found vital capacity of 15 mL/kg to be falsely positive in 15% and falsely negative in 63% of patients. In a study of ten patients with Guillain-Barré syndrome, Chevrolet and Deleamont[103] reported that vital capacity was helpful in guiding the weaning process. Patients with a vital capacity of less than 7 mL/kg were unable to tolerate as few as 15 minutes of spontaneous breathing. As vital capacity increased to greater than 15 mL/kg with recovery from the illness, patients were safely extubated. Apart from unique circumstances, such as patients with Guillain-Barré syndrome, vital capacity is rarely used as a weaning predictor.

Airway Occlusion Pressure

The pressure generated during the first 0.1 second of an airway occlusion ($P_{0.1}$) is widely used as an index of respiratory center motor output.[104,105] During resting breathing in normal subjects, $P_{0.1}$ is approximately 0.5 to 1.5 cm H_2O. Several investigators have evaluated the usefulness of $P_{0.1}$ as a predictor of weaning outcome (Table 58-5). In these studies, the threshold value of $P_{0.1}$ discriminating between weaning success and weaning failure ranged from 3.4 to 6.0 cm H_2O.

Reproducibility of Standard Weaning Predictors

As with any diagnostic test, it is important to have precise details of the instrumentation used for the measurement, the conditions of the measurement, key steps in making the measurement, and reproducibility of the values. Reproducibility should be assessed in terms of variation in measurements made by one individual on several occasions, and variations in measurements made by several individuals at one point in time. The reproducibility of weaning predictor tests has been assessed to varying extents.

Before worrying about reproducibility, the first requirement for measuring a physiologic variable is to ensure that the patient has achieved a steady state (before the recording is commenced). This requirement can be difficult to satisfy when measuring weaning predictors: The switch between assisted ventilation and autonomous breathing means that there will be some intervening period when a steady state will not be present. For example, if measurement of frequency and V_T commences immediately after disconnecting a patient from the ventilator (say, within 10 seconds of the last ventilator breath and continued over the next 60 seconds), the patient may initially experience apneas (consequent to ventilator-induced neuromechanical inhibition).[106,107] The recorded values of frequency and V_T will be different than if the investigators had waited a minute or so to first ensure that the patient had begun to breathe in a steady manner. Chatila et al[108] reported that measurements of f/V_T at 30 minutes into a weaning trial more accurately predict outcome than measurements in the first minute.[109] Although it is true that including data of the first 30 seconds or so may be unrepresentative, this does not mean that it takes 30 minutes to establish a steady state.

Jubran et al[22] studied the time required for f/V_T to reach a point of equilibration in thirty-five weaning-failure and twenty-five weaning-success patients. The median time to reach ±10% of the final value of f/V_T was 2 (IQR: 1 to 2) minutes in both the weaning-success and weaning-failure patients (see Fig. 58-6). Within 2 minutes of the onset of the T-tube trial, 77% of the failure patients and 73% of the success patients had reached ±10% of the final value of f/V_T. The rapid equilibration of f/V_T contrasts with the slower equilibration of swings in esophageal pressure. The median time to reach ±10% of the final value of swings in esophageal pressure was 7.5 (4.2 to 14.75) minutes in the failure

TABLE 58-5: ACCURACY OF OCCLUSION PRESSURE IN PREDICTING WEANING OUTCOME

Threshold cm H_2O	Sensitivity	Specificity	Positive-Predictive Value	Negative-Predictive Value	Number of Patients	Probability of Weaning Success	Authors
>2.8	0.67	0.52	0.21	0.89	130	0.88	Fernandez et al[82]
≥3.4	0.75	0.61	0.45	0.85	30	0.7	Gandia and Blanco[13]
≤4.0	0.83	0.90	0.93	0.78	20	0.6	Fernandez et al[188]
≤4.0	0.94	0.07	0.73	0.33	92	0.73	Conti et al[131]
≤4.2	0.78	1.00	1.00	0.89	20	0.35	Herrera et al[189]
	0.71	0.43	0.56	0.6	11	0.5	Montgomery et al[12]
≤4.5	1.00	1.00	1.00	1.00	13	0.46	Conti et al[190]
	0.75	0.55	0.7	0.62	217	0.58	Vallverdu et al[77]
5.0	0.87	0.91	0.96	0.65	75	0.82	Capdevila et al[15]
<5.5	0.91	0.36	0.56	0.82	68	0.75	Uusaro et al[78]
≤5.5	09.7	0.40	0.85	0.80	45	0.78	Sassoon and Mahutte[14]
≤6.0	0.86	0.29	0.55	0.67	11	0.5	Montgomery et al[12]
<6.0	1.00	1.00	1.00	1.00	12	0.58	Sassoon et al[11]

patients and 5 (2 to 8.5) minutes in the success patients. Based on these data, it is reasonable to usually commence measurement of f/V_T at 60 seconds after removal of the ventilator and then continue the measurement for another 60 seconds.

Yang and Tobin[59] investigated the methods used for measuring $\dot{V}_E$ and its subsets. In a survey of twenty-five hospitals, the most common condition for the measurement was unassisted breathing while receiving room air (thirteen hospitals). Ten hospitals made the measurement during assisted breathing while receiving oxygen supplied by three different methods. Two hospitals measured $\dot{V}_E$ during ventilator support. The latter error seemed laughable in 1991, but today it is even more widely made.

Yang and Tobin[110] measured $\dot{V}_E$ and its subsets in thirty-three patients, who were clinically stable and considered ready to undergo a trial of weaning. $\dot{V}_E$ was 11.9 ± 0.8 L/min while patients spontaneously breathed oxygen through the ventilator circuit (the same FI_{O_2} as patients had received during ventilator support; achieved Pa_{O_2} 89 ± 4 mm Hg). When the patients were switched to room air, $\dot{V}_E$ increased to 13.5 ± 1.1 L/min; frequency also increased from 30.1 ± 11.8 to 33.9 ± 2.2 breaths/min, whereas V_T did not change. Fifteen patients satisfied the $\dot{V}_E$ threshold to progress to a weaning trial ($\dot{V}_E$ <10 L/min) while they breathed oxygen, but seven of them (47%) no longer satisfied this threshold when switched to room air. The study illustrates a wide range of conditions under which $\dot{V}_E$ is measured, and emphasizes the need to control the conditions of the measurement.

Yang[111] examined the reproducibility of predictor measurements in thirty patients about to undergo a weaning trial. Repeat measurements were obtained by a single individual on three trials over 15 minutes. The coefficients of variation for the repeated measurements (during 1 minute of room air breathing) were 10.8 ± 2.1% for $\dot{V}_E$, 6.7 ± 1.2% for frequency, 7.6 ± 1.2% for V_T, and 9.5 ± 1.1% for f/V_T. The coefficient of variation for measurements of $P_I$max (measured with a one-way valve, ensuring a lung volume below functional residual capacity) was 10.6 ± 1.5%. Repeat measurements of vital capacity were the least reproducible, with a coefficient of variation of 19.6 ± 2.8%.

Multz et al[112] undertook a more detailed study of the reproducibility of $P_I$max (measured with an aneroid manometer) in fourteen ventilator-dependent patients. Triplicate measurements were obtained by five experienced investigators who encouraged the patients to make vigorous inspiratory efforts. Measurements of $P_I$max at a single sitting by a single investigator showed good reproducibility: coefficient of variation of 12 ± 1%. Much greater variation was observed when $P_I$max was measured in the same patient on the same day by different investigators: coefficient of variation 32 ± 4%.

Measurements of $P_{0.1}$ exhibit the greatest variability, perhaps because the pressures recorded are very small (normal: 0.5 to 1.5 cm H_2O) and the timing (0.1 second) must be precise. The coefficient of variation within individual subjects is approximately 50%.[113,114] The interindividual coefficient of variation is approximately 20% to 33% during a single set of measurements,[114,115] but on repeated measurements (during CO_2 rebreathing trials) it is approximately 60%.[116]

Gastric Tonometry

The reliability of gastric tonometry in predicting weaning outcome was discussed in considerable depth in the second edition of this book. The rationale for its use is that the gastrointestinal mucosa becomes ischemic early with the development of either hemodynamic compromise or a redistribution of blood flow.[78,117–121] New studies supporting the use of this technique for weaning prediction have not been published during the interval between the second edition and this edition. We are not aware of any research or clinical group that advocates the use of gastric tonometry as a weaning predictor and the topic will not be discussed.

B-Type Natriuretic Peptides

Pro-brain natriuretic peptide (BNP), a prohormone, is synthesized by cardiomyocytes in response to mechanical stretch as occurs with increased atrial or ventricular pressure, volume overload or both.[122] Once secreted, pro-BNP is immediately cleaved into the biologically active 32-amino acid carboxyl-terminal peptide (BNP) and its inactive 76-amino acid amino terminal (N-terminal) fragment (NT-proBNP).[123] Both systolic and diastolic dysfunction of the left ventricle can result in high levels of BNP and NT-proBNP in the bloodstream, and these biomarkers are widely used as screening tools in patients with suspected cardiac disorders. Several investigators have evaluated the accuracy of BNP and NT-proBNP in identifying the likelihood and presence of cardiac causes of weaning failure.

In 102 patients about to undergo a 1-hour weaning trial, Mekontso-Dessap et al[124] measured plasma BNP and repeated the measurement in the first sixty patients at the end of the trial. Forty-two patients (41.2%) were classified as outcome failures: thirty-seven patients failed the weaning trial and five patients failed extubation. Plasma BNP was higher in patients with an unsuccessful outcome. The area under the receiver operating characteristic (ROC) curve for plasma BNP that predicted an unsuccessful outcome was 0.89 ± 0.04; a cutoff value of 275 pg/mL provided the greatest diagnostic accuracy (86%). The higher value of BNP, however, before the weaning trial in the outcome failures does not necessarily mean that cardiac dysfunction was responsible for the failed weaning attempt. Plasma BNP can be elevated for reasons other than left-heart dysfunction, such as advanced age, female gender, renal dysfunction, sepsis, pulmonary hypertension, vigorous fluid management, and extensive use of agents such as diuretics, angiotensin-converting enzyme inhibitors, and β-blockers.[43,125] Moreover, the level of BNP did not significantly change

between the beginning and the end of the weaning attempt. Nine patients who failed the initial weaning attempt were successfully weaned after diuretic therapy, which was associated with a significant decrease in BNP from 517 to 226 pg/mL ($p = 0.01$).[124]

Grasso et al[125] measured plasma levels of NT-proBNP in nineteen patients with COPD before and at the end of a weaning trial. Eight patients (42%) were classified as having acute cardiac dysfunction at the end of the trial. Baseline NT-proBNP levels were significantly higher (median: 5000; IQR: 4218 pg/mL) in these patients than in patients without evidence of acute cardiac dysfunction (median: 1705; IQR: 3491 pg/mL). Plasma levels of NT-proBNP increased significantly at the end of the weaning trial only in patients with acute cardiac dysfunction (median: 12,733; IQR: 16,456 pg/mL; $p < 0.05$). The increase in NT-proBNP over the course of the weaning trial, but not baseline NT-proBNP, provided a good prediction of weaning-induced cardiac dysfunction: area under ROC curve, 0.909 (95% CI, 0.69 to 0.98; $p < 0.0001$, cutoff = 184.7 pg/mL). The response pattern is the opposite of that reported by Mekontso-Dessap et al,[124] who found that the baseline value of plasma BNP, but not the change in BNP over the course of a weaning trial, predicted weaning failure.

The relative accuracy of BNP and NT-proBNP for predicting and identifying cardiac dysfunction as the cause of weaning failure was investigated by Zapata et al[126] in a group of 100 patients who had received mechanical ventilation for more than 48 hours. Thirty-two patients failed the weaning trial, and twelve of these were classified as resulting from cardiac failure, diagnosed on the basis of PAOP greater than 18 mm Hg or echocardiographic features of elevated filling pressures. Before the weaning trial, BNP and NT-proBNP were higher in patients who went on to fail because of cardiac causes than in the remaining patients: Threshold values based on ROC curve analyses were 263 ng/L for BNP ($p < 0.001$) and 1343 ng/L for NT-proBNP ($p = 0.08$). The threshold value of BNP that most accurately predicted weaning-induced cardiac failure was lower than the value reported by Mekontso-Dessap et al,[124] plasma BNP of 263 and 275 ng/L, respectively, and the level of diagnostic accuracy was also lower, 68% and 85%, respectively. Both BNP and NT-proBNP increased significantly over the course of the weaning trial in patients who developed cardiac failure. BNP was superior to NT-proBNP both in predicting and making a diagnosis of cardiac failure. Zapata et al[126] attributed the superior performance of BNP to its shorter circulating half-life (20 minutes). The longer half-life of NT-proBNP (120 minutes) promotes increased accumulation of the peptide after secretion, and thus produces a wider range of plasma concentrations.

At this juncture, there is considerable divergence among the results of studies evaluating the ability of natriuretic peptides to predict weaning outcome. Some investigators report that baseline values have the greatest predictive power,[124] whereas others report that the change in a peptide over the course of a weaning trial is more reliable;[125] some investigators report that NT-proBNP is more reliable than BNP,[125] whereas others report the opposite;[126] and the threshold value that discriminate between weaning-success and weaning-failure patients differs considerably among the studies.

TECHNIQUES OF WEANING

Researchers who developed weaning predictors never recommended that patients be immediately extubated if a patient passed the predictor test. A one-step approach would be reasonable if the risks associated with the development of postextubation distress and the need for reintubation were trivial. Instead, clinicians decide whether to extubate a patient after performing two diagnostic tests in sequence (measurement of predictors followed by a weaning trial). The importance of this two-step approach is illustrated by the study of Zeggwagh et al.[127] They studied 101 patients, ventilated for more than 48 hours (mean: 10 ± 10 days; range: 2 to 60 days), who were considered ready for weaning by the unit team. The unit team then extubated the patients without first undertaking any formal weaning trial. (The extubation decision was based on relatively crude variables, and not the results of more sophisticated weaning predictor tests.) Of the 101 patients, thirty-seven required reintubation. This rate is double (or more) the rate reported in most other studies. These data of Zeggwagh et al[127] emphasize the need for a formal weaning trial before extubation.

The two-step strategy long employed by clinicians is consistent with the theoretical reasoning of the ideal approach to diagnostic testing. Clinicians first contemplate the possibility of a condition (typically a disease, but here it is the possibility of weaning success). At this stage they need a test with very high sensitivity. When the test results are negative (normal), the condition can be confidently ruled out.[53] If the test results are positive (abnormal), the clinician ideally follows the now stronger suspicion (based on the initial very sensitive test) with a second diagnostic test that is very specific. When the result of a very specific test is positive (abnormal), it essentially rules in a disease.[47] Studies of f/V_T have shown it to have a much higher sensitivity than specificity; several investigators have reported sensitivities of 0.90 or higher[1,77,81,118,128–131] or 0.97 or higher.[14,59,108,109,132,133]

For the second diagnostic test, a T-tube or some other weaning trial, clinicians operate on the assumption that it has a high specificity, although this assumption has never been formally tested. A test with high specificity has a low rate of false-positive results (patients who pass a T-tube trial, are extubated, but require reintubation). The usual rate of reintubation after passing a T-tube trial is 15% to 20%, although some investigators have reported reintubation rates as high as 29%.[78,80,118,129,134] The true-negative rate is also needed for calculation of specificity. Determination of the true-negative

rate for a T-tube trial would require the extubation of all patients who fail the trial and counting how many require reintubation, an experiment that is unethical.

A second rationale for the use of weaning techniques is that they somehow improve the patient's likelihood of tolerating extubation. That is, weaning techniques have some therapeutic action beyond their diagnostic role. This rationale is generally couched in terms of improved reconditioning of the respiratory muscles.

A weaning task force[62,63] has suggested that measuring predictors may inhibit expeditious weaning, and they advocated the bypassing of this step and starting weaning evaluation with a trial of spontaneous breathing. Yet in a study used to support this viewpoint, Ely et al[135] found that physicians refused to order a spontaneous breathing trial in 64% to 89% of patients who had already demonstrated satisfactory respiratory function on their weaning predictors. Respiratory therapists had demonstrated greater than 95% compliance in measuring f/V_T. It is difficult to understand how the demonstration of good physiologic performance on weaning predictors could have resulted in the failure to undertake a trial of spontaneous breathing in up to 90% of patients.

The major techniques that are used include T-tube trial, PS, intermittent mandatory ventilation (IMV), or some combination of these three.

Intermittent Mandatory Ventilation

Chapter 7 discusses IMV in detail. With IMV, the patient receives periodic positive-pressure breaths from the ventilator at a preset volume and rate. In addition, the patient can take spontaneous breaths between these mandatory breaths.

When IMV is used for weaning, the mandatory rate from the ventilator is reduced in steps of 1 to 3 breaths/min, and an arterial blood gas is obtained about 30 minutes after each change. Unfortunately, adjusting the number of ventilator breaths in accordance with the results of blood gases can lead to a false sense of security. As little as 2 to 3 positive-pressure breaths per minute can achieve acceptable blood gases, but these values provide no information about a patient's work of breathing, which may be excessive.

IMV was originally seen as the ideal mode for weaning: The ventilator breaths were expected to provide respiratory muscle rest, and the intervening spontaneous breaths to facilitate reconditioning. Accordingly, it was thought that respiratory muscle rest would be proportional to the number of positive-pressure breaths. Subsequent studies revealed that patients have difficulty in adapting to the intermittent nature of the assistance.[136,137] Studies revealed that inspiratory effort is equivalent for the assisted and unassisted breaths. At IMV rates of 14 breaths/min or less, tension–time index for both the assisted and unassisted breaths is above the threshold associated with respiratory muscle fatigue. At a moderate level of ventilator assistance (where the ventilator accounts for 20% to 50% of the total ventilation), electromyographic recordings reveal that activity of the diaphragm and sternomastoid muscles during assisted breaths is no lower than that during unassisted breaths.[137] These findings suggest that respiratory center output is preprogrammed and unable to adapt to breath-by-breath changes in load as occur with IMV. Consequently, IMV may contribute to the development of respiratory muscle fatigue or prevent recovery from it.

Pressure Support

Chapter 8 discusses pressure support (PS) in detail. Like IMV, PS provides graded assistance, but differs from IMV in that the clinician sets the level of pressure (rather than the volume) to augment every spontaneous respiratory effort. The level of pressure is usually adjusted in accordance with the patient's frequency. The frequency, however, that signals a satisfactory level of respiratory muscle rest has never been well defined, and recommendations range from 16 to 30 breaths/min.[90,138,139]

When PS is used for weaning, the level of pressure is reduced gradually, in decrements of 3 to 6 cm H_2O, titrated to the patient's frequency. PS is commonly used to counteract the work imposed by breathing through the endotracheal tube and ventilator circuit. Consequently, the notion arose that if a patient was able to sustain ventilation at this "compensatory level" of PS, the patient should be able to breathe without difficulty after extubation. Investigators have estimated this compensatory level of PS to range from 3 to 13 cm H_2O. No method has ever been shown to reliably estimate the compensatory level of PS required by an individual patient.

Individuals who recommended the addition of PS for overcoming resistance of the endotracheal tube failed to recognize that the upper airways become inflamed and edematous after an endotracheal tube has been in place for some time. When the endotracheal tube is removed, the resistance of the upper airway is higher than normal. This subject was investigated rigorously by Straus et al.[91] They studied fourteen patients who tolerated a 2-hour T-tube trial and were then extubated. Work of breathing did not change between the start and end of the trial, 20.0 ± 9.1 and 22.1 ± 10.6 J/min, respectively. Importantly, work did not decrease after extubation, 22.6 ± 9.7 J/min. The work dissipated against the supraglottic airway after extubation was almost identical to the work dissipated against the endotracheal tube before extubation (approximately 11% of total work of breathing). These data indicate that the addition of any level of PS will lead to underestimation of a patient's work of breathing after extubation—the very goal that is being attempted by a weaning trial that uses a low level of PS. Mehta et al[140] measured work of breathing in twenty-two patients before and 15 minutes after extubation. The work of breathing at PS 5 cm H_2O before extubation underestimated the work of breathing performed after extubation by 36%; work of breathing at CPAP 5 cm H_2O underestimated the work of breathing performed after extubation by 23%.

Most investigators have focused on the effect of PS on inspiratory muscle effort. The switch between inspiration and expiration can give rise to problems, particularly in

patients with COPD. With PS, ventilator assistance ceases when the patient's inspiratory flow falls to a preset amount (such as 25% of the peak flow). Air flow changes more slowly in patients with COPD, and these patients often begin to exhale while the ventilator is still pumping gas into their chests. In a study of patients with COPD who were receiving PS 20 cm H_2O, almost half recruited their expiratory muscles before the ventilator had completed mechanical inflation.[90]

T-Tube Trials

The oldest weaning technique is to undertake trials of spontaneous breathing through a T-tube circuit. In the past, these trials started with a duration of approximately 3 to 5 minutes, and were repeated every 30 minutes.[141] The duration of spontaneous breathing was progressively increased according to patient tolerance, as decided by physical examination and arterial blood-gas measurements. Patients were not extubated until they tolerated the T-tube trial for several hours: up to 8 hours in the classic study of Sahn and Lakshminarayan,[100] up to 16 hours in a study from the late 1980s,[97] and 12 hours in a study from the mid-1990s.[142] The need for frequent changes to the ventilator circuit (every hour or more often) placed enormous demands on the intensive care staff, and the approach became extremely unpopular. By the late 1980s, T-tube trials had been largely supplanted by IMV.[143]

Today, it is usual to limit a T-tube trial to 2 hours or less. We typically extubate a patient who does not develop distress during a 30-minute T-tube trial. If a patient fails a T-tube trial, we wait 24 hours before we undertake a subsequent trial. Our reasoning is based on the knowledge that most patients who fail a T-tube trial experience considerable stress on the respiratory muscles secondary to marked increases in their work of breathing. The respiratory muscles take 24 hours or longer to recover from this stress (Fig. 58-25).[144] Accordingly, we reinstitute full assistance with assist-control ventilation for at least 24 hours before reassessing the patient for another T-tube trial.

Optimal plumbing of the T-tube circuit is necessary to avoid imposing respiratory work. Humidified gas is commonly provided in the form of a heated or cool aerosol of water from a large-volume nebulizer. This system can provoke bronchospasm in patients with reactive airways disease. Such patients can be managed with a non–aerosol-generating system, such as a heated passover humidifier.

A T-tube trial serves as a diagnostic test. It is primarily a means of evaluating a patient's ability to sustain spontaneous ventilation. Patients are judged to have failed a T-tube trial when they develop severe tachypnea, increased accessory muscle activity, diaphoresis, facial signs of respiratory distress, oxygen desaturation, tachycardia, arrhythmias, or hypotension. The degree of change in these variables, however, varies from report to report.

A standardized approach to patient monitoring during a T-tube trial does not exist. Indeed, there is no agreement as to whether the monitoring of any variable helps in deciding whether to continue a T-tube trial for an initially planned duration, prolong it, or curtail it. We monitor all such patients with a pulse oximeter. In a report on more than 1000 spontaneous breathing trials, Ely et al[135] observed only one transient episode of desaturation—a rate so staggeringly low as to beggar belief. In a study of seventeen patients with COPD who failed a T-tube trial, Jubran and Tobin[17] found that severe hypoxemia (P_{O_2} ≤46 mm Hg) was the primary cause of failure in two patients. In a study of 100 spontaneous breathing trials in eighty-three patients, Salam et al[145] observed seven instances in which the results of arterial blood gases caused physicians to defer extubation in patients judged otherwise to have passed the trial. Recent data indicate that patients who fail a T-tube trial do not develop low-frequency fatigue.[29] These data, however, do not exclude the possibility of high-frequency fatigue.[27] Moreover, weaning-failure patients (on average) experience more than four times the normal level of inspiratory effort (at the end of a T-tube trial), and some patients experience more than six times the normal value.[17] Given the magnitude of these changes, we do not recommend the undertaking of a T-tube trial in a cavalier manner. Such large increases in respiratory effort cause severe dyspnea, and, apart from humanitarian considerations, we do not know what imprint severe dyspnea leaves on a patient's psyche.

Jubran et al[22] investigated whether repeated measurements of esophageal pressure throughout a trial of spontaneous breathing might provide additional guidance over a single measurement obtained during the first minute of the trial. They quantified the change in esophageal pressure over

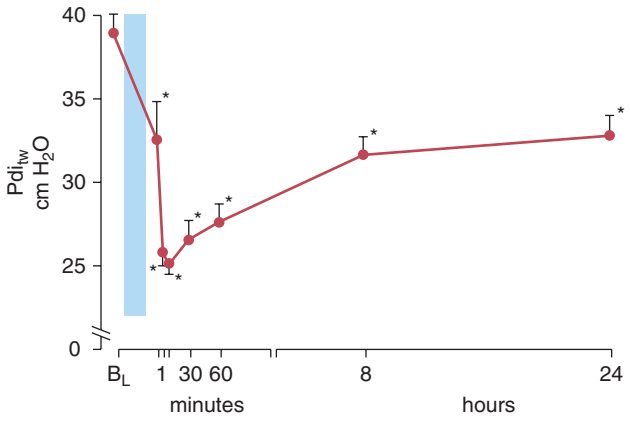


FIGURE 58-25 Induction of diaphragmatic fatigue (*stippled bar*) produced a significant fall in transdiaphragmatic pressure (Pdi) elicited by twitch stimulation of both phrenic nerves. Significant recovery of twitch pressure was noted in the first 8 hours after completion of the fatigue protocol; no further change was observed between 8 and 24 hours, and the 24-hour value was significantly lower than baseline. The delay in reaching the nadir of Pdi_{tw} probably results from twitch potentiation, induced by repeated contractions, which was present at the end of the protocol. Values are mean ± standard error (SE). *, significant difference compared with baseline value, p <0.01. (Used, with permission, from Laghi et al.[144])

the first 9 minutes of the trial using a multivariate adaptive regression spline procedure. In a study of sixty patients, an esophageal pressure–trend index had a sensitivity of 0.91 and specificity of 0.89. Specifically, an esophageal pressure–trend index reading of equal to or less than 0.44 was 8.2 times more likely to occur in weaning failure than in weaning-success patients. These data suggest that the continuous monitoring of esophageal pressure swings during a T-tube trial may provide additional guidance in patient management over tests used for deciding when to initiate weaning.

An implied goal of techniques that involve a gradual reduction in ventilator assistance—whether with IMV, PS, or T-tube trials of increasing duration—is to recondition the respiratory muscles, which may have been weakened during the period of mechanical ventilation. Theoretically, a once-daily trial of spontaneous breathing and a prolonged period of rest may be the most effective method of eliciting adaptive changes.[146,147] That approach meets the three principal requirements of a conditioning program: overload, particularity, and reversibility.[146] During a T-tube trial, patients breathe against an elevated intrinsic load, thus satisfying the overload requirement. Particularity is also satisfied, in that the trial is an endurance stimulus and the desired objective is enhanced endurance. Finally, the use of a daily trial prevents regression of the adaptive changes. This reasoning, however, is solely based on indirect evidence. The effect of different weaning techniques on respiratory muscle reconditioning has not been investigated.

Spontaneous Breathing Trials

During a T-tube trial, a patient is not connected to the ventilator. To convey the lack of assistance, T-tube trials were also described as trials of spontaneous breathing. The two labels were considered synonymous, and used interchangeably. Subsequently, the term "spontaneous breathing trial" was also used to describe patients who were breathing through the ventilator but not receiving any positive-pressure inspiratory assistance as occurs with use of "flow-by." Flow-by avoided the substantial respiratory work imposed by the demand valves in older ventilators, and became a popular alternative to a T-tube circuit for conducting a trial of spontaneous breathing.

Authors, unfortunately, now use the term "spontaneous breathing trial" to describe weaning trials conducted with a fixed level of PS, ranging from 5 to 10 cm H_2O. It is an oxymoron to label PS as spontaneous breathing. The word "support" is an antonym of "unassisted." The problem is not simply semantic. It is unscientific to regard positive-pressure assistance (of 5 to 10 cm H_2O) with every inspiratory effort as unassisted breathing. This unscientific thinking has led authors to believe that measurements of breathing pattern at PS of 5 to 10 cm H_2O is no different than measuring breathing pattern while a patient is disconnected from the ventilator. The argument that PS of 5 to 10 cm H_2O does no more than compensate for the work imposed by an endotracheal tube is now known to be invalid (see Pressure Support above).

The weaning of a patient from the ventilator boils down to making clinical judgments as to whether a patient will be able to sustain ventilation on his or her own, and if not, how much ventilator assistance is required. It is unfortunate that the same term—"spontaneous breathing"—is now used to describe both breathing without any ventilator assistance and breathing with the delivery of positive-pressure assistance with every inspiratory effort. An expression that formerly facilitated meaningful communication has been corrupted such that it misleads not only readers but also the authors themselves.

The sloppiness of communication has reached its apogee in the trials of noninvasive ventilation for management of postextubation distress. Before extubation, patients undergo a trial of "spontaneous breathing" at PS 5 to 8 cm H_2O. After extubation, the major intervention is the delivery of PS (perhaps at a lower level) by face mask. The nonchalant representation of PS 7 cm H_2O as "spontaneous breathing" signifies a fundamental misunderstanding of physiology.

Addition of Positive End-Expiratory Pressure to Replace "Physiologic Positive End-Expiratory Pressure"

Some clinicians recommend that all patients with an endotracheal tube should receive PEEP of 5 cm H_2O, claiming that this level of PEEP is replacing a loss of physiologic PEEP produced by intermittent narrowing of the vocal cords. These claims do not square with long-standing knowledge of pulmonary physiology. Lung volume at end-expiration generally approximates the relaxation volume of the respiratory system (i.e., the lung volume determined by the static balance between the opposing elastic recoil of the lung and chest wall).[148,149] The static recoil pressure of the respiratory system is thus zero at end-expiration in a healthy person.

The addition of PEEP of 5 cm H_2O is not without consequence. In ten ventilated patients who had PEEPi of 6.2 ± 1.0 cm H_2O, Smith and Marini[150] found that that the addition of external PEEP of 5 cm H_2O decreased work of inspiration by 19%. The addition of PEEP can also substantially increase cardiac output in patients with left-ventricular failure. In either circumstance, the rapid removal of PEEP may lead to rapid decompensation at the time of extubation. Thus, the generic order of "5 of PEEP" may cause physicians to underestimate the likely challenges that a patient will face after extubation.

Head-to-Head Comparisons

The first RCT of the three major weaning techniques was conducted by Brochard et al.[3] They randomized 109 difficult-to-wean patients (defined as failure to tolerate their first

2-hour T-tube trial) to three study arms. At 21 days, there were fewer weaning-failure patients among the PS group (2/26, 8%) than among the patients weaned by T-tube trials (10/30, 33%) or IMV (16/41, 39%). Also, less time was taken to wean with PS (5.7 ± 3.7 days) than with T-tube trials (8.5 ± 8.3 days) or IMV (9.9 ± 8.2 days). Statistically, however, the only difference was a shorter weaning time for PS patients (5.7 ± 3.7 days) than for the combined T-tube and IMV patients (9.3 ± 8.2 days; $p < 0.05$).

Esteban et al[4] undertook an RCT that had a similar design to that of Brochard et al. They randomized 130 difficult-to-wean patients (again defined as failure to tolerate their first 2-hour T-tube trial) to four study arms: IMV, PS, once daily T-tube trials, and intermittent spontaneous breathing trials (this terminology was used because six patients breathed through a circuit providing CPAP 5 cm H_2O; the remaining twenty-seven had T-tube trials; the trials were of gradually increasing duration, at least twice daily, with ≥1 hour of assist-control ventilation between each trial). At 14 days, mechanical ventilation was still required by 17% of IMV patients, 11% of PS patients, 3% of once-daily T-tube patients, and 3% of patients weaned by intermittent T-tube or CPAP trials. The time taken to wean was a median of 5 days for IMV (IQR: 3 to 11), 4 days (IQR: 2 to 12) for PS, 3 days (IQR: 1 to 6) for once-daily T-tube trials, and 3 days (IQR: 2 to 6) for intermittent T-tube/CPAP trials. The rate of successful weaning with once-daily T-tube trials was about three times faster than with IMV and two times faster than with PS; there was no difference between the speed of weaning with once-daily T-tube trials versus intermittent T-tube/CPAP trials.

These two studies concur in finding that IMV was the least-effective method for weaning a difficult patient. The steps taken in setting the IMV rate were largely the same in the two studies: The initial IMV rate was half the respiratory frequency seen during assist-control ventilation (IMV of about 10 breaths/min in both studies). Then, IMV rate was decreased by 2 to 4 breaths/min twice a day if the patient tolerated it. The point for extubation differed between the studies. In the study of Brochard et al, patients were extubated when they tolerated an IMV of 4 breaths/min for 24 hours. In the study of Esteban et al, patients were extubated when they tolerated an IMV of 5 breaths/min for 2 hours. This difference probably accounts for the shorter weaning time with IMV in the study of Esteban et al[4] versus that of Brochard et al[3]: 5 days versus 10 days.

The data appear to differ in the relative efficacy of PS and T-tube trials. The reason for the difference can again be understood by examining the two protocols. The initial level of PS was largely similar in the two studies: pressure titrated to respiratory frequency (20 to 30 breaths/min[3]; <25 breaths/min[4]). This resulted in a PS of 18 cm H_2O in both studies. PS was decreased by 2 to 4 cm H_2O twice a day in the study of Brochard et al, and by that amount or more in the study of Esteban et al. The point for extubation differed between the studies. In the study of Brochard et al, patients were extubated when they tolerated PS of 8 cm H_2O for 24 hours. In the study of Esteban et al, patients were extubated when they tolerated PS of 5 cm H_2O for 2 hours. This difference probably accounts for the shorter weaning time with PS in the study of Esteban et al than in the study of Brochard et al: 4 days versus 6 days. The approach to T-tube trials also differed. Brochard et al performed trials of increasing duration twice a day. Esteban et al used two approaches to T-tube trials: One arm consisted of T-tube trials once a day, and the second arm consisted of intermittent spontaneous breathing trials. The point for extubation differed between the studies. In the study of Brochard et al, extubation was contemplated when patients tolerated a 2-hour T-tube trial, but there could be as many as three separate 2-hour trials. In the study of Esteban et al, patients were extubated when they first tolerated a 2-hour trial.

The investigators of the two preceding studies[3,4] set the duration of T-tube trials at 2 hours. In a subsequent study, conducted in 526 patients who had received more than 48 hours of ventilation, Esteban et al[151] found that the rate of weaning failure was equivalent for trials lasting 30 and 120 minutes: 12% (33/270) and 16% (40/256), respectively. The rates of reintubation were virtually identical (13%); approximately 74% of patients in the two arms were successfully extubated. This study consisted of patients undergoing a first weaning attempt, unlike the two earlier trials that were limited to patients with demonstrable difficulty in being weaned. The findings, however, suggest that most patients can be weaned after a 30-minute trial, which simplifies management by freeing staff time for other patient care tasks. With a similar goal, Perren et al[152] found that the rate of weaning failure was equivalent when ninety-eight patients were randomized to breathe with PS of 7 cm H_2O for 30 or 120 minutes: 6.5% (3/46) and 11.5% (6/52). The rates of reintubation did not differ significantly (7% and 4%, respectively).

Koh et al[153] investigated whether adding a 1-hour T-tube trial would alter outcome in patients who had already undergone progressive decreases in PS (3 to 5 cm H_2O every hour) to a level estimated to offset imposed respiratory work (by the endotracheal tube and ventilator circuit: mean: 7.6 ± 0.4 cm H_2O [SE]; range: 4 to 13 cm H_2O). The rate of weaning failure was not significantly different in patients who were extubated after the additional T-tube trial and those extubated directly, 45% (10/22) and 30% (6/20), respectively, nor did the rates of reintubation differ, 18% (4/22) and 20% (4/20), respectively.

Matic and Majeric-Kogler[154] studied 260 patients who had received mechanical ventilation for more than 48 hours and who had who satisfied several criteria of readiness for weaning (such as frequency <35 breaths/min, V_T >5 mL/kg, f/V_T <100, and P_{O_2} >60 mm Hg on FI_{O_2} <0.40). Patients were randomized to a 2-hour T-tube trial or a 2-hour trial of PS 8 cm H_2O. Of the 150 patients in the PS trial group, 120 (80.0%) passed the trial and were extubated. Of the 110 patients in the T-tube trial group, eighty (72.7%) passed the trial and were extubated ($p = 0.06$). The remaining patients who failed the initial weaning trial were returned to assist-control

ventilation, and the previously assigned weaning technique was again attempted after 24 hours (or when the patient's condition permitted). The rate of weaning success was higher in the PS group than in the T-tube trial group: twenty-six of thirty (86.7%) versus twenty-one of thirty (70%). In addition, the time for weaning was shorter for the PS group, 54 (IQR: 47 to 88) versus 94 (IQR: 79 to 132) hours, as was total time for mechanical ventilation, 215 hours (IQR: 187 to 259) versus 262 hours (IQR: 216 to 328). The rate of reintubation was equivalent for the PS and T-tube trial groups: one (3.5%) versus two (6.7%) patients.

Vitacca et al[155] studied seventy-five patients with COPD who had been transferred to a long-term weaning unit. The patients had required more than 15 days of mechanical ventilation, and all had a tracheostomy. Of the seventy-five patients, twenty-three (31%) tolerated a T-tube trial for 48 hours and were studied no further. The remaining fifty-two patients failed the T-tube trial after 290 ± 452 minutes, and were randomly assigned to weaning by PS or T-tube trials. Weaning was deemed successful when patients tolerated spontaneous breathing for 48 hours or longer. Clinical outcomes were equivalent in the PS and T-tube trial groups: weaning success rate 73% (19/26) versus 77% (20/26); mortality 11.5% (3/26) versus 7.6% (2/26); ventilator duration 181 ± 161 versus 130 ± 106 hours; weaning unit stay 33 ± 12 versus 35 ± 15 days; and hospital stay 49 ± 27 versus 50 ± 32 days. The investigators also retrospectively compared fifty-five patients managed by the protocols of this study with sixty-two control patients managed in the same institution during the 2 years preceding the study. The study patients exhibited better outcomes than the historical control group: 30-day weaning success rate 87% versus 70%; ventilator duration 103 ± 144 versus 170 ± 127 hours; weaning unit stay 27 ± 12 versus 38 ± 18 days; and hospital stay 38 ± 17 versus 47 ± 18 days.

Weaning by Protocol versus Usual Care

Several investigators have examined whether formalizing weaning steps into a systematic protocol might alter weaning outcome. Many of these studies were motivated by the results of a 1996 study by Ely et al,[156] who combined two steps from previous studies—measurement of f/V_T (and other predictors) and a 2-hour T-tube trial—into an algorithm. They randomized 300 patients into an intervention arm and a usual-care arm. Patients in the intervention arm were screened in the early morning. To pass the screen, patients had to meet all of the following five criteria: f/V_T less than 105; Pa_{O_2}/FI_{O_2} greater than 200; PEEP equal to or less than 5 cm H_2O; adequate cough during suctioning; and no infusions of vasopressors or sedatives (with the exception of dopamine ≤5 mcg/kg/min and intermittent sedative boluses). Patients who passed the screen automatically underwent a trial of spontaneous breathing (a T-tube trial or flow-by and CPAP 5 cm H_2O) later that morning (without requiring an order from the primary physician). If the patient tolerated the trial, the primary physician was informed both orally and by a note in the chart.

The time taken to wean (from the point of satisfying the predictor criteria until the discontinuation of mechanical ventilation) was shorter in the intervention group than in the usual-care group: median 1 day (IQR: 0 to 2) versus 3 days (IQR: 2 to 7). The duration of ventilation was also shorter: 4.5 days (IQR: 2 to 9) versus 6 days (IQR: 3 to 11). Reintubation was less common in the intervention group than in the usual-care group: 4% versus 10%. This study demonstrates that a two-step approach—systematic measurement of predictors followed by a single daily T-tube (or flow-by/CPAP) trial—was superior to usual care.

A closer inspection of the data illustrates some important points about weaning. Among the 149 patients in the intervention group, 113 (76%) met the predictor criteria. Of these 113 patients, eighty-eight (78%) passed the spontaneous breathing trial. Yet, extubation was not attempted that day in 45% (40/88) of the patients who passed the trial. In a subsequent analysis of the data, Ely et al[157] noted that eighty-four of the 300 patients never satisfied the weaning predictor thresholds. Of these eighty-four patients, fifty-nine (70.2%) were never extubated. The remaining twenty-five patients (25/300; 8.3% of the overall study group) were successfully extubated despite never satisfying the predictor thresholds. Of these twenty-five patients, fifteen (15/300) had Pa_{O_2}/FI_{O_2} ratios less than 200 (5% of the overall study group) and ten (10/300) (3.3% of the overall study group) had f/V_T readings higher than 105. These data highlight that (a) the major source of delay in weaning of patients in the intervention group resulted from the failure of physicians to take action in patients who passed a spontaneous breathing trial (extubation was delayed in 45% of these patients), (b) almost 80% of patients who meet predictor thresholds will tolerate an immediate spontaneous breathing trial, and (c) f/V_T (105) falsely identifies approximately 3% of patients who can be extubated.

Ely and members of the Evidence-Based Medicine Task Force on weaning[62,158] subsequently argued that the data from the 1996 study provided evidence in support of the use of formalized protocols in weaning management. To claim that use of a protocol per se improves patient outcome, the weaning approach must be the same in both the protocol arm and nonprotocol arm of a research study. In the 1996 study,[156] however, 76% of patients in the usual-care arm were managed with IMV, whereas no patient in the intervention arm was weaned using IMV. Several studies had already shown that IMV impeded weaning. Such a study design lacks internal validity and cannot be used as the basis for claims that use of a weaning protocol per se expedites weaning.[159]

The next study to test the benefit of protocolized management of weaning was undertaken by Kollef et al.[2] They randomized 179 patients to a protocol group and 178 patients to usual care. The study was conducted in four intensive care units (ICUs), and weaning techniques were a mixture of PS, CPAP, and IMV. Overall, the duration of mechanical ventilation was shorter for the protocol group than for the

usual-care group: median 35 hours (IQR: 15 to 114) versus 44 hours (IQR: 21 to 209). The difference, however, was significant in only one of the four ICUs. Moreover, interpretation of the data for this ICU is not straightforward. Patients in the usual-care group were significantly sicker than were the patients in the protocol group: Acute Physiology, and Chronic Health Evaluation (APACHE) II scores were 15.4 versus 13.6. In separate analysis, the investigators found that APACHE II score was at least as important as protocol management as a determinant of the duration of mechanical ventilation. In the other three ICUs, there was no difference in duration of mechanical ventilation between the protocol and usual-care groups; in one ICU, the trend was in the opposite direction.

Marelich et al[160] undertook a randomized comparison of weaning by protocol versus usual care in 335 patients, about half of whom were in the medical ICU and half in the surgical ICU. They randomized 186 patients to a protocol arm and 189 patients to a usual-care arm. The duration of mechanical ventilation was shorter for the protocol arm than for the usual-care arm: 68 hours (IQR: 33 to 164) versus 124 hours (IQR: 54 to 334) ($p = 0.001$).[160] Benefit, however, was confined to the medical ICU. Protocol management achieved no advantage in the surgical ICU.

Namen and members of the Ely research group[161] investigated the benefit of protocolized weaning in a neurosurgical ICU. There were forty-nine patients in the protocol arm and fifty-one patients in the usual-care arm. Implementation of protocolized weaning had no beneficial effects on any patient outcome, such as number of days of mechanical ventilation, costs, morbidity, or mortality.

Randolph et al[162] randomized 182 children who had failed to satisfy criteria for extubation (and had been ventilated for >24 hours) to three arms: PS protocol, volume-support ventilation protocol, usual care. The rate of weaning failure was equivalent for PS, volume-support ventilation, and usual care, 15%, 24%, and 17%, respectively, as was the median duration of weaning, 1.6, 1.8, and 2.0 days, respectively. The authors concluded that protocols did not shorten the duration of weaning.

Krishnan et al[163] did an RCT in 154 patients assigned to weaning by protocol and 145 patients weaned according to usual care. The duration of mechanical ventilation was equivalent for protocol weaning and usual care, 60.4 versus 68.0 hours, as was the rate of successful weaning, 74.7% versus 75.2%.

Of the six RCTs that have tested the benefits of weaning protocols, three research groups have reported that protocolized weaning is superior to usual care. Two of these studies, those by Ely et al[156] and Kollef et al,[2] have internal-validity problems of such magnitude that the data cannot be accepted as valid evidence on which to base a claim that protocols per se expedite weaning. The third study, that by Marelich et al,[160] revealed no benefit in one of the two ICUs in the study. The trials conducted by Namen et al,[161] Randolph et al,[162] and Krishnan et al[163] revealed no benefit for protocolized weaning. Thus, only half of a study (out of six studies) revealed valid support for protocolized weaning, with the remainder providing no evidence of benefit.

In addition to these studies of weaning protocols in ICU patients, Vitacca et al[155] investigated the benefits of protocolized management of patients admitted to a long-term weaning facility. The investigators concluded that protocolized weaning significantly decreased the duration mechanical ventilation as compared with usual care: 103 ± 144 versus 170 ± 127 hours (Fig. 58-26). Inspection of the Kaplan-Meier curve, however, reveals that the plots differ only at time zero; thereafter, the two plots superimpose on one another. On first evaluation, more than 30% of patients classified as "difficult-to-wean" were immediately weaned. That is, benefit was not derived from use of a protocol, but from the presence of a "thinking" doctor at the bedside.

There is a deeper reason why protocolized management does not lead to improvements in weaning outcome. This relates to a fallacy in historiography (the methodology employed by historians) known as the Whig-interpretation-of-history fallacy: the tendency among historians to write their account on the side of the winners, to praise military strategists and revolutionaries provided they have been successful.[164] The fallacy can be best appreciated by first considering an example, and then reflecting on the implications for clinicians and researchers.

Numerous computer versions of the Battle of Gettysburg exist on the market. These reproduce with great accuracy the terrain, corps involved, and serial chronology of events in the battle. A moderately good player taking the Confederate side can beat the Union side.[165] Yet, Robert E. Lee, universally regarded as the best strategist and tactician on either side, lost. How could a moderately accomplished player outperform Lee? The player today knows from the outset what Lee did not know. Lee did not know that the battle was going to take place at the specific location of Gettysburg. Lee did not know precisely which units would be involved and where, the time scale of preliminary stages of the battle, the constraints imposed by the terrain, and all the trivial contingencies that powerfully influenced the final outcome of the battle. The determinate shape of the battle was conferred only retrospectively by its outcome. There are no conclusive reasons that the series of events turned out the way they did—each could have turned out otherwise. It is impossible to incorporate all possible contingencies into a battle plan. Simply, the computer version does not reproduce the situation that Lee faced; instead, it is what historians call a Whig illusion.

The error committed by Whig historians is that endings seem inevitable—but only after the fact. Nothing, however, could ever happen if reality did not kill all the other potentialities originally inherent in any given situation.[166] From a historical perspective, every sequence of events appears as though it could not have happened otherwise. This produces an existential illusion. Weaning researchers who expect protocols to improve clinical outcome are committing the Whig fallacy. At the outset of a weaning attempt, there is not a set of determinate, enumerable factors, the totality of which

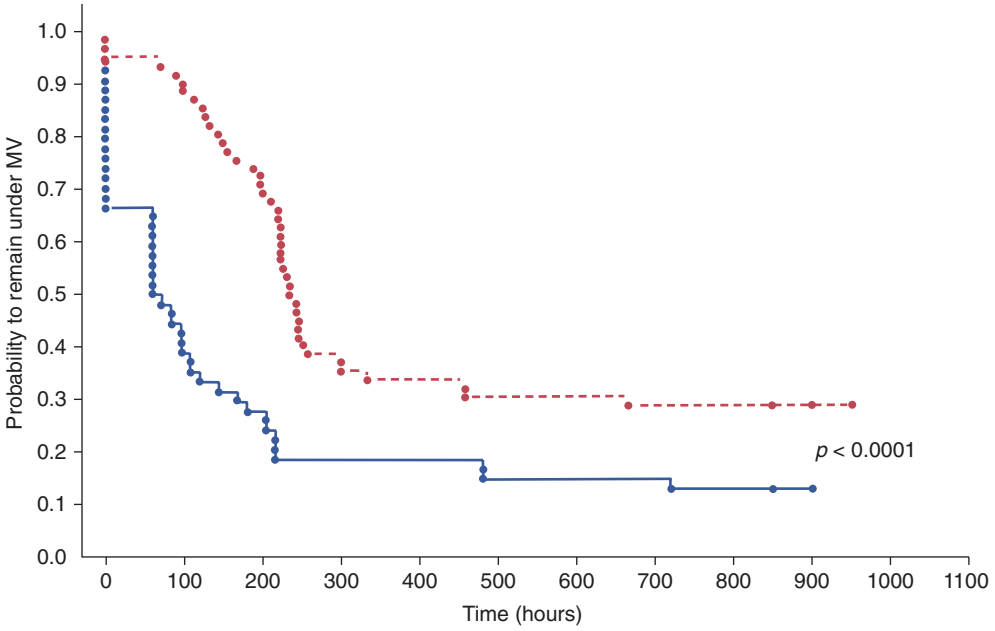


FIGURE 58-26 Kaplan-Meier curves of probability of continued mechanical ventilation (MV) in patients managed by a weaning protocol versus usual care. The time of continued mechanical ventilation was significantly shorter with protocolized weaning as compared with usual care: 103 ± 144 versus 170 ± 127 hours (p <0.0001). (Used, with permission, from Vitacca et al.[155])

comprises the situation—like the set of steps used to provide the proof for a theorem in Euclidean geometry. To suppose otherwise is to confuse an a posteriori (retrospective) perspective with an a priori (prospective) perspective. This is the fallacy committed by protocol advocates, Whig historians, and malpractice attorneys.

Computerized Approaches to Weaning

Investigators have attempted to apply various forms of artificial intelligence to mechanical ventilation.[129,167,168] These approaches have been most fruitful in the management of weaning. A specially constructed ventilator based on these efforts was compared against usual care in a multicenter RCT conducted by Lellouche et al.[169] The computerized system was embedded in an Evita 4 ventilator (Dräger, Lübeck, Germany). The modified ventilator continuously monitored respiratory frequency, tidal volume, and end-tidal CO_2 tension, and repeatedly altered the level of delivered PS based on iterative changes in these three variables. Depending on a patient's response, the computerized system periodically and automatically decreased the level of PS by 2 to 4 cm H_2O. Importantly, the algorithm accepted transient instabilities, such as a brief increase in respiratory frequency, without making changes in a patient's classification. The pace of pressure reduction was tailored according to the needs and performance of each individual patient. Once a predesignated minimal level of PS was reached, the ventilator automatically subjected the patient to a weaning trial, conducted at a low level of PS. If the patient performed satisfactorily, a message was displayed on the screen recommending the removal of the ventilator. Lellouche et al[169] enrolled 144 patients from five medical–surgical ICUs into the study. The patients had received at least 24 hours of ventilator assistance, and were enrolled at an early stage of their course, at a point when weaning predictor tests did not signal readiness to wean. In four of the five ICUs, usual care involved the use of paper-based weaning protocols. Compared with usual care, the computerized system decreased weaning duration from a median of 5 to 3 days ($p = 0.01$) and decreased total duration of mechanical ventilation from 12 to 7.5 days ($p = 0.003$).

This study provides support for the use of computerized ventilators as a method to expedite weaning. The study also carries lessons for the better management of weaning using conventional ventilators. Of the seven stages of weaning, stage 2, the period of diagnostic triggering—the time when a physician begins to think that the patient just might be ready come off the ventilator—is the most critical (see Fig. 58-1). RCTs on weaning techniques have revealed that 60% to 80% of patients ventilated for a week or more were successfully disconnected from the ventilator successfully on the first day they were evaluated for weaning.[3,4] If weaning-predictor tests had been performed in these patients at an earlier time, it is highly likely that many of them could have been removed from their ventilator a day, or several days, sooner than was the case.

With the artificial-intelligence-operated ventilator,[169] screening tests were performed repeatedly and automatically, and thus the delay inherent in diagnostic triggering (stage 2) was bypassed. Moreover, once a predesignated readiness threshold was reached, a confirmatory test—a weaning trial that advises on the appropriateness of extubation—was

automatically performed, without requiring any action (or decision making) on the part of the staff. For patients in the usual-care arm of the trial, Lellouche et al[169] calculated that the number of T-tube trials performed according to patient readiness was only 51%. The delay in human decision making and action was further emphasized by the lapse of more than 14 hours (0.6 ± 2.65 days) between the time that a message first indicated that a patient had passed a weaning trial until removal of the endotracheal tube. Indeed, only 42% of the patients were extubated on the day that the message was first displayed.

Rose et al[170] undertook an RCT of the ventilator employed by Lellouche et al,[169] which now goes by the name SmartCare. A total of 102 patients in an Australian ICU were equally divided between the computerized ventilator and usual care. The median time from the first identified point of suitability for weaning commencement until the display of a message indicating that a patient had passed a weaning trial was 20 hours (IQR: 2 to 40) for the computerized ventilator versus 8 hours (IQR: 2 to 43) for usual care ($p = 0.3$). The adjusted probability of reaching separation potential was estimated to be 31% lower with the computerized ventilator as compared to usual care (95% CI, 5l% lower to 9% greater). At least two factors are likely to have contributed to the markedly different outcome in the two studies. First, 68% of enrollees in the study of Lellouche et al[169] were medical patients, whereas 78% of enrollees in the Australian study[170] were surgical patients, which are typically less challenging to wean. Second, the nurse-to-patient ratio in the Australian ICU was 1:1.

A third RCT of computerized weaning versus usual care was undertaken by Taniguchi et al.[171] These Brazilian researchers employed a different computerized system, termed *mandatory rate ventilation,* from that used in the studies of Lellouche et al[169] and Rose et al.[170] An algorithm, embedded in a Taema-Horus ventilator, automatically adjusted the level of PS according to a target respiratory rate. If the patient's respiratory rate (averaged over four respiratory cycles) exceeded the target by more than 3 breaths/min, the level of PS was increased by 1 cm H_2O, and vice versa. Taniguchi et al[171] found no difference in weaning duration with the two approaches. The level of PS was lower with usual care than with the computerized ventilator (over at least the first three hours of the study). Similar to the study of Rose et al,[170] enrollees in the study of Taniguchi et al[171] consisted solely of postoperative patients. Another important factor that contrasts with the research team of Lellouche et al[169] is that both the Brazilian and Australian clinicians knew they were competing against a machine that they did not help to create.

Respiratory Muscle Training

Over the past 25 years, researchers have emphasized that respiratory muscle fatigue is likely to be more important than respiratory muscle weakness in causing weaning failure (see Pathophysiology of Weaning Failure: Respiratory Muscles above). There is growing recognition that this attribution is misplaced. Recordings of twitch pressures with the use of phrenic-nerve stimulation have revealed that many weaning-failure patients have very severe respiratory muscle weakness.[172,173] A renewed focus on respiratory muscle strength has gathered impetus from a recent RCT, which revealed that deliberate measures aimed at improving respiratory muscle strength resulted in a significant increase in the weanability of patients.

Martin et al[174] enrolled sixty-nine patients in a single-blind RCT designed to determine whether inspiratory muscle-strength training would improve weaning outcome. The patients had received mechanical ventilation for approximately 40 to 50 days before entry into the study. Thirty-five patients were randomized to strength training and thirty-four patients to sham therapy.

Strength training was achieved with the use of a commercial threshold inspiratory muscle trainer (Threshold PEP; Respironics Inc., Murrysville, PA), which required patients to generate inspiratory pressures of −4 to −20 cm H_2O at the onset of an inspiration. During a training session, a patient was removed from the ventilator and the threshold device connected to the tracheostomy tube (keeping the cuff inflated). The patient was then required to perform four sets of six to ten threshold-loaded inspirations; between each set, the patient was returned to the ventilator for 2 minutes. The setting on the threshold device was adjusted to the highest pressure setting that the patient could consistently open during each inspiration (airway pressures at the tracheostomy tube were monitored). Over the course of the study, the pressure setting on the device was increased according to patient tolerance. Patients in the sham arm inspired through an inspiratory muscle training device that contained a large hole, with the result that little pressure was required to generate airflow. Sessions were performed 5 days a week (Monday to Friday).

In addition to the inspiratory muscle-strength training sessions, all patients were subjected to weaning trials of progressively longer duration. These trials involved the use of automatic tube compensation, CPAP, or low levels of PS. Weaning trials were conducted 7 days a week according to a predesignated scheme.

Upon completion of the study, twenty-five of the thirty-five (71%) patients in the strength-training arm were weaned as compared with sixteen of thirty-four (47%) patients in the sham arm ($p = 0.039$). Over the course of the study, the inspiratory pressure setting on the threshold device became more negative: −9.54 ± 3.70 (SD) versus −14.52 ± 4.59 cm H_2O ($p = 0.0004$). Corresponding pressures in the sham arm were −3.10 ± 1.54 and −3.36 ± 2.08 cm H_2O ($p = 0.86$). Over the course of the trial, patients in the strength-training arm exhibited an increase in $P_I$max from 44.4 ± 18.4 to 54.1 ± 17.8 cm H_2O ($p < 0.0001$); corresponding values of $P_I$max in the sham arm were 43.5 ± 17.8 and 45.1 ± 19.5 cm H_2O.

The results of this study suggest that use of a simple device (a threshold loader) can markedly increase the

weanability of patients. The challenge now is to reproduce these findings and find out whether further adjustments to the training regimen might achieve an even greater level of success. The positive outcome highlights the importance of respiratory muscle strength as a determinant of weanability. The results also suggest that other methods of increasing respiratory muscle strength, such as the use of transcutaneous neuromuscular electrical stimulation or novel biologic or pharmacologic compounds, may also expedite weaning.

Physical and Occupational Therapy to Aid Weaning

The use of techniques aimed at whole-body rehabilitation, including formal physical and occupational therapy, shortly after the initiation of mechanical ventilation, holds considerable promise for improving long-term functional performance after discharge from the ICU, but it may also expedite weaning. Preliminary research in this area had shown promise,[175] but interest was heightened by a recent RCT.[176]

Schweickert et al[176] sought to determine whether early implementation of a program of formal physical and occupational therapy would lead to improvements in functional outcomes in ventilated patients. At two university hospitals, investigators enrolled patients who had received less than 72 hours of mechanical ventilation, which was expected to continue for at least another 24 hours; enrollees were also required to have exhibited functional independence 2 weeks before admission. From an initial screening of 1161 patients, 104 were enrolled: Forty-nine were randomized to early exercise and mobilization (physical and occupational therapy), starting on the day of enrollment, and fifty-five to usual care. (Usual care at the two study sites did not include routine physical therapy for ventilated patients.)

Each day, infusions of sedative agents were interrupted in both groups; by the end of the study, no differences in sedation and analgesia practices were observed in the two groups. In the intervention arm, patients also underwent passive range of motion exercises for all limbs, delivered by a physical and occupational therapist, every morning. Once patient interaction was achieved, sessions began with active assisted exercises in the supine position. If these exercises were tolerated, treatment was advanced to bed mobility activities, including transferring to upright sitting, followed by participation in activities of daily living. Such therapy took place on 87% of days of the study in the intervention group. During mechanical ventilation, the median duration of physical and occupational therapy differed between the groups: median 0.32 hours a day (IQR: 0.17 to 0.48) in the intervention arm and 0 hours a day in the control arm. Therapy commenced at a median of 1.5 days (IQR: 1.0 to 2.1) after intubation in the intervention group versus 7.4 days (IQR: 6.0 to 10.9) in the control group.

The primary end point, the number of patients returning to independent functional status at hospital discharge, was reached by twenty-nine (59%) patients in the intervention group and nineteen (35%) patients in the control group ($p = 0.02$): odds ratio 2.7 (95% CI 1.2 to 6.1). Over the first 28 days of the study, patients in the intervention arm had a higher number of ventilator-free days, 23.5 (IQR:7.4 to 25.6), than did patients in the control group, 21.1 days (IQR:0.0 to 23.8; $p = 0.05$); overall duration of mechanical ventilation was also shorter in the intervention group, 3.4 days (IQR:2.3 to 7.3) versus 6.1 days (IQR:4.0 to 9.6; $p = 0.02$). Use of formal physical and occupational therapy resulted in a higher number of independent activities of daily living and greater unassisted walking distance at hospital discharge than achieved in the control group.

Although efforts to mobilize ventilator-supported patients, including attempts to help them walk while receiving ventilator assistance, have been employed for decades as an aid to weaning,[141] the impressive results achieved by Schweickert et al[176] crystalizes the components of physical and occupational therapy that are crucial to achieve success.

Role of Sedation in Weaning

Pharmacologic agents that produce sedation are almost invariably used in patients receiving mechanical ventilation with the goals of decreasing anxiety and agitation, enhancing patient–ventilator synchronization, and facilitating patient care. Commonly, sedative drugs are administered by means of continuous intravenous infusions. Sedative agents accumulate in the body far beyond the treatment period, especially in critically ill patients, as a result of impaired renal or hepatic function. Sedative agents also hinder the assessment of mental function, leading physicians to suspect organic brain disorders when none exist. To determine whether the accumulation of sedative agents hinders ventilator management, Kress et al[177] undertook an RCT in 128 adult patients receiving mechanical ventilation in a medical ICU. In the intervention arm, an investigator interrupted the infusion of midazolam, propofol, or morphine on a daily basis until the patients were awake and could follow instructions or until they became uncomfortable or agitated. A patient was considered "awake" if the patient was able to perform at least three of the following four actions: open the eyes in response to a voice, use the eyes to follow the investigator, squeeze a hand, and stick out the tongue on request. In the control group, sedative infusions were interrupted only at the discretion of the intensivist.

Daily awakenings resulted in a shorter duration of mechanical ventilation, median of 4.9 days versus 7.3 days in the control group ($p = 0.004$), and shorter ICU stay, 6.4 days versus 9.9 days ($p = 0.02$). Interruption of sedation also reduced the number of diagnostic tests (brain scan, lumbar puncture) ordered to assess changes in mental status, six versus sixteen in the control group ($p = 0.02$).

Girard et al[178] extended these findings by combining daily interruption of sedation with spontaneous breathing trials.

The investigators randomized 336 ventilated patients to an intervention arm, consisting of paired use of sedative interruption and systematic use of spontaneous breathing trials versus a control arm, consisting of spontaneous breathing trials and the administration sedative agents at the discretion of the intensivist. The paired intervention resulted in more days breathing without ventilator assistance (3.1 days in the 28-day study, 95% CI 0.7 to 5.6), and earlier discharge from both the ICU and hospital. In an accompanying editorial, Brochard[179] pointed out several problems with the experimental design of the study—the absence of a requirement to stop sedatives in the control group before a spontaneous breathing trial, the timing of weaning onset, and markedly increased rate of failed weaning trials in the control arm—that render the interpretation of this study highly problematic.

Strøm et al[180] went a step further than previous investigators and sought to determine whether total withholding of sedative agents would prove superior to daily interruption of sedation. Patients in the control arm received propofol for the first 48 hours and midazolam thereafter, titrated to reach a Ramsay score of 3 to 4; sedation was interrupted every day until patients were awake. Patients in the intervention arm received bolus doses of morphine (2.5 or 5 mg), as did patients in the control arm, but did not receive intravenous infusions of sedatives or analgesics. No sedation was associated with significantly more days without ventilator assistance (mean: 4.2 days, 95% CI 0.3 to 8.1 days), and earlier discharge from both the ICU and hospital. Agitated delirium was more frequent in the intervention group than in the control group (20% vs. 7%; $p = 0.04$), and the use of haloperidol was also more frequent (35% vs. 14%). Moreover, an extra person was needed at the bedside for 2.5 days to comfort and reassure patients more often in the intervention group than in the control group (20% vs. 5%). Follow-up data have not been published on these patients to determine whether they are more or less prone to posttraumatic stress disorder or other psychological problems.

CONCLUSION

The hazards of mechanical ventilation make it imperative to wean patients at the earliest possible time in their clinical course. Premature weaning attempts, however, cause considerable respiratory distress that may set back a patient's course. Premature extubation is also hazardous. To minimize both delayed weaning and premature extubation, a two-step diagnostic strategy is recommended: measurement of weaning predictors followed by a weaning trial. Because each step constitutes a diagnostic test, clinicians must be mindful of the scientific principles of clinical decision making when interpreting the information generated by each step.

The critical step is for the physician to contemplate the possibility that a patient just might be able to tolerate weaning. Such diagnostic triggering is facilitated through use of a screening test, which is the rationale for measurement of weaning predictor tests. It is important not to postpone this first step by waiting for a more complex diagnostic test, such as a T-tube trial. A positive result on a screening test (weaning predictor test) is followed by a confirmatory test (weaning trial), to increase the likelihood that a patient will tolerate extubation.

Many complex facets of pulmonary pathophysiology impinge on weaning management. Thus, weaning requires individualized care at a high level of sophistication. Few other activities undertaken by physicians in the ICU require a greater intellectual input and carry greater potential for improving patient outcome than the application of physiologic principles in the weaning of patients.

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59

EXTUBATION

Martin J. Tobin
Franco Laghi

It is easy to merge decisions about extubation with decisions about weaning in everyday practice. Indeed, much patient mismanagement is caused by conflating these two subjects. But the conflation is not confined to clinicians. Many researchers have also merged the two subjects, such as using weaning predictors to predict reintubation in a patient who has already tolerated a weaning trial. The result is scientific confusion.

When a patient tolerates a weaning trial without distress, a clinician feels reasonably confident that the patient will be able to sustain spontaneous ventilation after extubation. But this is not the only consideration. The clinician also has to consider whether the patient will be able to maintain a patent upper airway after extubation.

Removal of an endotracheal tube is typically performed under controlled conditions. The patient has satisfactorily tolerated a weaning trial. Enteral feeding is temporally withheld for approximately 4 hours. The patient is usually positioned in a sitting posture. The endotracheal tube, mouth, and upper airway are suctioned, paying attention to the collection of secretions above an inflated cuff. Some clinicians recommend keeping a suction catheter in place (aiming for the catheter to barely protrude from the distal end of the endotracheal tube) as the cuff is deflated; this step is taken in an attempt to capture any secretions sitting on top of an inflated cuff, which might fall into the airway after deflating the cuff. Some clinicians forcefully inflate the lungs with an Ambu Bag immediately before pulling out the endotracheal tube, hoping that the larger than usual ensuing exhalation will push secretions upward and outward. After removal of the endotracheal tube, the patient is given supplemental oxygen, titrated to oxygen saturation (S_{O_2}), being particularly cautious with a patient who is at risk of carbon dioxide retention. Patients may have impaired airway protection reflexes immediately after extubation. If speech is impaired for more than 24 hours, indirect laryngoscopy should be undertaken to assess vocal cord function. Oral intake should be delayed in patients who have been intubated for a prolonged period.

In the hours following extubation, patients are carefully monitored for ability to protect the upper airway and sustain ventilation. Most patients will display progressive improvement, allowing the discontinuation of supplemental oxygen and ultimate discharge from the intensive care unit (ICU).

POSTEXTUBATION DISTRESS

Between 2%[1,2] and 30%[3–6] of patients experience respiratory distress in the postextubation period (Table 59-1). Many, but not all, require reinsertion of the endotracheal tube and mechanical ventilation. These patients are commonly classified as *extubation failures*, a term popularized by Demling et al.[7] These investigators defined extubation failure as the need for reintubation within 7 days. Unfortunately, the

TABLE 59-1: FREQUENCY OF REINTUBATION AND MORTALITY

Authors	Number of Patients	Percent Reintubated	Percent Mortality	Time Frame
Tahvanainen et al[73]	47	19.1	22.2	—
DeHaven et al[74]	48	6.3	NR	—
Demling et al[7]	400	4.4	40	7 days
Demling et al[7]	299	3.3	10	7 days
Krieger et al[75]	269	10.4	NR	—
Mohsenifar et al[76]	29	14.3	NR	24 hours
Sassoon et al[77]	40	12.5	NR	48 hours
Brochard et al[78]	109	11	NR	48 hours
Lee et al[79]	52	17	33.3	NR
Capdevila et al[80]	67	17.9	NR	48 hours
Esteban et al[81]	530	15.6	NR	48 hours
Torres et al[29]	170	23.5	35	—
Chatila et al[82]	100	9.5		<24 hours
Dojat et al[3]	38	29.4	40	48 hours
Ely et al[83]	300	3.7	NR	48 hours
Leitch et al[1]	163	1.8	NR	<24 hours
Miller et al[35]	88	17	NR	NR
Epstein et al[12]	289	14.5	42.5	—
Esteban et al[28]	484	18.6	27	48 hours
Jacob et al[84]	183	4.5	NR	24 hours
Kollef et al[85]	357	11.5	NR	NR
Vallverdu et al[86]	217	15.5	NR	48 hours
Esteban et al[15]	526	13.5	32.8	48 hours
Zeggwagh et al[33]	101	37	NR	48 hours
Coplin et al[45]	136	17.6	NR	NR
Koh et al[87]	36	19	NR	48 hours
Maldonado et al[5]	24	26.7	NR	24 hours
Khamiees et al[43]	91	12.8	NR	72 hours
Namen et al[13]	100	16	NR	NR
Cohen et al[4]	35	28.6	10	48 hours
De Bast et al[22]	76	18.4	NR	24 hours
Perren et al[88]	98	6.7	33	48 hours
Smina et al[16]	95	11.3	—	72 hours
Conti et al[2]	92	1.7	NR	48 hours
Fernandez et al[89]	130	18	NR	48 hours
Francois et al[21]	343	8	0.3	24 hours
Thille et al[31]	168	15.5	50%	72 hours

Abbreviation: NR, not reported.

meaning of extubation failure varies among authors, leading to scientific confusion. Even when authors employ it as a synonym for reintubation, the period under study varies—within 24, 48, or 72 hours, or as long as 7 days.

Extubation failure is most often defined as the need for reintubation. The corollary of this definition is that all patients who do not require reintubation should be classified as extubation successes no matter how much difficulty they experience. A number of patients develop stridor after extubation, which resolves with inhalation of racemic epinephrine or other therapy without requiring reintubation. If extubation failure is defined as reintubation, such patients should be excluded. But if researchers are investigating the development of respiratory distress after extubation, all patients with significant postextubation stridor should be included. Much confusion could be avoided if researchers used the term *reintubation* when that is their sole criterion for extubation failure. If researchers use the term *extubation failure*, it seems logical to assume that their study population includes some patients with postextubation distress who did not require reintubation. In many reports, however, researchers do not make it clear which approach they are adopting—whether (or not) their category of extubation failure included some patients who developed distress after extubation but who did not require reintubation.

Investigators have variably classified patients who required noninvasive ventilation (NIV) after extubation as satisfying or not satisfying the definition of extubation failure. De Lassence et al[8] specified that they excluded patients who were managed by NIV in a cohort of extubation failure patients. Maldonado et al[5] included patients managed by NIV among their group of extubation failures, as did Haberthur

et al[9] and Jiang et al.[10] Moreover, Haberthur et al[9] extended the term *extubation failure* to include patients experiencing unjustified delay in extubation with one particular weaning technique if that patient tolerated extubation after being switched to an alternative weaning technique.

If patients die from a cardiorespiratory cause without being reintubated, it seems unscientific to classify them as extubation successes. Some authors[11] have specified that their definition of extubation failure included both the need for reintubation or unexpected death within 72 hours. Most authors, however, do not address this issue. Some extubated patients refuse reintubation (as part of a decision for withdrawal of life support) and die. How should these patients be classified? Demling et al[7] classified fatal outcomes as extubation failures, Epstein et al[12] excluded such patients from their group of extubation failures, and Namen et al[13] classified such patients (who died) as extubation successes.

How should patients who experience unplanned extubation followed by reintubation be classified? In a group of forty-two extubation failures, Epstein et al[12] included four unplanned extubations (who required reintubation within 72 hours) because these occurred while a weaning trial was in progress, but excluded sixteen other unplanned extubations (requiring immediate extubation) because these did not occur during weaning trials. If patients are extubated because of a defective endotracheal tube and then reintubated, how should they be classified? Epstein and Ciubotaru[14] excluded such patients, but many authors do not state clearly how such patients are classified.

Some patients may be inappropriately reintubated because of poor clinical judgment. What criteria should be set for judging a reintubation as appropriate? Epstein and Ciubotaru[14] listed the following criteria: increase in arterial carbon dioxide tension (P_{CO_2}) greater than 10 mm Hg and decrease in pH of 0.10; arterial oxygen tension (P_{O_2}) less than 60 mm Hg or less than 90% with an inspired oxygen concentration (FI_{O_2}) greater than 0.50; signs of increased work of breathing (high respiratory rate, accessory muscle use, or paradoxical breathing); and inability to protect the airway (secondary to upper airway obstruction or excess secretions). Many of these criteria are similar to those used for defining weaning failure, but it is more difficult to ensure their rigorous and consistent application as criteria for reintubation. Weaning failure typically occurs under controlled conditions, usually within 1 hour of starting a weaning trial. Reintubation for postextubation distress may not occur until many hours after extubation, and the listing of satisfied criteria may not be entered on a data form until hours after the event.

CAUSES AND PATHOPHYSIOLOGY OF POSTEXTUBATION DISTRESS

The listed indications for reintubation vary considerably from study to study. Of these, postextubation stridor has attracted the most attention.

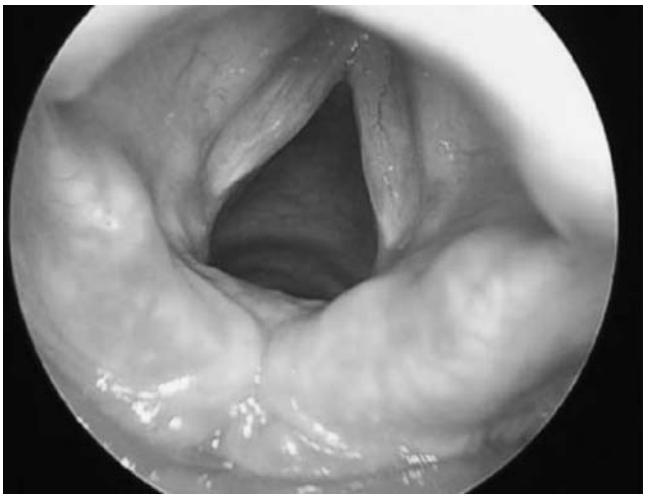

FIGURE 59-1 Mild postextubation laryngeal edema as seen with a rigid laryngoscope. (Used, with permission, from Antonaglia et al.[102])

Postextubation Upper Airway Obstruction

A number of investigators have reported that upper airway obstruction accounts for approximately 15% of patients requiring reintubation (15% in the study of Epstein and Ciubotaru;[14] 14.7% in that of Esteban et al;[15] and 15.4% in that of Smina et al[16]). These investigators, however, did not report what proportion of patients who developed clinical manifestations of upper airway obstruction did not require reintubation. Upper airway obstruction may result from edema of the subglottic area or the vocal cords, reflex closure of the vocal cords (laryngospasm), or compromise of the tracheal lumen (tracheomalacia or compression by a hematoma) (Figs. 59-1 and 59-2). The laryngeal edema that occurs in intubated

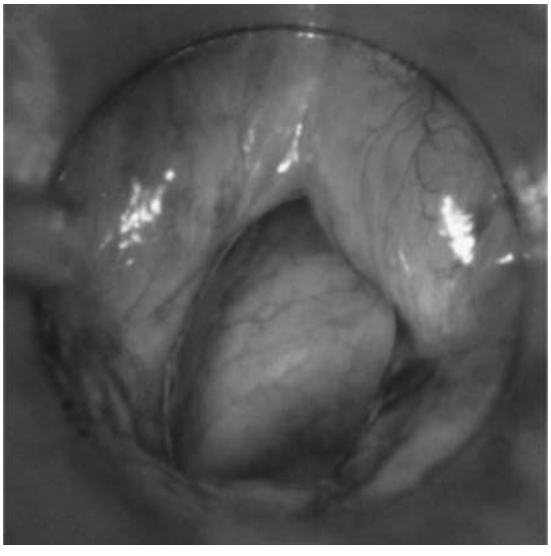

FIGURE 59-2 Moderately severe postextubation laryngeal edema as seen with a rigid laryngoscope. (Used, with permission, from Antonaglia et al.[102])

patients is believed to arise from direct mechanical trauma to the larynx by the endotracheal tube. Almost every patient intubated for 4 days or more develops laryngeal edema and mucosal ulcerations, usually located posterior to the level of the vocal cords, where the tube exerts the highest pressure.[17] Laryngeal edema is usually transient and self-limiting, and most of the lesions resolve within 1 month.[18]

Upper airway obstruction causes stridor only if the patient is capable of generating sufficient airflow; if airflow is insufficient, obstruction may cause hypercapnia, hypoxemia, or paradoxical breathing. Of 110 extubated patients, Sandhu et al[19] observed that thirteen (11.8%) developed stridor, but less than half of the patients with stridor (6/13) required reintubation (no patient required reintubation for any reason other than stridor in this series). Jaber et al[20] observed stridor in thirteen of 112 (11.6%) extubated patients, and nine of the thirteen required reintubation (only 2% [2/99] of patients without stridor required reintubation). Francois et al[21] undertook a randomized controlled trial of the effect of steroids on postextubation laryngeal edema in 761 critically ill patients requiring at least 36 hours of mechanical ventilation. Of the 343 patients in the placebo arm, seventy-six (22%) exhibited features of postextubation laryngeal edema. Twenty-six of the 343 extubated patients (8%) required reintubation, and the reintubation was linked to laryngeal edema in fourteen (54%[14/26]) of these patients. Forty-six percent of the patients with postextubation stridor or endoscopic laryngeal edema did not require reintubation, indicating that the development of stridor is not a particularly strong predictor of the need for reintubation.[17]

In the above studies, upper airway obstruction was typically diagnosed on the basis of clinical manifestations. De Bast et al[22] undertook fiber-optic examination before reintubation or directly inspected the glottis during reintubation to confirm the presence of laryngeal edema. Of seventy-six patients who had been intubated for at least 12 hours, fourteen required reintubation within 24 hours of extubation (reintubation rate, 18.4%). Of these fourteen patients, eight (57.1%) had laryngeal edema.

When upper airway obstruction occurs, it is typically manifested soon after extubation. Of the seventy-six patients who developed features of laryngeal edema in the study of Francois et al,[21] 47% (36/76) developed it within 5 minutes of extubation, 34% (26/76) developed it between 6 and 30 minutes after extubation, and 18% (14/76) developed it 30 minutes or longer after extubation.

Although laryngeal edema can develop as early as 6 hours after intubation,[22] many, but not all,[23] investigators have noted that the rate of postextubation stridor increases in proportion to the duration of ventilation. Jaber et al[20] observed that duration of intubation was longer in thirteen patients with stridor than in ninety-nine patients without stridor: 10.9 versus 5.5 days. Sandhu et al[19] likewise observed a longer duration of intubation in six patients who developed postextubation stridor than in ninety-seven patients who did not: 6.5 ± 1.9 versus 2.6 ± 2.6 days. Darmon et al[24] observed that stridor was more common among patients intubated for longer than 36 hours than among patients intubated for a shorter time: 7.2% (25/346) versus 0.9% (3/317).

Women are more susceptible to postextubation stridor than men, and the rate may vary with ethnicity. In a series from France, Darmon et al[24] observed stridor in 7.4% (20/284) of women and 2.1% (8/379) of men. In a series from Taiwan, Ho et al[23] observed stridor in 39% (7/18) of women and 17% (10/59) of men.

Other risk factors associated with the development of laryngeal edema include traumatic intubation, excessive tube size, excessive tube mobility secondary to insufficient fixation, a patient fighting against the tube or trying to speak, excessive pressure in the cuff, too frequent or too aggressive tracheal suctioning, occurrence of infections or hypotension, and the presence of a nasogastric tube that predisposes to gastroesophageal reflux.[22] It is also possible that a biochemical reaction between the tube material and the airway mucosa may cause laryngeal edema.[22] Compared with the ninety-nine patients without stridor, the thirteen patients who developed stridor in the series of Jaber et al[20] were more likely to have the following: a traumatic and/or difficult intubation (54% vs. 7%), a history of self-extubation (38% vs. 4%), a higher balloon cuff pressure (83 vs. 40 cm H_2O), a higher simplified acute physiology score (SAPS) II score (50 vs. 38), and a medical rather than a surgical reason for admission (46% vs. 18%).

Other Causes of Postextubation Distress

Conditions other than upper airway obstruction that cause postextubation distress vary from study to study. In a report on reasons for reintubation, Epstein and Ciubotaru[14] noted upper airway obstruction in 15%; other reasons for reintubation included respiratory failure (28%), congestive heart failure (23%), aspiration or excessive secretions (16%), encephalopathy (9%), and other conditions (8%). The frequency of a particular reason differs among studies. For example, cardiac failure accounted for 23% of the cases of Epstein and Ciubotaru[14] and 6.6% (4/61) of the cases of Esteban et al,[15] but none of the cases of Smina et al[16] or De Bast et al.[22] Because of the limited rigor of these studies, there is little point in attempting a more detailed analysis of the relative incidence of other causes of reintubation.

Pathophysiology

None of the studies of reasons for postextubation cardiorespiratory distress can be considered as studies of pathophysiologic mechanisms in the same sense as are studies of the pathophysiology of weaning failure. For studies of postextubation distress, investigators filled out case report forms. These forms constitute post hoc incident reports completed after some event. In many cases, investigators are making a best guess as to what might explain a patient's deterioration.

In contrast, research into the pathophysiology of weaning failure is based on the simultaneous recording of several signals, starting before a weaning trial and continuing until after its completion. In this way, it is possible to understand the relative roles of control of breathing, respiratory muscle activity, derangements of lung and chest wall mechanics, gas exchange, and cardiovascular performance in weaning failure. Conducting similar types of studies to delineate the mechanisms of postextubation cardiorespiratory distress will be challenging.

The first challenge is instrumentation. The recording of swings in intrathoracic pressure, as reflected by esophageal pressure, is relatively easy. But on its own, esophageal pressure is of limited value. Derivation of most indices, such as airway resistance, compliance, and intrinsic positive end-expiratory pressure, require a simultaneous measurement of airflow. It is extremely difficult to obtain a meaningful measure of airflow or tidal volume in a recently extubated patient.[25] The use of a mouthpiece or face mask causes marked distortion of the breathing pattern. Inductive plethysmography provides a means for overcoming this problem. For example, Tobin et al[26] used this technique to study changes in breathing pattern in ten patients at the point of extubation (Fig. 59-3). During the first 15 minutes after extubation, both minute ventilation and mean inspiratory flow (a measure of respiratory motor output) increased, accompanied by a decrease in the degree of abdominal paradox. By the end of the first hour after extubation, respiratory drive and minute ventilation had returned to preextubation levels. No further change in breathing pattern was observed over the subsequent 24 hours. The investigators did not study any patients who developed postextubation distress. When inductive plethysmography is combined with esophageal pressure recordings, great care is required to ensure that the two signals are perfectly aligned. The smallest misalignment will cause major errors in estimates of intrinsic positive end-expiratory pressure and other measures of lung mechanics. A requirement not faced by researchers studying the pathophysiology of weaning failure is the need to record the development of laryngeal obstruction. As such, additional research instrumentation includes fiber-optic endoscopy.

Perhaps an even greater challenge than the instrumentation is the timing. Weaning failure almost invariably occurs within the first hour of attempted spontaneous breathing. The time course for the development of postextubation cardiorespiratory distress extends over a longer span. In the study of Epstein and Ciubotaru,[14] for example, only 33% of reintubations occurred within the first 12 hours after extubation, and 42% occurred after 24 hours.

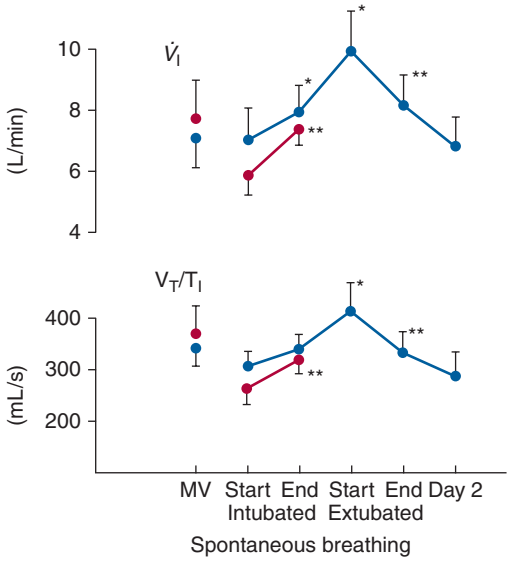

FIGURE 59-3 Recordings of minute ventilation ($\dot{V}_I$) and mean inspiratory flow (V_T/T_I), a measure of respiratory motor output, during mechanical ventilation (*MV*), at the start and end of a T-tube trial, the first 15 minutes after extubation, 45 to 60 minutes after extubation, and 24 hours after extubation. Ten patients who tolerated the T-tube trial and were extubated are shown in *blue* and seven patients who failed the T-tube trial and were reconnected to the ventilator are shown in *red*. Bars represent ±1 standard error (SE); *, $p < 0.05$; **, $p < .01$ compared with the value during the immediately preceding time-block of spontaneous breathing. (Used, with permission, from Tobin et al.[26])

CONSEQUENCES OF POSTEXTUBATION DISTRESS

Many, but not all,[27] investigators have reported that mortality is many times higher in patients who require reintubation than in patients who tolerate extubation (Table 59-2). Three explanations have been offered to account for the increased mortality: complications associated with the act of reintubation itself; development of a new problem in the interval between extubation and reintubation; and the need for reintubation is simply serving as a marker for a poor prognosis.

Endotracheal intubation is typically performed under elective and controlled conditions. It is more challenging to perform intubation in a patient developing acute distress in the period after extubation. Complications have been reported to occur at the time of reintubation in 15%,[28] 18%,[15] and 28% of patients.[14] In a study of forty consecutive

TABLE 59-2: ASSOCIATION BETWEEN REINTUBATION AND MORTALITY

Reference	Mortality in Reintubated Patients	Mortality in Patients Tolerating Extubation
Daley et al[27]	8%	6.5%
Epstein et al[12]	43%	9.1%
Esteban et al[28]	27%	2.6%
Esteban et al[15]	33%	4.6%
Perren et al[88]	33%	3.6%
Thille et al[31]	50%	4.9%

patients requiring reintubation (for any reason), Torres et al[29] reported that 47% (19/40) developed nosocomial pneumonia after reintubation, as compared with 10% of matched control patients (odds ratio [OR]: 5.9). In a study of 297 intubations performed under emergency conditions (in 238 adults), Schwartz et al[30] reported seven deaths (mortality: 2.4%) at the time of or within 30 minutes after intubation; five of the deaths were associated with a systolic blood pressure less than 90 mm Hg. In contrast to the experience of Torres et al,[29] only 4% of patients developed a radiographic infiltrate compatible with a new aspiration pneumonia.[30] In a study by Esteban et al,[15] mortality was no greater among the eleven patients who developed complications at the time of reintubation than in the remaining fifty patients (45.4% and 30.0%, respectively; $p = 0.53$). Based on the above considerations, it seems unlikely that the higher mortality in reintubated patients is a direct consequence of complications associated with the act of reintubation itself.

A second explanation is the development of a new problem during the interval between extubation and reintubation. In support of this possibility is the observation of Epstein and Cibotaru[14] that mortality increases in proportion to the time between extubation and reintubation: mortality of 69% in patients reintubated between 49 and 72 hours after extubation (17% of the group), 24% in patients reintubated in the first 12 hours after extubation (33% of the group), and 39% in patients reintubated between 13 and 24 hours after extubation (25% of the group).

The third explanation for higher mortality in reintubated patients is that reintubation is simply serving as a marker for a poor prognosis. Sicker patients are more likely to undergo reintubation. Epstein and Ciubotaru[14] have argued against this explanation. They note that reintubation continues to have a strong independent effect on mortality even after controlling for generalized severity of illness at weaning onset, comorbidity, age, and need for acute dialysis. It is, however, possible that the need for reintubation is measuring some additional aspect of disease severity not captured by the above variables.

Thille et al[31] have argued that reintubation has a direct and specific effect on patient outcome because it is frequently followed by marked clinical deterioration. They studied twenty-six patients who failed extubation and required reintubation within the subsequent 72 hours; 50% of the reintubated patients died in the ICU. At the time of extubation, the Sequential Organ Function Assessment (SOFA) score was not significantly different between the twenty-six patients who subsequently required reintubation and 142 patients who tolerated extubation. In the first 24 hours after extubation, the SOFA score increased significantly from 3.4 ± 2.9 to 4.7 ± 3.4 in the failed extubation group, mainly as a result of hemodynamic and respiratory deterioration. Patients who tolerated extubation showed an improvement in their SOFA score over the same interval, essentially because of removal of the ventilator. These data suggest that reintubation leads to adverse consequences, and it is not simply a marker for a poor prognosis.

PREDICTORS OF POSTEXTUBATION DISTRESS

Because reintubation causes serious complications in some patients, attempts are made to predict its likely occurrence. A number of physiologic variables have been evaluated for their ability to predict this likelihood. For some patients, the likelihood of reintubation is considered so high that a clinician may proceed to tracheotomy without first attempting extubation.

Ability to Sustain Spontaneous Ventilation

It is extremely uncommon to undertake planned extubation without first assessing a patient's ability to sustain spontaneous ventilation. This assessment typically consists of observing a patient breathing through a T-tube circuit or while assisted by a low level of pressure support or intermittent mandatory ventilation. A weaning trial serves primarily as an additional diagnostic test, with the aim of predicting whether a patient will develop distress after extubation and need reintubation. The predictive accuracy of a weaning trial as a diagnostic test has never been evaluated in a rigorous scientific manner.

A true-positive result of a T-tube trial is defined as a patient who tolerates the trial without distress, is then extubated, and does not require reintubation. The usual rate of reintubation is 15% to 20% (sometimes lower), but higher reintubation rates have been reported by some investigators: 23.5%,[29] 25%,[32] 26.7%,[5] 28.6%,[4] and 29.4%.[3] These false-positive test results mean that the positive-predictive value and specificity of passing a T-tube trial in predicting that a patient will not require reintubation is much less than 100%. To measure the false-negative rate would require extubating patients who fail a T-tube trial, and counting how many do not require reintubation. For obvious ethical reasons, we do not know this number. Given the natural caution of physicians, we can confidently assume that it is higher than 0%. As such, sensitivity and negative-predictive value will be less than 100%. It is no surprise that the ability of a T-tube trial to predict reintubation has a sensitivity and specificity of less than 100%; no diagnostic test is perfect. But a weaning trial is not solely used as a diagnostic test for predicting the likelihood of reintubation. The outcome of a weaning trial is also used as a reference standard against which the accuracy of weaning predictor tests are measured.

Weaning Predictor Tests

Several investigators have investigated the ability of weaning predictor tests to predict the development of distress after extubation. The question posed is along these lines: "Does frequency-to-tidal-volume ratio (f/V_T), or some other predictor test, measured before a T-tube trial, predict the likelihood of reintubation?" To answer this question with

scientific validity, it is imperative that the investigators take clearly defined steps to ensure that clinicians are *not* taking the results of the T-tube trial into account when deciding whether to extubate the study patients. (In other words, a decision to extubate the patient must be taken before the T-tube trial, and must proceed even if the patient exhibits significant distress during the trial.) If researchers allow clinicians to use results of a T-tube trial (done after measurement of the weaning predictor test) when deciding whether or not to proceed with extubation, the researchers need a different experimental design because they are asking a different research question. The question is now, "In what instances do weaning predictor tests override the results of a subsequently undertaken T-tube trial?"

Before we discuss the findings of studies on the use of tests to predict the likelihood of postextubation distress, we ask the reader to undertake a simple thought experiment. You, as the patient's clinician, record f/V_T, and obtain a reading of 60. You then proceed to a T-tube trial. If the patient develops severe distress during the trial, would you extubate the patient? (Please exclude circumstances in which you believe that the internal diameter of the endotracheal tube is the main cause of distress.) We believe that most experienced clinicians will answer"no." Consider another scenario: A resident measures f/V_T in your patient, obtains a value of 120, and proceeds to a T-tube trial. If the patient tolerates the trial without significant distress, would you defer extubation? We believe most experienced clinicians would again answer "no," although they might monitor the postextubation period more closely than if the patient had an f/V_T reading of 90 before the trial.

For both of the preceding scenarios, we believe that few if any experienced clinicians would allow a measurement of f/V_T (made before a T-tube trial) to override a judgment based on how well a patient tolerates a T-tube trial. Given the results of the thought experiments, it makes little sense to undertake research studies of the accuracy of weaning predictor tests (measured before a weaning trial) to forecast a patient's likely need for reintubation (in a patient who passes a weaning trial). It makes even less sense when one considers that a clinician's action based on the patient's performance during the weaning trial will have inevitably muddied the experimental waters. Let us consider a patient in whom a weaning predictor test predicts a high likelihood of respiratory distress. A weaning trial is nevertheless undertaken. The patient develops distress, and so is not extubated. By excluding such patients from a study, the investigators are markedly underestimating the true-negative rate of the test for predicting distress after extubation (where the test predicts distress and the patient actually develops distress).

It is difficult to understand why so many investigators have undertaken this type of research. We suspect they have been seduced by affirmative answers to two subsidiary questions. "Do patients with satisfactory weaning predictors usually tolerate a spontaneous breathing trial?" Yes. "Do patients who tolerate a spontaneous breathing trial usually avoid reintubation?" Yes. It might seem logical to conflate these two issues, and ask:"Do patients with satisfactory weaning predictors usually avoid reintubation?" The only way to address this question in a scientific manner is to measure weaning predictors and extubate the patient without an intervening weaning trial. Zeggwagh et al[33] are the only group of investigators to undertake such a study.

The investigators prospectively studied 101 patients (ventilated for 10.4 ± 10.3 days) at the point that their ICU physicians contemplated weaning. They measured a series of physiologic measurements during 2 minutes of spontaneous breathing; the results of these measurements were not communicated to the primary team. The team then extubated the patients without first undertaking any form of weaning trial. The extubation decision was made by the ICU team, based on the following criteria: improvement or resolution of the condition precipitating the need for mechanical ventilation; good level of consciousness with cessation of all sedative agents; temperature less than 38°C (100.4°F); respiratory frequency less than 35 breaths/min; S_{O_2} greater than 90% on FI_{O_2} equal to or less than 0.40; hemodynamic stability; and the absence of electrolyte disorders, acid–base disturbance, or hemoglobin less than 10 g/dL. Reintubation was necessary in 37% of the patients. Several variables predicted the need for reintubation with a reasonable degree of accuracy. For example, f/V_T had a sensitivity of 0.77 and a specificity of 0.79, with an area under a receiver operating curve (ROC) curve of 0.81 ± 0.06; maximum expiratory pressure had a sensitivity of 0.52 and a specificity of 0.92, with an area under an ROC curve of 0.73 ± 0.07. The investigators developed a model based on three variables: f/V_T, maximum expiratory pressure, and vital capacity. The area under the ROC curve for the model was 0.91 ± 0.04 for a development data series and 0.86 ± 0.06 for a validation data series.

This study by Zeggwagh et al[33] suggests that undertaking a weaning trial before extubation is useful because their rate of reintubation is about double that reported in studies in which weaning trials precede extubation. The clinicians in the study by Zeggwagh et al[33] based their decision for extubation on only the most rudimentary clinical assessment. If the clinicians had made the decision to extubate using more sophisticated physiologic predictors (but still did not undertake a weaning trial), it is likely that the rate of reintubation would have been lower. The accuracy of weaning predictors in this study contrasts sharply with their accuracy in studies in which the investigators permitted a weaning trial (which altered clinician's extubation decisions) between measurement of the predictors and extubation (see Table 58-1 in Chapter 58).

Cuff-Leak Test

Some patients show satisfactory recovery of lung function but develop upper airway obstruction after extubation. The difficulty in defining the relationship between upper airway injury and postextubation stridor is that the presence of the endotracheal tube precludes direct visualization of the upper

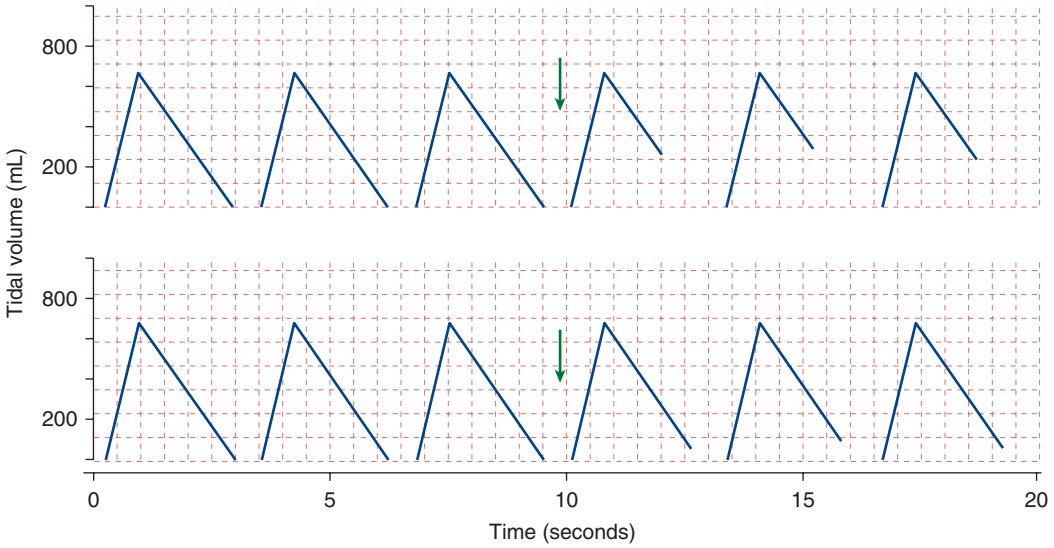

FIGURE 59-4 Cuff-leak test. Schematic of tidal volume during inhalation (*up going*) and exhalation (*down going*) in two patients before and after deflation of the cuff on the endotracheal tube (*arrow*). *Upper panel:* The patient develops a large leak after cuff deflation (positive-test result), as signified by the expired tidal volume being markedly smaller than the inspired tidal volume. *Lower panel:* The patient develops a small leak after cuff deflation (negative-test result), as signified by the expired tidal volume being only approximately 40 to 75 mL or 6% to 12% less than the inspired tidal volume.

airway before extubation. Several investigators have tested the hypothesis that the volume of air leaking around the outside of an endotracheal tube on deflating the balloon cuff will be inversely related to the degree of laryngeal obstruction generated by laryngeal edema (Fig. 59-4). The idea was first reported by Adderley and Mullins[34] who studied thirty-one planned extubations in twenty-eight children with croup. After extubation, reintubation was required in 13% (3/23) of children who had an audible leak (on coughing or when plateau pressure was 40 cm H_2O), and reintubation was required in 38% (3/8) of children without a leak. The cuff-leak test has since been evaluated with varying degrees of scientific rigor (Table 59-3).

Miller and Cole[35] undertook the first systematic evaluation of the cuff-leak test. They studied 100 intubations in eighty-eight ventilated patients. During assist-control ventilation, they noted that the set inspired tidal volume (V_T) and displayed expired V_T were always within 20 mL of each other (they did not state the volume setting). To measure the leak, they deflated the cuff and recorded expiratory V_T over the subsequent six cycles; they used the average of the three lowest values to calculate the leak. After extubation, 17% of patients required reintubation. Of the six patients who developed stridor, reintubation was required in three. The leak (measured during the 24 hours before extubation) was smaller in patients who subsequently developed

TABLE 59-3: ACCURACY OF THE CUFF-LEAK TEST

Authors	No[a]	Leak Criterion	Outcome Criterion	Sensitivity	Specificity	PPV	NPV
Adderley et al[34]	31	Audible	Reintubation	0.80	0.50	0.87	0.38
Miller et al[35]	100	<110 mL	Stridor	0.67	0.99	0.80	NR
Engoren[90]	531	<110 mL	Leak <110 mL	0.00	0.96	0.00	1.00
Sandhu et al[19]	110	<10% inspV$_T$	Stridor or reintubation	NR	0.96	NR	NR
De Bast et al[22]	76	<15.5% inspV$_T$	Reintubation secondary to laryngeal edema	0.75	0.72	0.25	0.96
Jaber et al[20]	112	<130 mL or <12% inspV$_T$	Stridor and leak <130 mL or <12% of inspV$_T$	0.85	0.95	0.69	0.98
Maury et al[44]	115	Audible	Stridor	1.0	0.80	0.15	1.0
Kriner et al[91]	462	<110 mL	Stridor or reintubation	0.50	0.84	0.12	0.97
Chung et al[36]	95	<140 mL	Laryngeal edema on endoscopy	0.89	0.90	0.84	0.93

Abbreviations: insp, inspiratory; *NPV*, negative-predictive value; *NR*, not reported; *PPV*, positive-predictive value; V_T, tidal volume.

[a]Number of extubations.

postextubation stridor than in patients who did not: 180 ± 157 versus 360 ± 157 mL. ROC curve analysis indicated that a leak of less than 110 mL provided the best threshold for predicting postextubation stridor. A leak of less than 110 mL had a sensitivity of 0.67, a specificity of 0.99, and a positive-predictive value 0.80 (negative-predictive value was not reported).

A representative example of the methodology employed in subsequent investigations is illustrated by the approach used by Jaber et al[20] who evaluated the cuff-leak test in 112 patients. The leak was smaller in thirteen patients who developed postextubation stridor than in the ninety-nine patients who did not develop stridor after extubation: 59 ± 92 versus 372 ± 170 mL (with V_T 10 to 12 mL/kg during assist-control ventilation); expressed in terms of relative volumes, 9 ± 3% versus 56 ± 20%. Reintubation was required in 69.2% (9/13) of the patients with stridor as compared with 2.0% (2/99) of patients without stridor. They used ROC curve analysis to find the best threshold; they considered a true-positive test as a leak less than 130 mL or less than 12% of inspired V_T together with postextubation stridor. At this threshold, sensitivity was 0.85, specificity 0.95, positive-predictive value 0.69, and negative-predictive value 0.98.

A more rigorous methodology was employed by De Bast et al[22] who prospectively studied seventy-six patients who had been intubated 12 or more hours. They measured cuff leak as a percentage:

$$[(\text{Expired } V_T \text{ with cuff inflated} - \text{Expired } V_T \text{ with cuff deflated})/\text{Expired } V_T \text{ with cuff inflated}] \times 100.$$

They took the average of six measurements that varied by less than 30%. The measurements were not available to the staff in charge of patients. If patients developed stridor associated with signs of respiratory distress within 24 hours of extubation and required reintubation, laryngeal edema was confirmed or excluded by fiber-optic examination before the reintubation, or by direct examination of the glottis during reintubation. The investigators excluded patients who were reintubated for reasons other than laryngeal edema.

Within the first 24 hours, 10.5% (8/76) of the patients of De Bast et al[22] required reintubation for laryngeal edema. These patients had smaller leaks than did the other patients: 9% (3, 18; twenty-fifth, seventy-fifth percentiles) versus 35% (13, 53; twenty-fifth, seventy-fifth percentiles). (Of the ten patients who developed postextubation stridor, eight were reintubated.) ROC curve analysis revealed that the best threshold was a leak of 15.5%. This threshold had a sensitivity 0.75, specificity 0.72, positive-predictive value 0.25, and negative-predictive value 0.96. The low positive-predictive value, 0.25, indicates that 75% of the patients with a leak less than 15.5% were successfully extubated (without laryngeal edema or requiring reintubation). Thus, a low leak volume should not be used to postpone extubation indefinitely. The negative-predictive value of 0.96 means that when patients exhibit a large leak (a negative test result), they are not likely to require reintubation (because of laryngeal edema). A leak greater than 23% excluded all patients who required reintubation because of laryngeal edema.

Chung et al[36] also used endoscopic examination of the upper airway in a study involving ninety-five patients. The average duration of translaryngeal intubation was quite long, 28.1 ± 17.6 (standard deviation [SD]) days. Employing video bronchoscopy, the Taiwanese investigators observed a high rate of severe laryngeal edema, 36.8% (35/95). They used ROC curve analysis to select the most discriminatory cuff-leak threshold. At a threshold volume of 140 mL, 39% (37/95) of patients had positive test results. The performance of the cuff-leak test was superior to that observed by most other investigators (see Table 59-3).

Prinianakis et al[37] undertook a study to determine the physiologic determinants of the volume being leaked when the cuff-leak test is performed. The volume of the leak is calculated by obtaining several measurements of expired V_T after deflation of the cuff and subtracting the average value from the set inspired V_T. With the cuff deflated, however, the inspiratory V_T reaching the alveoli is also decreased. Thus, the measured leak has both inspiratory and expiratory components. By adding an inspiratory pause, Prinianakis et al[37] measured expiratory leak unaffected by the inspiratory leak. In fifteen critically ill patients receiving neuromuscular blocking agents, the expiratory leak was consistently lower than the total leak. To elucidate the physiologic determinants of the expiratory leak, the investigators employed a mechanical lung model. The cross-sectional area around an endotracheal tube was not the only factor affecting the magnitude of a leak, it was also influenced by the inspiratory component. The total leak was inversely related to inspiratory flow and system compliance. Although this study explains some of the imprecision of the cuff-leak test, it does not mean that clinicians should start using a more pure measure of expiratory leak in everyday practice. Prinianakis et al[37] did not compare the accuracy of the more pure measure of expiratory leak in predicting the occurrence of postextubation laryngeal edema or the need for reintubation.

In summary, the studies of the cuff-leak test are of varying quality. The method for performing the test has not been standardized. In particular, none of the investigators addressed the setting of inspired V_T, which may influence the size of the leak. The method for quantifying the leak varies between absolute units (milliliters) and percentage of inspired V_T. The outcome criterion is not always clearly stated: rate of reintubation for any reason, occurrence of stridor of any severity, or occurrence of stridor that requires reintubation. The rates of stridor vary considerably among studies, suggesting that investigators used different criteria (admittedly, it is not obvious that severity of stridor can be graded in any reproducible manner). Only De Bast et al[22] and Chung et al[36] used an objective method (fiber-optic endoscopy) to verify the presence of laryngeal edema.

In some studies, it is not clear whether the investigators carefully excluded reasons for reintubation other than stridor. If a patient is reintubated because of left-ventricular failure, it is not logical to expect the cuff-leak test to predict such

an event. What is the best reference standard? Should a true-positive test result be restricted to postextubation stridor that requires reintubation? Is it important to predict the development of postextubation stridor that will respond to aerosolized epinephrine? The manner of reporting test performance is not consistent. The thresholds for defining a significant leak vary. All calculations of test performance are inevitably overestimates, because none of the investigators split their data set into training and validation subsets. A fundamental problem with all of the studies is that the leak criterion used to define a positive test has been based on the assumption that the clinical consequences of false-positive and false-negative results are equal. Instead, physicians need to customize the threshold value according to the clinical circumstances. In cases where tracheal intubation is expected to be difficult, physicians may use a higher leak volume as the threshold for a positive test result. Conversely, when there is greater fear of the hazards of delayed extubation, physicians may accept a lower leak volume as the threshold for a positive test result.

Secretions and Cough

A proportion of patients fail either a weaning attempt or an extubation attempt because of excessive airway secretions. This proportion varies among reports, largely because there is no consistent definition of "excessive secretions" or even how best to quantify secretions. If one quantifies secretions according to the volume obtained by suctioning over a fixed time interval, a patient who coughs and expels secretions without difficulty may get classified as having a greater secretion problem than a patient who has thick viscid secretions that cannot be dislodged from the lower airways.

The act of suctioning per se is associated with a number of serious complications, such as life-threatening hypoxemia, mucosal trauma, hemorrhage, bronchoconstriction, atelectasis, cardiac arrhythmias, and even cardiac arrest.[38–41] Jubran and Tobin[42] investigated the possibility that a sawtooth pattern on the flow-volume curve might provide a noninvasive means of detecting secretions. In fifty intubated patients, the presence of a sawtooth pattern on flow-volume curves recorded during 1 minute of spontaneous breathing was a strong predictor of the presence of secretions (positive-predictive value: 94%), and the absence of this pattern suggested that secretions were unlikely to be present (negative-predictive value: 77%) (Fig. 59-5). Expressed in terms of likelihood ratios, a sawtooth pattern was approximately six to eight times more likely to be found in patients who had secretions than in patients without secretions. Conversely, a smooth flow-volume curve was about one-quarter as likely to be found in patients with secretions as in those without secretions. Clinical examination had much higher false-positive and false-negative rates (42% and 43%, respectively) than the flow-volume curves (12% and 14%, respectively). Accordingly, reliance on clinical examination will lead to unnecessary suctioning in patients without secretions and inadequate suctioning in patients with secretions.

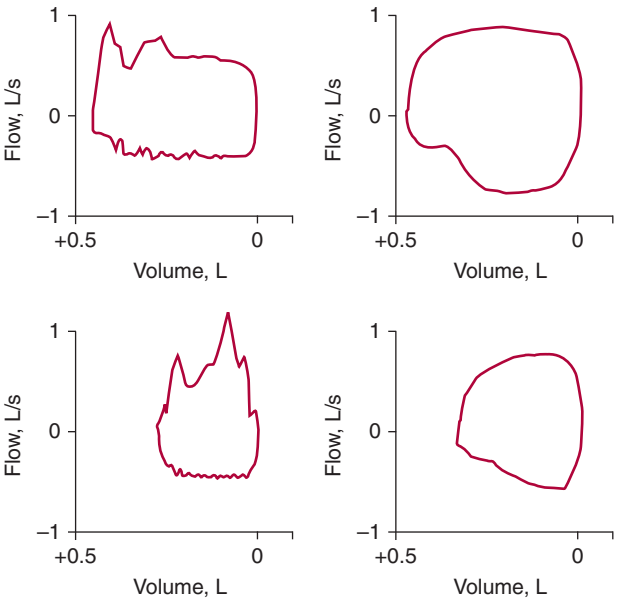

FIGURE 59-5 *Left panels, upper and lower*: Inspiratory and expiratory flow-volume curves obtained in two patients with secretions exhibit a sawtooth pattern. *Right panels, upper and lower*: Flow-volume curves obtained in two patients without secretions have a smooth contour. (Modified, with permission, from Jubran and Tobin.[42])

Measurement of secretions has been evaluated as a predictor of postextubation distress. Khamiees et al[43] attempted to quantify cough strength by placing a white card at 1 to 2 cm from the end of the endotracheal tube and requesting the patient to cough as many as three to four times just before extubation. Any wetness on the card was classified as a positive test (assessment was made by a single observer). This test was seen as a test of cough strength and not of the amount of secretions present. They studied 100 extubations in ninety-one patients; eighteen patients were classified as extubation failures and eleven were reintubated within 72 hours of extubation (the criteria for classifying the other seven patients as extubation failures are not clear). Extubation failure was three times more likely in patients with a negative white-card test (no secretions coughed onto the card). Three other measures also predicted extubation failure. Extubation failure was four times more likely among patients who had a weak or absent cough than in patients with a moderate or strong cough. Extubation failure was eight times more likely in patients classified as having moderate or abundant secretions by the nursing staff in the 4 to 6 hours preceding extubation than in patients with absent or mild secretions. Extubation failure was sixteen times more likely among patients whose secretions required suctioning every 2 hours or less.

Smina et al[16] of the same research group studied the ability to predict reintubation after 115 extubations in ninety-five patients (on this occasion, the investigators specify that extubation failure was synonymous with reintubation). Reintubation within 72 hours was required in 11.3%. The

magnitude of secretions was not associated with extubation failure, which contrasts with their previous report that extubation failure was increased sixteen times if patients required frequent suctioning. This failure to reproduce an earlier observation illustrates a common problem with all studies of clinical predictors. After the report of findings of an initial study, physicians modify their approach to a particular problem; in statistical terminology, clinicians change their pretest probability (based on the report). When a research team reinvestigates the same phenomenon in a new group of patients, they fail to reproduce the original finding. Many patients in the second study who had secretions were not advanced to extubation, leading to a decrease in the number of true-positive test results. The study of Khamiees et al[43] indicated that frequent suctioning was associated with a high reintubation rate. Smina et al,[16] however, found that only 4% of patients in their follow-up study had greater than 20 mL of secretions per hour before extubation. Clearly, physicians in the second study had reduced the number of extubations attempted in patients with larger volumes of secretions. The physicians had altered their pretest probability of extubation failure based on the need for frequent suctioning. The physicians refused to advance such patients to extubation (test-referral bias), and thus, the results of the study give an erroneous impression that frequent suctioning is not a good predictor of reintubation.

Maury et al[44] hypothesized that the occurrence of a cough in the first few seconds after complete deflation of the cuff on an endotracheal tube results from secretions, which had previously accumulated above the cuff and had now passed into the lower airways. They reasoned that the presence of a cough associated with respiratory gurgling (heard without a stethoscope and related to secretions) upon cuff deflation would indicate patency of the upper airway, whereas the absence of a cough would suggest upper airway edema—the same line of thinking on which the cuff-leak test is premised. They tested the hypothesis during 115 extubations in ninety-nine patients. The absence of a cough following cuff deflation was a strong predictor of postextubation stridor (negative predictive value: 0.98); positive-predictive value, however, was only 0.12.

Neurologic Assessment

Some ventilated patients demonstrate good respiratory function and tolerate a T-tube trial without distress, yet their physicians are reluctant to extubate them because they fear that the patients will not be able to protect their airway after extubation. Although widely used, the term *protecting the airway* is rarely clearly defined. We take it to mean that a patient has unsatisfactory neural control over the airway, such that the tongue (of a recumbent patient) may fall back and occlude the airway lumen (as happens in patients with sleep apnea), or the patient has impaired laryngeal (and other upper airway) reflexes, placing the patient at risk of aspiration of secretions (from the mouth and airways) or ingested food.

Concern about protecting the airway most often arises in a patient with evidence of brain injury. Three groups of investigators have studied the role of brain function in patients being considered for extubation. The most rigorous study is that by Coplin et al,[45] who studied 136 brain-injury patients. They evaluated patients for extubation using a broad screen: absence of neurologic deterioration on physical examination; intracranial pressure less than 20 mm Hg; satisfactory oxygenation, lung mechanics, f/V_T, blood pressure, and heart rate; and absence of a specific indication for mechanical ventilation (such as surgery planned within the subsequent 72 hours).

Of the 136 patients, 72.8% (99/136) were extubated within 48 hours of meeting the above readiness criteria; the other 27.2% (37/136) remained intubated for a median of 3 days (range: 2 to 19 days). They defined a delay in extubation as the time from meeting readiness criteria to the time of extubation, but subtracted 48 hours (to allow for time needed for communication among caregivers). Neurologic evaluation based on the Glasgow Coma Scale (GCS) score was performed daily. (This scale ranges from 3 to 15, with 15 indicating the best brain function and 3 indicating severe brain dysfunction; a score ≥13 indicates *possible* mild brain injury, 9 to 12 moderate injury, and ≤8 severe brain injury.)

Sixty patients were judged comatose (score ≤8 on the GCS) on the day of meeting extubation readiness criteria; extubation was delayed in 48.3% (29/60) as compared with 10.5% (8/76) of patients not classified as comatose. The two groups, however, exhibited considerable overlap. Of sixty comatose patients (score ≤8), 51.7% (31/60) were extubated without delay. Indeed, among patients with more severe brain injury, with GCS scores of 4 and lower, 40% (4/10) were extubated without delay. Conversely, 10.5% (8/76) of patients with scores ≥9 experienced delayed extubation. Coplin et al[45] assessed whether the decision to extubate was influenced by change in neurologic status over time: 57% (21/37) of patients improved between the day of meeting the readiness criteria and extubation, but the remaining 43% showed no change or deterioration in neurologic function.

Absence of a gag reflex has been considered a contraindication to extubation in the past. Approximately 20% of healthy people, however, do not have a gag reflex, and aspiration pneumonia may still occur in people who do.[46] The importance of the gag reflex in the extubation period was addressed by Coplin et al:[45] 89% (32/36) of patients with a weak or absent gag reflex were successfully extubated.

A major reason to postpone extubation in a neurologically impaired patient is the fear of aspiration pneumonia. The occurrence of pneumonia, however, was higher in patients experiencing delayed extubation: 38% versus 21%.[45] These patients also had longer stays in the ICU (8.6 vs. 3.8 days) and in hospital (19.9 vs. 13.2 days). Based on their data, Coplin et al[45] concluded that a depressed level of consciousness should never be used as the sole indication for prolonged intubation.

In contrast to Coplin et al,[45] Namen et al[13] concluded that the GCS helps in predicting successful extubation. They studied 100 brain-injury patients, whose mechanical ventilations were managed by neurosurgeons. On ROC curve analysis, a score of ≥8 on the GCS provided the best discrimination of extubation outcome. Extubation was successful in 36% of patients with GCS scores ≤7 as compared with 75% of patients with a score ≥8. The area under the ROC curve for GCS score, however, was only 0.681. A more fundamental problem is that twenty-two patients were extubated as part of the withdrawal of life-support therapy (all these patients died). Because these patients were not reintubated, it appears that the authors classified them as extubation successes. Irrespective of how these twenty-two patients were classified, it is impossible to interpret data on extubation predictors where half of the extubations arose from a decision to withdraw life support.

The studies of Coplin et al and Namen et al were conducted in patients with brain injury, whereas Salam et al[47] studied neurologic function as a predictor of reintubation in eighty-eight medical-cardiac ICU patients who underwent 100 extubations. Neurologic performance was quantified by requesting patients to perform four simple tasks[48]: to open their eyes, to follow an observer with their eyes, to grasp the observer's hand, and to stick out their tongue. Reintubation within 72 hours was required in 15.9% (14/88) of the patients. Patients tolerating extubation performed a higher number of tasks than did the reintubated patients: 3.8 ± 0.1 versus 2.9 ± 0.5. Patients who were unable to complete all four tasks were 4.3 times more likely to require reintubation than were patients who could complete all four tasks. The failure to perform any of the four tasks had a sensitivity of 0.42 and specificity of 0.91 in predicting reintubation.

TREATMENT OF POSTEXTUBATION LARYNGEAL EDEMA

Epinephrine

Trials of therapies for postextubation respiratory distress have largely been confined to patients with laryngeal edema. For decades, patients with postextubation stridor and other upper airway disorders have been treated with aerosolized racemic epinephrine. Racemic epinephrine consists of equal amounts of the dextro (D)-isomer and levo (L)-isomer. Most of epinephrine's pharmacologic action results from the levo-isomer, which is thirty times more potent than the dextro-isomer.[49] Popularity of the more expensive racemic form is based on the supposition that it produces epinephrine's vasoconstrictor action without rebound vasodilation; thus, less tachycardia, hypertension, and tremor is expected with aerosolized racemic epinephrine than with levo-epinephrine. The stated different actions, however, may have arisen from comparisons of inappropriate dosages.

Nutman et al[50] randomized twenty-eight children with postextubation stridor (average age: 1 year) to receive 0.25 mL of either 2.25% racemic epinephrine or 1% levo-epinephrine, each diluted with 2 mL of isotonic saline. These dosages were selected to reflect the relative potency of the two compounds. Each was delivered over 15 minutes by face mask. Both groups exhibited significant improvement: 71.4% of the levo-epinephrine group and 76.9% of the racemic group exhibited decreases of 2 points on an 8-point stridor score after 40 minutes. By 8 hours, the stridor score was less than 1 in both groups. These data reveal that levo-epinephrine is as effective as the more expensive racemic epinephrine in children with postextubation stridor, although it is not known how likely the stridor would have resolved without any aerosolized therapy.

Glucocorticoids

The ability of dexamethasone to prevent postextubation stridor in children has been evaluated by three groups of investigators. In the first two studies, dexamethasone (0.5 mg/kg every 6 hours for 6 doses, beginning 6 to 12 hours before extubation) was compared against placebo. In their study of 153 children, ranging from under 1 year old to older than 5 years, Tellez et al[51] observed postextubation stridor requiring therapy in 21.1% (16/76) of the dexamethasone group and 29.9% (23/77) of the control group. Reintubation was required in 11.8% (9/76) of the dexamethasone group and 5.2% (4/77) of the control group. In a study of sixty-six children younger than 5 years old, Anene et al[52] observed stridor at 10 minutes in 45.2% of the dexamethasone group and 87.5% of the control group. Epinephrine aerosol was required in 12.9% (4/31) of the dexamethasone group and 68.8% (22/32) of the control group. Reintubation was required in 0/31 of the dexamethasone group and 21.9% (7/32) of the control group. Apart from the different conclusions on the benefit of dexamethasone, the different outcomes in the two control groups is striking: postextubation stridor requiring therapy was reported in 68.8% of the patients of Anene et al[52] as contrasted with 29.9% of the patients of Tellez et al;[51] the respective rates for reintubation were 21.9% and 5.2%.

A more recent trial was undertaken by Cesar and de Carvalho[53] who randomized sixty-four children, ranging in age from younger than 1 year to 12 years, to intravenous dexamethasone (0.2 mg/kg every 6 hours), with or without nebulized levo-epinephrine (0.5 mg/kg every 4 hours), versus nebulized or intravenous isotonic saline solution in the control groups. Neither dexamethasone nor nebulized levo-epinephrine, alone or in combination, decreased the frequency of laryngeal edema.

Early randomized controlled trials of the administration of glucocorticoids before extubation in adult patients were negative. Darmon et al[24] randomized 663 patients to a bolus of dexamethasone 8 mg or placebo 1 hour before extubation. The overall incidence of laryngeal edema was 4.2% (28/663), and reintubation was necessary in 1% (7/663). No difference was seen between patients receiving dexamethasone or placebo. Ho et al[23] randomized seventy-seven intubated

patients to hydrocortisone 100 mg or placebo, given 1 hour before extubation. Overall, 22% (17/77) developed stridor within 24 hours, and only one patient required reintubation. Outcomes were equivalent for patients receiving hydrocortisone and placebo. More recent trials indicate that glucocorticoids can be beneficial, especially when administered for 12 or more hours before extubation to patients at high risk of postextubation laryngeal edema.

Cheng et al[54] selected a group of high-risk adults intubated for more than 24 hours with a decreased cuff-leak volume (<24% of inspired V_T). Patients were randomly assigned to multiple doses of methylprednisolone (40 mg every 6 hours for 4 doses) before a planned extubation, a single dose of methylprednisolone 24 hours before the planned extubation, or placebo (4 injections of saline every 6 hours). Postextubation stridor developed in 30.2% of placebo group, and 18.6% required reintubation. Treatment with either a single dose or multiple doses of methylprednisolone decreased the rate of postextubation stridor, 11.6% and 7.1%, respectively, and also the rate of reintubation, 4.7% and 7.1%, respectively. There was no difference between the effects of single and multiple doses of methylprednisolone.

In 761 adult patients admitted to fifteen medical-surgical ICUs and receiving more than 36 hours of mechanical ventilation, François et al[21] conducted a double-blind controlled trial. Patients were randomized to intravenous methylprednisolone—initiated 12 hours before planned extubation at a dose of 20 mg and continued every 4 hours with the last injection immediately before tube removal (total dose: 80 mg)—or placebo. Methylprednisolone decreased the incidence of postextubation laryngeal edema (11/355 [3%] vs. 76/343[22%]) and the overall reintubation rate (13/355 [4%]vs. 26/343 [8%]). The need for reintubation as a result of laryngeal edema was all but eliminated (1/355 [0.3%] vs. 14/343 [4.1%]). The number needed to treat to prevent one reintubation caused by laryngeal edema was slightly more than twenty-six. Although the number needed to treat was large, the number of adverse events in the intervention group was small; thus, methylprednisolone appears have a satisfactory risk-to-benefit ratio in this setting.

Lee at al[55] conducted a randomized, double-blind trial in eighty-six patients who were at high risk of postextubation airway obstruction, in that they had a cuff-leak volume of less than 110 mL. Patients were randomly assigned to receive placebo or dexamethasone 5 mg every 6 hours for 24 hours, and were extubated 24 hours later. Compared with placebo, dexamethasone produced an increase in cuff-leak volume, approximately 115 mL at 24 hours versus approximately 40 mL, and decreased the incidence of postextubation stridor, 10% versus 27.5%. The rate of reintubation did not differ between the dexamethasone and placebo group: 2.5% versus 5%.

Cheng et al[56] undertook a second randomized, controlled trial, and like their previous trial they selected a group of high-risk adults with a decreased cuff-leak volume (<24% of inspired V_T). Four hours before planned extubation, thirty-eight patients received a single injection of methylprednisolone, 40 mg, and thirty-three patients received normal saline. Methylprednisolone resulted in a lower incidence of postextubation stridor (15.8% vs. 39.4%) and lower reintubation rate (7.9% vs. 30.3%). The beneficial effects were accompanied by the upregulation of interleukin (IL)-4 and IL-10 and the downregulation of IL-6 and IL-8.

Jaber et al[57] conducted a meta-analysis of randomized controlled trials of the effects of glucocorticoids on postextubation stridor and reintubation. Fifty-six trials have been conducted, and Jaber et al[57] selected seven that satisfied predefined methodologic criteria. These included the above discussed trials of Darmon et al,[24] Ho et al,[23] Cheng et al,[54] François et al,[21] and Lee et al,[55] and two other studies—Shih et al[58] and Cheng et al[59]—that had only been presented in abstract form; the abstracted Cheng et al study has since been published as a full report.[56] Among an aggregate of 1846 patients, those receiving glucocorticoids had a lower incidence of stridor (relative risk [RR]: 0.48;95% confidence interval [CI] 0.26 to 0.87) and lower rate of reintubation (RR: 0.58; 95% CI 0.41 to 0.81). Subgroup analysis revealed that glucocorticoids decreased the risk of reintubation more strikingly in high-risk patients, defined as those with an abnormally low volume on the cuff-leak test. In this subgroup, the rate of reintubation decreased from 19.8% to 8.6% (RR: 0.38; 95% CI 0.21 to 0.72). The benefit of glucocorticoids was not as striking in patients who were not selected on the basis of risk of reintubation (RR: 0.67; 95% CI 0.45 to 1.00).

In patients at risk of postextubation laryngeal edema, glucocorticoids are presumed to exert their beneficial effect by inhibiting the release of inflammatory mediators and decreasing capillary permeability.[57] The initial antiinflammatory effects commence 1 to 2 hours after intravenous administration and are maximal between 2 and 24 hours later. Consistent with this knowledge, clinical trials in which glucocorticoids were administered 1 hour or less before planned extubation did not decrease postextubation stridor or the rate of reintubation benefit,[23,24] whereas benefit was observed in trials when glucocorticoids were administered as long as 24 hours before extubation.[21,54,55] It has been proposed that physicians should select patients for glucocorticoid therapy on the basis of the cuff-leak test and then wait for 24 hours to allow the agent to take effect. This proposal, however, is problematic, as it would unnecessarily prolong intubation by 24 hours in three of every four patients with a low cuff-leak volume. If the recent observation of Cheng et al[56] is confirmed—that a single dose of methylprednisolone, 40 mg, administered 4 hours before extubation is beneficial in patients with a low cuff-leak volume—such an approach would represent a satisfactory risk-to-benefit ratio.

INTERVENTION TO REDUCE NEED FOR REINTUBATION

Pronovost et al[60] investigated the effect of a new quality improvement intervention on the frequency of reintubation in their surgical ICU. Their study was undertaken in three

phases. In the first phase, they identified risk factors associated with reintubation. In the second phase, ten ICU physicians engaged in a Delphi process, attempting to develop clinical practice guidelines. The physicians could not agree on priorities; they concluded that there were too many conditional probabilities that would require the use of so many decisional nodes, as to render a guideline impractical. This group used data collected in the first phase to develop a preextubation worksheet designed to highlight factors associated with reintubation. In discussion with a patient's nurse and respiratory therapist, physicians listed several variables on this form. Variables included whether intubation had been difficult, ventilator settings, oxygen saturation, arterial blood-gas results, f/V_T, frequency of suctioning, and mental status. In the third phase of the study, they studied the effect of implementing the preextubation worksheet on physician behavior. Staff was instructed not to extubate a patient if the worksheet had not been filled out.

The rate of reintubation before the quality improvement intervention was 8 per 1000 ventilator days. After the intervention, reintubation decreased to 1.5 per 1000 ventilator days. In another (control) surgical ICU in the same hospital, the rate of reintubation did not change over the same period (Fig. 59-6). The average duration of mechanical ventilation decreased from 4.6 days in the first phase of the study to 3.4 days in the third phase. Three factors were associated with reintubation: suctioning more often than every 4 hours (OR: 11.3); being agitated or sedated versus alert (OR: 4.5); and S_{O_2} less than 95% on FI_{O_2} 0.40 (OR: 4.0). The accuracy of these and other variables is clearly influenced by test-referral bias. The authors speculate that the preextubation worksheet helped to bring directly to the staff's attention the most important factors to consider when deciding to extubate.

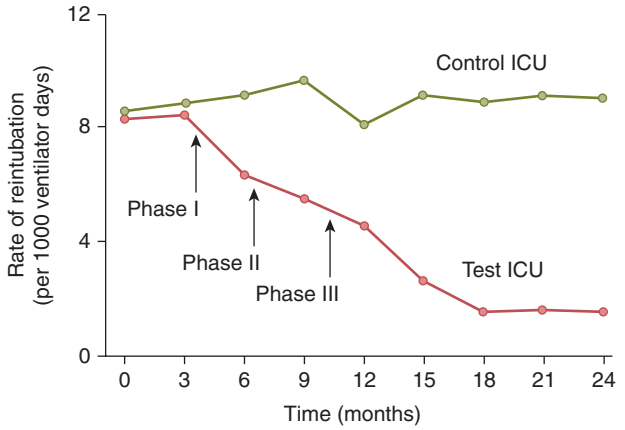

FIGURE 59-6 The rate of reintubation per 1000 ventilator days in a surgical ICU that introduced a new quality improvement intervention and in a control surgical ICU. The intervention was introduced in three phases in the study ICU. The intervention led to a decrease in the rate of reintubation from 8 to 1.5 per 1000 ventilator days. The rate of reintubation did not change in the control ICU. (Used, with permission, from Pronovost et al.[60])

NONINVASIVE VENTILATION IN WEANING AND EXTUBATION

Many investigators have sought to see if NIV can assist with the process of weaning and extubation. Some investigators have employed NIV as a bridge to ventilator discontinuation, where NIV is used in a patient who is believed to be not quite ready for extubation.[61] Other investigators have employed NIV as rescue therapy, where NIV is used in a patient who develops respiratory distress several hours after extubation.[6] The various studies that have addressed the use of NIV for these two purposes were discussed in considerable depth in the second edition of this book.

Three groups of investigators—Nava et al,[61] Girault et al,[62] Ferrer et al[63]—have evaluated the use of NIV as a weaning aid. These investigators instituted NIV at a point where a patient had failed a T-tube trial; patients typically received inspiratory positive airway pressure of 10 to 20 cm H_2O, and expiratory positive airway pressure of to 5 cm H_2O.[61,63] Patients in the intervention arm were placed on NIV immediately following extubation and were compared to a control group of patients who were reconnected to the ventilator and underwent conventional weaning (daily T-tube trials). Although the particularities of benefit differed among the three studies, all three research groups observed that the use of NIV as a bridge or weaning aid led to fewer days of mechanical ventilation, and two of the groups[61,63] observed a decrease in mortality as compared with conventional weaning.

These findings contrast with the use NIV as rescue therapy. Keenan et al[64] observed that institution of NIV at the point when a recently extubated patient developed respiratory distress, typically some hours after extubation, did not result in improved clinical outcome. Esteban et al[6] also employed NIV as rescue therapy in patients who developed postextubation distress. In contrast with all previous studies, they reported that NIV resulted in a greater mortality than observed with usual care: 25% versus 14%. Questions have been raised about the limited expertise of clinicians using NIV in the latter study and also that the employed level of pressure support was not reported. A striking feature was the outcome in twenty-eight patients in the usual care who crossed over to NIV. Despite being the sickest subgroup of the 107 patients in the usual-care group, mortality in the crossover subset was 11%—the lowest mortality of all groups requiring ventilator support.

Another feature that differs between the three studies with favorable outcomes[61–63] and the two studies with unfavorable outcomes[6,64] was that only 10% to 11% patients in the unfavorable studies had chronic obstructive pulmonary disease as contrasted with 44.2%,[63] 51.5%,[62] and 100%[61] in the studies with favorable outcomes. Patients who have hypercapnia as a result of chronic respiratory disorders, typically chronic obstructive pulmonary disease, have been shown repeatedly to exhibit an especially favorable response to NIV, and thus it becomes important to focus on the use of NIV as an extubation aid in such patients.

In 106 patients with chronic respiratory disorders who had received mechanical ventilation for at least 48 hours and

who exhibited a partial pressure of arterial carbon dioxide (Pa_{CO_2}) greater than 45 mm Hg during a T-piece weaning trial, Ferrer et al[65] randomly allocated fifty-four patients to NIV for the next 24 hours and fifty-two patients to conventional management. The primary end point was avoidance of respiratory failure (defined on meeting a number of predesignated laboratory or clinical criteria) within 72 hours following extubation. Such respiratory failure arose in fewer patients allocated to NIV than in those assigned to conventional management: eight of fifty-four (14.8%) versus twenty-five of fifty-two (48.1%); OR: 5.32 [95% CI 2.11 to 13.46], $p < 0.0001$).

When patients in either the NIV or control group met criteria for respiratory failure following extubation, but did not fulfill criteria for immediate reintubation, NIV was employed as rescue therapy. Among this subgroup, NIV resulted in avoidance of reintubation in two of seven patients assigned to NIV and fifteen of twenty controls. Overall, NIV was independently associated with a lower risk of respiratory failure after extubation (adjusted OR: 0.17 [95% CI 0.06 to 0.44]; $p < 0.0001$). Ninety-day mortality was lower in patients assigned to NIV than in those allocated to conventional treatment: six of fifty-four (11.1%) versus sixteen of fifty-two (30.8%); $p = 0.015$.

Given the impressive results achieved in this trial, it is important to note details of the way that Ferrer et al[65] employed NIV. The investigators used a ventilator specifically designed for NIV (BiPAP Vision, Respironics, Murrysville, PA), which provided effective compensation for leaks and real-time assessment of mask pressure. Inspiratory positive airway pressure was adjusted (12 to 20 cm H_2O) to achieve a respiratory rate less than 25 breaths/min (mean pressure: 17 ± 3 [SD] cm H_2O), expiratory positive airway pressure was fixed at 5 to 6 cm H_2O, and inspired oxygen concentration was titrated to achieve oxygen saturation of more than 92%. NIV was delivered for as much time as possible during the 24 hours that followed extubation (mean: 18 ± 7 [SD] hours); meals were not allowed during the first 24 hours.

In summary, data to date support the use of NIV as an aid to weaning patients who have chronic respiratory disorders and who exhibit hypercapnia during a weaning trial. In these patients, NIV appears to be beneficial as a bridge to ventilator discontinuation and also as rescue therapy in patients who develop respiratory failure following extubation. In patients who have underlying disease states other than a chronic respiratory disorder or who do not exhibit hypercapnia during a weaning trial, the role of NIV as a weaning aid is less clear. If it is to be used, it is likely to achieve greater success if instituted immediately after extubation[61–63] than employed as rescue therapy in patients who develop respiratory failure several hours after extubation.[6,64]

UNPLANNED EXTUBATION

Chapter 39 discusses unplanned extubation in detail. The subject is of particular importance for research on weaning because of the insight it may offer into unnecessary delays in the discontinuation of ventilation. The reported frequency of unplanned extubation ranges from less than 1% to 42% of intubated patients; a frequency of 8% to 12% is most commonly reported (Table 59-4). Unplanned extubation

TABLE 59-4: FREQUENCY OF UNPLANNED EXTUBATION AND SUBTYPES

Author	Total Number[a]	Unplanned Extubation	Self-Extubation		Accidental Extubation		
		Percent of Total	Reintubation (%)	Percent of Unplanned	Reintubation (%)	Percent of Unplanned	Reintubation (%)
Zwillich et al[92]	354	8.5	47	30	47		
Stauffer et al[93]	226	12.8	NR				
Whelan et al[94]	319	7.2	78.2	91.3		8.7	
Tindol et al[95]	460	2.8	46.2	92.3		7.7	
Listello et al[96]	NR	NR	48.2				
Tominaga et al[72]		15.2	NR				
Boulain[97]	426	10.8	60.9				
Betbese et al[69]	750	7.3		78			
Chevron et al[98]	414	16	37.0	87			
Jiang et al[99]	97	42	37.8				
Kapadia et al[100]	5046	0.7					
Epstein et al[71]	682	11	56.0	94.7		5.3	
De Lassence et al[8]	750	8	76.7	63.3	63	36.7	100
Esteban et al[101]	5183	3.4	41.3				
Moons et al[67]	627	26	4.2	76.9	45	23.1	100
Thille et al[31]	340	9.1	64.5	67.7	47.6	32.2	100

Abbreviation: NR, not reported.

[a]Total number of ventilated or intubated patients.

is divided into two major subsets. Self-extubation refers to the deliberate removal of an endotracheal tube by a patient for whom the physician considers intubation beneficial. Accidental extubation refers to inadvertent extubation by a caregiver during a bedside procedure. Both of these situations differ from the usual planned extubation. Between 63% and 95% of unplanned extubations are self-extubations.

The rate of reintubation after unplanned extubation ranges from 4% to 78%, with many investigators reporting rates of 35% to 60%. These rates are considerably higher than reintubation rates of 10% to 20% after planned extubation. The rate of reintubation after accidental extubation is especially high, 83%[66] to 100%.[8,67] That 40% or more of self-extubated patients do not require reintubation is often used as evidence that physicians delay extubation unnecessarily. Extubation is undoubtedly delayed in some patients, but the two groups of patients may not be strictly comparable. Patients who have enough strength—and wit—to self-extubate may be less sick than the average ventilated patient, and thus would be expected to experience a lower reintubation rate. Moreover, it is totally unclear as to what the source of the delay is in these self-extubated patients. Is it caused by clinicians who are not aware of a patient's readiness for extubation because they have yet to measure weaning predictor tests? Is it because the predictor test readings represent false-negative results? Is it because the physician interprets the predictor test results incorrectly? Is it because the physician delays in ordering a weaning trial?[68] Is it because the physician delays extubating a patient who has passed a weaning trial?[68] A considerable body of data[13,68] suggests that the most likely source of delay is in ordering a weaning trial and extubating a patient who has passed the trial.

The rate of reintubation after unplanned extubation is lower in patients who have already entered the phase of weaning than in patients who are still receiving full ventilator support. Betbese et al[69] reported that 16% of thirty-two patients who experienced unplanned extubation during weaning required reintubation, as contrasted with 82% of twenty-seven patients who experienced unplanned extubation while receiving full ventilator support. Razek et al[70] reported reintubation after unplanned extubation in 15.2% of thirty-three weaning patients and 60.7% of twenty-eight patients requiring full ventilator support. And Epstein et al[71] reported reintubation after unplanned extubation in 30% of thirty-three weaning patients and 76% of forty-two patients requiring full ventilator support. Epstein et al[71] noted that patients who tolerated unplanned extubation tended to have shorter time from the onset of weaning to extubation than did a control group, 0.9 versus 2.0 days ($p = 0.06$), although the overall duration of mechanical ventilation did not differ.

Moons et al[67] found that most unplanned extubations occurred on the same day that extubation had been planned (42.9%), or the subsequent (42.9%) or preceding day (14.3%). Compared to a control group of forty-eight patients that did not experience unplanned extubation, a study group of twenty-six patients experiencing unplanned extubation had a lower Ramsay Sedation Scale score, 2 (1, 5; twenty-fifth, seventy-fifth percentiles) versus 5 (3.3, 6; twenty-fifth, seventy-fifth percentiles), and a higher GCS score, 12 (8, 13; twenty-fifth, seventy-fifth percentiles) versus 4 (3, 7; twenty-fifth, seventy-fifth percentiles). The difference between the two groups was confined to the subgroup experiencing deliberate self-extubation; patients experiencing accidental extubation were comparable to the control group. In a multiple logistic regression analysis, deliberate self-extubation was associated with a lower sedation score (OR: 2.04) and higher level of consciousness on the GCS (OR: 1.40). The model explained 67.3% of variance of deliberate self-extubation. These data suggest that the weaning period is a high-risk time for deliberate self-extubation because patients are receiving less sedative agents and have a higher level of consciousness.

De Lassence et al[8] undertook a prospective multicenter study of the morbidity and mortality associated with unplanned extubation. Compared with forty-five of 690 patients who required reintubation after planned extubation, the forty-six (of sixty) patients who were reintubated after an unplanned extubation experienced a longer duration of mechanical ventilation, 17 versus 6 days; longer ICU stay, 22 versus 9 days; and longer hospital stay, 34 versus 18 days. The frequency of nosocomial pneumonia was higher after unplanned extubation than after planned extubation: 28% versus 14%; this increase was entirely explained by accidental extubation. ICU mortality was 40.9% in patients with accidental extubation, 21.1% in patients with self-extubation, and 38% in the control group—these rates did not differ statistically.[8] In a retrospective case-control study, Epstein et al[65] also observed no difference in mortality between patients experiencing unplanned extubation, 32%, and a control group, 30%. The mortality in the control groups of both these series[8,71] is considerably higher than the mortality of less than 10% usually reported in successfully extubated patients.

Tominaga et al[72] undertook a prospective study of four interventions designed to influence the frequency of unplanned extubation. At baseline, 15.2% of intubated patients experienced unplanned extubation. When the investigators switched from their usual method of securing the endotracheal tube, cloth or Velcro ties, to the use of waterproof tape around the tube, upper lip, and face, the frequency of unplanned extubations decreased to 4% (8/213). The frequency was not altered by the more liberal use of sedative or paralytic agents. A decrease in the use of hand restraints led to an increase in the rate of unplanned extubations.

Thille et al[31] found that the distance between the endotracheal tube and the carina was significantly less in thirty-one patients who experienced unplanned extubation than in 168 instances of planned extubation: 4.1 ± 1.8 versus 5.6 ± 2.6 (SD). Given the high mortality rate in patients requiring reintubation, greater attention to the location of the tip of the endotracheal tube at the time of viewing chest radiographs could decrease this adverse event (Fig. 59-7).

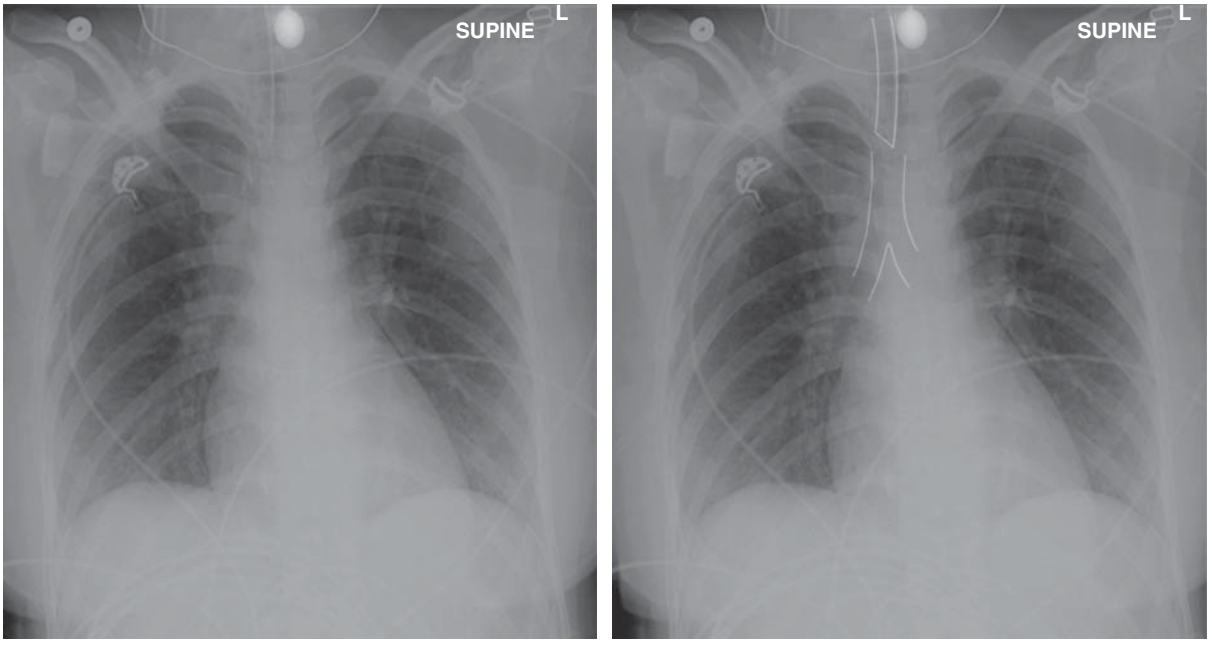

FIGURE 59-7 Endotracheal tube positioned too high. Portable anteroposterior chest radiograph of a 24-year-old woman intubated as a result of anaphylactic shock. The endotracheal tube is 5.5 cm above the carina.

CONCLUSION

The development of severe respiratory distress after removal of an endotracheal tube, if sufficient to require reintubation, is associated with a high mortality rate. Clinicians are accordingly cautious and try to avoid premature extubation. Despite such caution, as many as two of every ten extubated patients require reintubation. To improve accuracy in forecasting extubation outcome, clinicians use diagnostic testing. The major diagnostic test for this purpose is a weaning trial. But unlike weaning predictor diagnostic tests, the diagnostic accuracy of weaning trials in predicting the outcome of a trial of extubation is unknown. Moreover, the accuracy is impossible to determine, because the experiments necessary to measure the sensitivity and specificity of a weaning trial (for predicting extubation outcome) are unethical. The mechanisms of weaning failure have been intensely investigated. Enhanced understanding of the pathophysiology has led to new approaches to the timing of the weaning process, prediction of outcome, and techniques used for weaning. In contrast, understanding of the pathophysiology of severe respiratory distress in the postextubation period is rudimentary to nonexistent. Acquiring such knowledge poses a great research challenge, but holds great promise for significantly advancing patient care.

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ADJUNCTIVE THERAPY

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SURFACTANT

James F. Lewis
Valeria Puntorieri

Pulmonary surfactant lines the inner layer of the lung and serves to lower surface tension at the air–liquid interface, thereby maintaining alveolar stability. In the absence of surfactant, the work of breathing increases markedly ultimately resulting in respiratory failure secondary to atelectasis, alveolar flooding, and severe hypoxemia. The clinical correlate of surfactant deficiency is the neonatal respiratory distress syndrome (NRDS) in preterm infants, which before the mid-1980s was a devastating and fatal disease. Since the advent of exogenous surfactant replacement therapy, however, newborn mortality from NRDS has decreased approximately 56% from 1987 to 1995.[1] The primary surfactant deficiency of NRDS is now a well-characterized condition, and does not appear as complex as the various surfactant changes occurring during acute lung injury (ALI) and/or the acute respiratory distress syndrome (ARDS). Alterations of the endogenous surfactant system in the mature lungs of patients with these disorders are not as well understood, but currently represent an area of intense investigation. This complexity has resulted in inconsistent results of clinical trials evaluating exogenous surfactant administration in this patient population.

This chapter reviews surfactant metabolism and function in the mature lung and its role in maintaining normal lung homeostasis, including its more recently described host defense functions. The metabolism and function of surfactant in the injured lung is also outlined, with particular reference to the effects of mechanical ventilation on the alveolar surfactant system. Subsequently, the status of clinical trials evaluating exogenous surfactant administration in patients with ALI or ARDS is addressed, as are the various factors that may influence a host's response to this therapy. Future research directions relevant to the understanding of the role of surfactant both in ALI and ARDS and other lung diseases conclude the chapter.

SURFACTANT COMPOSITION AND METABOLISM

Composition

The composition of surfactant is remarkably similar among mammalian species, consisting of approximately 80% phospholipids, 10% surfactant-associated proteins,[2–4] and approximately 10% neutral lipids, among which cholesterol is the most abundant (80% to 90% by weight).[5,6] The major phospholipid component is phosphatidylcholine, half of which is the disaturated species, dipalmitoylphosphatidylcholine (DPPC).[4] This latter molecule is the major surface-active component responsible for lowering surface tension at the air–liquid interface, and is an essential component of all exogenous surfactant preparations currently available for clinical use. Other lipids include phosphatidylglycerol and a few minor lipid species, which are thought to be important in the generation and maintenance of the surface film.

The surfactant-associated proteins have been designated as SP-A, SP-B, SP-C, and SP-D.[7,8] SP-B and SP-C are small, hydrophobic proteins closely associated with the phospholipids, where they play a major role in generating and maintaining the surface tension-reducing surface film.[9–11] SP-B is an 18-kDa dimer, whereas SP-C is a 4-kDa monomer, the latter being the more hydrophobic of these two proteins.[12,13] The most clinically effective exogenous surfactant preparations currently in use contain at least one of these natural hydrophobic proteins, or similar types of synthetic and/or recombinant molecules. SP-A is an octodecamer made up of six trimers in a "bouquet" arrangement.[14,15] Under reducing conditions, it is a 28-kDa monomer with a 35-kDa glycosylated form. SP-D is a large, multimeric cruciform structure, which is 42 kDa under reducing conditions. Both proteins are very hydrophilic and belong to the collectin family of proteins. They are not components of any of the available natural exogenous preparations consequent to their removal with purification processes, and are not yet available as synthetic or recombinant molecules. Recent evidence suggests that they play a more important role in host defense than in biophysical functions, so there has been renewed interest in developing exogenous preparations containing some form of these proteins.[14–17]

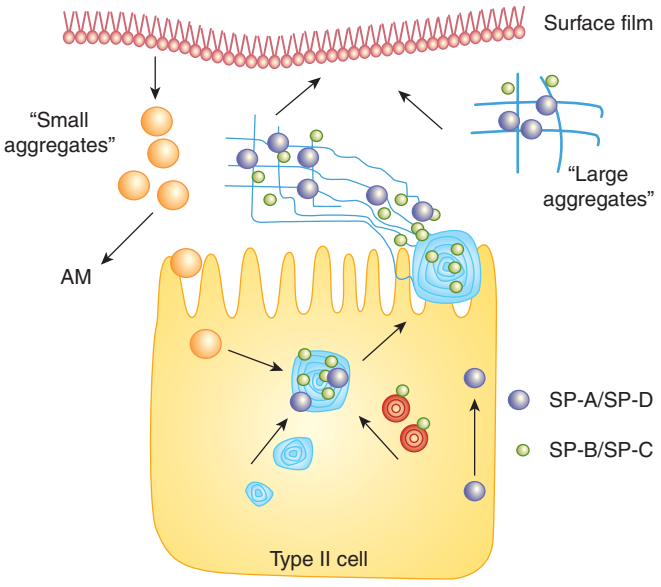

FIGURE 60-1 Surfactant metabolism starts with synthesis within the type II cell, secretion into the airspace as lamellar bodies containing both lipid and protein components, and formation of tubular myelin structures. Large aggregates are composed of tubular myelin and freshly secreted lamellar bodies and represent precursors to the surface film. With respiratory motion, small aggregates are formed, which are taken back up into type II cells or cleared via alveolar macrophages (*AM*).

Intracellular Metabolism

Surfactant is synthesized within alveolar type II cells (Fig. 60-1).[18] Initial assembly occurs in the endoplasmic reticulum with intracellular transport via the Golgi apparatus. Surfactant is stored within lamellar bodies of the type II cell and is secreted into the airspace via exocytosis.[19,20] Studies that have investigated the intracellular metabolic pathways of surfactant lipids and proteins have used radiolabeled precursors injected both intravenously and intratracheally. Basically, these studies have shown that although the hydrophobic proteins are assembled and secreted in conjunction with the lipids, SP-A and D are metabolized separately.[21] For example, the dominant route for SP-A secretion is by direct, constitutive pathways independent of lamellar body exocytosis, although smaller amounts undergo regulated secretion in association with these organelles.[22–24] SP-D is also metabolized independently of surfactant lipids, and, unlike the other surfactant proteins, has been identified in nonpulmonary organs such as the gut.[25,26] Within the healthy lung, various pharmacologic agents, such as β-agonists can stimulate surfactant secretion, as can physical stretch of alveolar type II cells.[27] This latter phenomenon is particularly relevant to specific aspects of mechanical ventilation because higher tidal volumes increase the stretch of the alveolus, leading to immediate surfactant secretion from type II cells. These effects are relatively short-lived, however, and may be quite different within the injured lung, where the preexisting health of type II cells, before the onset of mechanical ventilation, may be compromised.

Recent studies have focused on the extracellular metabolism of pulmonary surfactant, once the material has been secreted from the type II cell into the alveolus (see Fig. 60-1). Within the airspace, mechanical ventilation has a significant and immediate impact on the surfactant system by influencing the metabolism of extracellular surfactant aggregate forms. Because this effect may have important clinical consequences in patients with ALI or ARDS, and is directly affected by different modes of mechanical ventilation, a more detailed discussion of this area is warranted.

Extracellular Metabolism

Once secreted into the airspace, alveolar surfactant undergoes physical rearrangement from the lamellar structures into tubular myelin, a process involving SP-A, SP-B, DPPC, phosphatidylglycerol, and calcium.[28,29] After differential centrifugation of isolated lung lavage, large lipid structures containing SP-A, SP-B, and SP-C, representing the heavier and functionally active forms of alveolar surfactant form a pellet, and are called large aggregates (LA).[30,31] They adsorb rapidly to the air–liquid interface and are subsequently converted into smaller, vesicular forms called small aggregates (SA) (see Fig. 60-1). The SA subfractions are poorly functioning, contain little surfactant protein, and are thought to represent surfactant forms that have left the surface film and are subsequently available for reuptake via type II cells for resynthesis into new LA, and/or are cleared entirely from the airspace via catabolism, mainly within alveolar macrophages.[32–34]

The process of conversion of the functionally active LA forms into inactive SA within the airspace is specifically relevant when discussing the effects of mechanical ventilation on surfactant metabolism. In vitro studies using the surface area cycling technique show that this conversion of LA into SA is mediated by two main factors: a carboxylesterase enzyme called *convertase* and a phasic change in surface area.[31,35–37] The phasic change in surface area factor has been investigated *in vivo* using different tidal volumes to mechanically ventilate normal rabbits. These studies show that increasing tidal volume, but not positive end-expiratory pressure, results in an increased conversion of LA into SA, and that this conversion occurs relatively soon after the onset of ventilation (Fig. 60-2).[38] In normal lungs, these changes do not result in significant alterations in aggregate pool sizes, presumably because of the capabilities of the normal alveolar environment to regulate surfactant metabolism. This does not appear to be the case in the injured lung, however, where alterations in surfactant metabolism occur both intracellularly and extracellularly.[39,40] For example, within the lungs of patients with ALI or ARDS, increased aggregate conversion associated with higher tidal volumes is thought to result in increased SA pools, which, together with the associated decrease in functionally active LA pools, may contribute to progressive lung dysfunction. Indeed, these specific changes have been demonstrated in animal models of lung injury and have not only underscored the importance of instituting and maintaining optimal modes of mechanical ventilation within injured lungs, but also in the setting of exogenous surfactant, both during and after administration. This latter situation is discussed in more detail in subsequent sections.

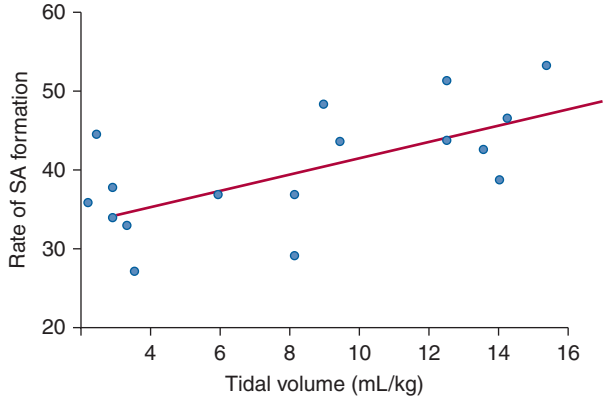

FIGURE 60-2 The rate of small aggregate (*SA*) formation increases in direct proportion to the tidal volumes used to ventilate normal adult rabbits. SA formation was determined by measuring ^{3}H-label recovery in the SA fraction of surfactant 1 hour after injection of a trace dose of ^{3}H-labeled large aggregates into the animals' lungs. (Reprinted with permission of the American Thoracic Society. Copyright © 2012 American Thoracic Society. From Ito Y, Veldhuizen RA, Yao LJ, et al. Ventilation strategies affect surfactant aggregate conversion in acute lung injury. *Am J Respir Crit Care Med.* 1997;155(2):493–499. Official Journal of the American Thoracic Society.)

SURFACTANT PHYSIOLOGY IN THE NORMAL LUNG

Biophysical Function

The major role of the surfactant system is related to its biophysical function of lowering surface tension at the air–liquid interface.[3,4,41] This is most evident clinically in preterm infants born deficient in surfactant who quickly die of respiratory failure unless supplemented with an exogenous surfactant preparation.[42–44] As noted previously, the major lipid component contributing to lowering surface tension is DPPC, although the hydrophobic proteins and some other lipids are also essential.[10–13] Full-term babies born deficient in SP-B develop severe lung dysfunction resistant to traditional surfactant therapy and ultimately require lung transplantation for survival.[45] Likewise, mice deficient in this protein suffering a similar outcome have also been shown to have abnormal processing of SP-C.[46] Mice deficient in SP-C alone, on the other hand, have relatively minor biophysical abnormalities, which predominantly manifest only at low lung volumes, suggesting a potential role for this protein in the surface film stabilization.[47]

From a physiologic perspective, the initial discovery that surface tension was important for lung stability was made by von Neergaard in 1929, when he observed that it took more pressure to inflate air-filled than saline-filled lungs.[48] This was the direct result of the surface tension forces existing at the air–liquid interface. This concept is further advanced by the Laplace law, which states that the pressure gradient across a sphere, which we can roughly extrapolate to an alveolus, is directly related to the surface tension within the sphere divided by the radius of the sphere ($\Delta P = 2\delta/r$), where P is pressure, δ is surface tension, and r is radius. From this equation, it is clear that during exhalation, when the alveolar radius decreases, the tendency for this alveolus to collapse increases (i.e., ΔP) unless surface tension decreases as well. Because of its strategic location at the air–liquid interface, and the presence of both hydrophobic and hydrophilic regions, a surfactant film lining the air–liquid interface is able to lower surface tension to near zero levels as the film is compressed at low lung volumes. This decrease in surface tension not only serves to maintain alveolar stability and decrease the work of breathing, but also prevents alveolar flooding because high surface tension tends to draw fluid from the interstitium into the airspace.[49] Finally, because surfactant also lines the conducting airways, its biophysical function serves to maintain the patency and stability of small airways and enhance ciliary clearance of particles.[50,51] These latter observations suggest that surfactant function may also be relevant in diseases such as asthma, chronic bronchitis, and cystic fibrosis.

Host-Defense Function

As noted previously, the surfactant proteins SP-A and SP-D are members of the collectin family and, secondary to their

molecular composition and structure, can bind a variety of bacteria, fungi, allergens, and viruses, thus mediating phagocytosis by immune cells and the killing of pathogens within the lung.[14,16,52] In addition, these proteins, as well as some of the hydrophobic components of surfactant, can influence production of nitric oxide, oxygen radicals, and inflammatory mediators from activated cells.[53–56] Underscoring the importance of SP-A in host-defense functions are *in vivo* studies demonstrating that mice deficient in this protein (which are phenotypically normal when not stressed) had increased pulmonary inflammation compared to wild-type animals when bacteria, viruses, or lipopolysaccharide was instilled into their lungs.[57,58] These changes were mitigated when exogenous SP-A was administered to these animals. Similar, albeit slightly modified functions of SP-D have been shown both *in vitro* and *in vivo*; unlike the normal phenotype of the SP-A null mice, however, the phenotype of unstressed SP-D knockout animals is abnormal with enlarged airspaces and significantly altered surfactant pool sizes.[59,60]

Although critical for the spreading and stabilization of the surfactant film, SP-B and SP-C also seem to contribute to the host-defense properties of surfactant. Mice deficient in SP-C show greater susceptibility to respiratory syncytial virus infection[61] and have increased pulmonary inflammation, decreased macrophage phagocytic activity, and decreased survival compared to wild-type animals following intratracheal instillation of bacteria.[62] The role of SP-B in host defense appears to be related to the aminoterminal propeptide of the protein, which improves phagocytosis and has antimicrobial activity at acidic pH.[63]

The host-defense functions of the various surfactant lipids have also been evaluated. It has been shown that these phospholipids downregulate inflammation and nitric oxide production, presumably because of their "coating" effects on particles and cells.[17,64–66] Additionally, surfactant lipids, and DPPC in particular, could have a direct effect in down-modulating the inflammatory response of immune cells, through the regulation of specific molecular pathways responsible for reactive oxygen species production.[67] Given the emerging role of the various surfactant components in host defense, future studies involving exogenous surfactant administration may focus more on inflammatory outcomes in addition to biophysical and physiological benefits.

SURFACTANT PHYSIOLOGY IN THE INJURED LUNG

Surfactant Alterations in Acute Lung Injury and Acute Respiratory Distress Syndrome

The definitions of ALI and ARDS are rather simplistic and are based on physiologic criteria more than specific etiologies. For example, any acute inflammatory insult that ultimately affects the lungs causing decreased lung compliance, hypoxemia, and bilateral infiltrates on chest radiography (not of cardiac origin) essentially fulfills the diagnostic criteria of ALI and ARDS.[68,69] The pathophysiologic changes that occur during this process, including the surfactant alterations reported in numerous studies, are complex and reflect the lack of effective treatments for this disorder.

The first postmortem descriptions of the lungs of patients dying from ARDS suggested that surfactant dysfunction may have played a role in their demise.[70] Subsequently, many studies have reported consistent changes in the surfactant system in lavage samples obtained from these patients, including decreased phosphatidylcholine and DPPC levels, decreased phosphatidylglycerol levels, decreased SP-A, SP-B, SP-C, and SP-D levels, and a decrease in the functionally active LA forms relative to SA.[71–73] Interestingly, in these severely ill patients, serum levels of SP-A and SP-D were shown to be elevated, likely consequent to the associated marked increase in pulmonary permeability in this setting.[74,75] The biophysical consequence of these collective changes in the endogenous surfactant system is an inability to adequately reduce surface tension, resulting in decreased lung compliance, increased permeability with edema formation, and hypoxemia. The next section addresses the mechanisms responsible for the surfactant changes observed in these patients. Only with a better understanding of these mechanisms will optimal treatment strategies be developed that are aimed at restoring normal surface tension forces within injured lungs, or perhaps, more importantly, preventing the development of these changes.

Mechanisms Responsible for Surfactant Alterations

Unlike NRDS, in which the preterm animal represents a reasonable correlate of the clinical condition of NRDS and is thus suitable for reliable mechanistic and therapeutic studies, no one animal model adequately reflects the complexity of patients with ALI or ARDS. Proposed mechanisms in the latter setting are, therefore, derived from many different animal models, a factor that needs to be considered when extrapolating results of such studies to the clinical situation.

The observed changes in the phospholipid composition of endogenous surfactant within the injured lung represent a relatively late finding in models of ALI when severe lung dysfunction is present. These changes are likely related to abnormal synthetic and/or secretory pathways within the type II cell, as well as alterations in the degradation process of some lipids within the airspace via increased phospholipase activity (Fig. 60-3).[76–79] A similar mechanism is likely responsible for the decreased surfactant protein levels observed in these lungs, although with the permeability abnormalities demonstrated in these patients, there may also be transfer of SP-A, SP-B, and SP-D across the alveolar–capillary barrier into the serum.[74,75] Interestingly, clinical studies show that serum levels of SP-A and SP-B are inversely related to oxygenation values in patients with

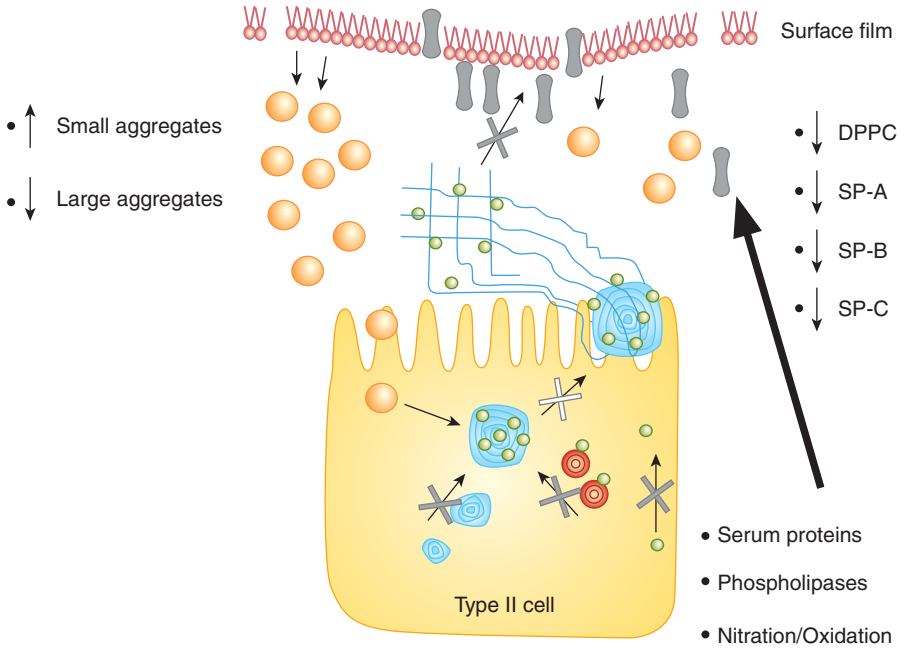

FIGURE 60-3 Mechanisms leading to surfactant alterations in the injured lung include abnormal type II cell metabolism, increased phospholipase activity, nitration and oxidation of surfactant, increased conversion of large aggregates into small aggregates, and inhibition of surfactant by serum proteins leaking into the airspace. See text for details.

ARDS, and serum SP-D levels positively correlate with the survival of these patients.[74,75] In addition to these quantitative changes in surfactant protein levels, there may also be modifications to their composition in the form of nitration and/or oxidation, which would also compromise their function but may not impact measurable levels.[80–82]

The mechanisms responsible for the changes observed in surfactant aggregate forms were alluded to earlier. Briefly, decreased LA pools may be caused by decreased type II cell synthesis and/or secretion in the severely injured lung, but an increased conversion of LA into SA forms likely occurs at earlier stages of the disease, particularly in patients undergoing mechanical ventilation.[37–40] This was recently investigated in animal studies in which spontaneously breathing septic rats with relatively mild lung dysfunction had unchanged LA pools, whereas SA pools were significantly decreased compared to sham animals.[83] These changes were opposite to those documented in severely injured lungs; it was hypothesized that they may have represented the host's compensatory response aimed at maintaining endogenous surfactant in LA forms. For example, by utilizing smaller tidal volumes (with higher respiratory rates), these animals would decrease LA conversion secondary to the smaller changes in alveolar surface area, thereby attempting to maintain lung function. Indeed, very soon after the onset of mechanical ventilation of these animals, which involved using higher tidal volumes than those associated with spontaneous breathing, conversion of LA into SA increased dramatically and lung function deteriorated rapidly.[84] Of clinical relevance, however, was the ability to mitigate both the aggregate conversion and progressive lung dysfunction observed by using lower tidal volumes from the onset of ventilation. In fact, high-frequency oscillation (HFO), a strategy involving extremely small tidal volumes with high respiratory rates, proved to be superior to all other "lung-protective" modes of ventilation with respect to aggregate conversion, lung function, and inflammatory changes.[85] Interestingly, these laboratory results are consistent with recent clinical trials evaluating different modes of mechanical ventilation in patients with ALI. One large trial showed that lower tidal volumes resulted in superior outcomes compared to higher tidal volumes in patients with ALI or ARDS.[86] Results of phase III clinical trials evaluating the outcome of patients specifically ventilated with HFO are pending.

Recent studies suggest another potential mechanism for surfactant dysfunction within the injured lung. Alterations in the cholesterol-to-phospholipids ratio of surfactant alter surfactant function. As noted earlier, cholesterol is the major neutral lipid in surfactant and when present in physiologic amounts, it enhances adsorption at the air–liquid interface. Studies focused on the specific role of neutral lipids and cholesterol in lung injury are scarce. *In vitro* studies that have altered the cholesterol-to-phospholipid ratio show that supraphysiologic levels of cholesterol affect surfactant film stability leading to the inhibition of its function.[87] This cholesterol-mediated dysfunction appears to be relevant *in vivo* as well, because surfactant isolated from animals exposed to high tidal-volume ventilation showed abnormal biophysical activity, which was subsequently restored upon cholesterol removal.[88]

Interestingly, these experimental results are consistent with clinical observations. Markart et al showed that

patients with ARDS had increased levels of the neutral lipid component in isolated LA forms, and impaired biophysical activity of their endogenous surfactant.[89] The source of the increased cholesterol in the surfactant of injured lungs is currently unknown. Altered synthesis by alveolar epithelial type II cells and/or leakage from the circulation into the alveolus are potential mechanisms, although this has not been formally evaluated. Further studies are necessary to address these issues, as well as to understand the biophysical mechanisms leading to cholesterol-mediated inactivation of surfactant.

Finally, within a permeable lung, characteristic of patients with ARDS, serum proteins such as albumin, hemoglobin, and fibrinogen can leak into the airspace and competitively inhibit the function of remaining LA forms.[90] This latter mechanism has been extensively studied over the past several years, and it has been shown that this inhibitory phenomenon may be overcome via the administration of large amounts of an effective exogenous surfactant preparation, thus providing important rationale for this therapeutic approach.[91]

EXOGENOUS SURFACTANT ADMINISTRATION IN THE INJURED LUNG

Results of Phase II and Phase III Clinical Trials

Exogenous surfactant administration has been evaluated in patients with ARDS based on the rationale that surfactant alterations contribute, at least in part, to the lung dysfunction associated with this disorder. Moreover, preclinical studies evaluating the efficacy of exogenous surfactant administration in animal models of ALI have shown promising results. Unfortunately, the outcomes of clinical trials conducted to date have been variable (Table 60-1). For example, the first large, randomized phase III clinical trial, involving more than 700 patients, administered aerosolized Exosurf (a preparation with no surfactant proteins) to patients with severe, sepsis-induced ARDS over a 5-day period.[92] Mortality was similar in the treatment (41%) and standard care (41%) groups. A subsequent, albeit smaller trial, with approximately fifty patients, evaluated tracheally instilled Survanta (a natural bovine preparation) in a relatively similar patient population with good results: a mortality of 19% compared to 44% in the control group.[93] In this latter study, the surfactant preparation contained both SP-B and SP-C, and much larger quantities of the material reached the airspace compared to the Exosurf trial. Other, relatively small clinical studies have included a phase II trial that used a porcine natural surfactant preparation, HL-10, which also contained SP-B and SP-C. The surfactant was instilled in large doses into the lungs of patients with severe ALI or ARDS. After somewhat promising results, a much larger, randomized phase III clinical trial was conducted, but was stopped prematurely for lack of efficacy.[94]

Surfaxin, a synthetic surfactant preparation containing an SP-B–like peptide (KL-4), was tested in twelve patients with severe ARDS and administered via a lung-lavage procedure.[95] Although these initial results were promising, there has been nothing further reported regarding results of a larger study.

Results from a large, randomized phase III trial that tested the efficacy of an exogenous surfactant preparation composed of a recombinant SP-C protein with lipids (Venticute) have been published.[96] The material was instilled into the lungs of patients with severe ARDS caused by multiple etiologies, and results showed no overall difference in mortality between the surfactant-treated group (36%) and standard therapy (32%). A post hoc analysis of these results however, showed a significant interaction between the surfactant treatment and the mechanism of lung injury. Patients with "direct" lung injuries, induced by pneumonia and/or aspiration, had a statistically significantly higher survival rate when treated with surfactant compared to standard therapy; no such relationship existed for patients with "indirect" causes of ARDS, such as sepsis and trauma.

This analysis resulted in a follow-up, prospective, randomized, blinded phase III clinical trial focused on the administration of the recombinant SP-C–based surfactant in patients with severe, direct lung injuries. Surprisingly, the results showed that exogenous surfactant instillation did not improve mortality, oxygenation, or the incidence of nonpulmonary organ failures and the study was stopped for futility.[97] This unexpected lack of efficacy was unexplained, but was thought to be related, in part, to a possible inactivation of the material during the reconstitution procedure.

TABLE 60-1: PUBLISHED PHASE II AND PHASE III CLINICAL TRIALS INVOLVING EXOGENOUS SURFACTANT

Surfactant Preparation and Concentration	Delivery Method	Dose	Mortality (vs. Standard Therapy)	Ref.
Exosurf (13.5 mg DPPC/mL)	Aerosolization	112 mg/kg/day × 5 days	41% vs. 41%	92
Survanta (25 mg DPPC/mL)	Bolus instillation	4 or 8 doses of 50 or 100 mg/kg	19% vs. 44%	93
Venticute (25 mg DPPC/mL)	Bolus instillation	Up to 4 doses of 50 mg lipid/kg	36% vs. 32%	96

Although results of clinical trials are inconsistent and certainly disappointing, the information gained from these trials, as well as preclinical studies, is insightful and supports the need for further research in this area. In the next section, the various factors that influence a host's response to exogenous surfactant are reviewed.

Factors Influencing the Efficacy of Exogenous Surfactant

SURFACTANT PREPARATION

A number of surfactant preparations have been tested in clinical trials involving patients with ARDS, and are generally classified based on their surfactant protein content (Table 60-2). Natural surfactant products contain various amounts of SP-B and SP-C along with natural lipids. They are derived from either bovine (Survanta, Infasurf, Alveofact, and bovine lipid extract surfactant [BLES]) or porcine (Curosurf and HL-10) sources, and have consistently been shown to have excellent biophysical activity. Currently available synthetic surfactant preparations contain either synthetic or recombinant surfactant-specific proteins combined with commercially available lipids. These preparations include Venticute and Surfaxin. Venticute is composed of a recombinant SP-C protein together with DPPC and smaller amounts of palmitoyloleoylphosphatidyl glycerol (POPG) and palmitic acid.[96] Surfaxin contains a synthetic SP-B–like peptide as well as DPPC, POPG, and palmitic acid.[95] Both Venticute and Surfaxin have been tested in preclinical studies involving models of ALI and phase II and phase III clinical trials. Two other synthetic surfactant preparations previously used in neonates with NRDS and tested in patients with ARDS include Exosurf (DPPC; hexadecanol, and tyloxapol) and artificial lung-expanding compound (ALEC, DPPC, and phosphatidylglycerol).[98] These preparations contain no surfactant proteins, perhaps explaining the poor results of these latter trials. No further studies are being conducted with these preparations at this time. Animal studies that have directly compared the various surfactant preparations have generally shown that those containing surfactant proteins, either from natural or synthetic or recombinant sources, are superior to those having no proteins.[99,100] Furthermore, meta-analyses of several studies involving neonates with NRDS also show that clinical trials utilizing natural products result in better outcomes than those using the synthetic preparations with no surfactant proteins.[101]

Based on preclinical data and results of these clinical trials, it is likely that some type of protein-containing surfactant will be required for optimal results in patients with ALI or ARDS. Whether the natural products will be more effective than the protein-containing, synthetic surfactants in this setting is unknown, and will be difficult to prove in this complex patient population. As a result, other factors may need to be considered when making this decision. For example, although animal-based products may well be as effective or superior to any synthetic products available (or to be developed in the future), they have the theoretical potential of transmitting molecules and/or infectious agents to the host. This, however, has not been demonstrated over the past 20 years of use in neonates. In addition, given the potentially large patient population that would ultimately benefit from this therapy, even if natural products are shown to be superior, availability may be a factor because of resource limitations. These issues do not exist for the recombinant and synthetic preparations, perhaps favoring further development of effective and easily manufactured synthetic products.

TABLE 60-2: EXOGENOUS SURFACTANT PREPARATIONS

Brand Name	Source/Composition
Natural Protein-Containing	
Survanta	Bovine-lung tissue extract
BLES	Bovine-lung lavage extract
Infasurf	Bovine-calf lavage extract
Alveofact	Bovine-lung lavage extract
Curosurf	Porcine-lung tissue extract
HL-10	Porcine-lung tissue extract
Synthetic/Recombinant Protein-Containing	
Surfaxin	DPPC, POPG, PA, "SP-B–like peptide"
Venticute	DPPC, POPG, PA, rSP-C
Non–Protein-Containing	
ALEC	DPPC, PG
Exosurf	DPPC, hexadecanol, tyloxapol

Abbreviations: ALEC, artificial lung-expanding compound; *BLES*, bovine lipid extract surfactant; *DPPC*, dipalmitoylphosphatidylcholine; *PA*, palmitic acid; *PG*, phosphatidyl glycerol; *POPG*, palmitoyloleoylphosphatidyl glycerol; *rSP-C*, recombinant human SP-C.

SURFACTANT DELIVERY AND DOSING

The various delivery methods that have been utilized for administering exogenous surfactant to patients with ALI include: (a) instillation of a liquid bolus through the endotracheal tube,[96] (b) bronchoscopic instillation of smaller aliquots of surfactant to the various segments of the lung,[102] (c) sequential segmental lavage of lung units with a surfactant preparation via the bronchoscope,[95] and (d) aerosolization of surfactant via a nebulizer, either in liquid form or as a dry powder.[92,103] For all methods of delivery, the common goal is to deliver sufficient amounts of material to the distal lung in an optimal distribution pattern. Unfortunately, the lung injury in critically ill patients is often non-uniform and varies over time as lung dysfunction deteriorates. As a result, it is likely that individual treatment strategies may have to be tailored to the specific patient involved. For example, patients with severe lung dysfunction with a nonuniform distribution of injury would not benefit from any aerosolized surfactant preparation delivered to the whole lung, because relatively small quantities of surfactant are deposited within lung tissue and most of the material would be deposited in the most

compliant regions of the lung, areas that need it the least.[104] In this situation, delivering large amounts of surfactant as a liquid bolus (50 to 200 mg lipid/kg body weight), either through the endotracheal tube or in sequential aliquots (with or without segmental lavage) via the bronchoscope, may be superior. The lavage approach may offer the advantage of removing inflammatory cell products and serum proteins, which tend to inhibit surfactant function, while leaving sufficient quantities of surfactant behind in the alveoli to improve lung function.[95,105] Although this latter approach is rather invasive, more time-consuming, and requires a skilled bronchoscopist to perform the procedure when compared to the bolus instillation technique, it may be optimal for specific types of severely ill patients. Currently, there is little doubt that patients with severe lung injury will require relatively large doses of surfactant to overcome surface tension inhibitory forces within the injured lung, the latter being induced either by serum proteins leaking into the airspace or inactivation of surfactant via nitration or oxidation or cholesterol, as previously described.[55,80,81,87,88,90]

Aerosolization would likely only be applicable to patients with milder disease who require smaller amounts of material and have relatively uniform injuries, a situation in which exogenous surfactant administration has yet to be tested in the clinical setting. In addition, a consistent and cost-effective nebulizer able to deliver reasonable amounts of surfactant over an extended period of time is not yet available, although dry powder delivery devices may achieve these objectives in the future.

Despite the numerous studies that have evaluated these various delivery methods in animals and humans, it is still not clear which delivery method should be used for specific types of patients, how much surfactant should be delivered per dose for the various delivery methods available, and how many doses will be required over time for each patient to achieve an optimal outcome. More research is certainly required in this area.

EFFECTS OF MECHANICAL VENTILATION

Mechanical ventilation is an important supportive therapy for patients with ALI or ARDS, and has recently been shown to impact the outcome of these patients.[86] Similar to its impact on the endogenous surfactant system, the specific mode of mechanical ventilation used in surfactant-treated lungs can influence the metabolism of the administered material. For example, animal studies have shown that lower tidal volumes resulted in superior physiologic responses compared to higher tidal volumes after exogenous surfactant was delivered as a liquid bolus; this was associated with less conversion of the administered LA forms into dysfunctional SA.[106,107] Clinically, these findings suggest that the mode of mechanical ventilation may have a significant impact on the duration of response to a particular dose of surfactant, which, in turn, would decrease the number of doses required. It is also important to optimize ventilation during and immediately after surfactant administration in order to optimize the distribution of the material and prevent airway obstruction. Positive end-expiratory pressure levels must be maintained during instillation to prevent alveolar collapse, and adequate tidal volumes must be delivered immediately after instillation to maintain recruitment and enhance peripheral distribution of the material.[106–108]

Similar to the situation in the non–surfactant-treated lung, the use of recruitment maneuvers in conjunction with exogenous surfactant is somewhat controversial, with both beneficial and even harmful effects reported.[109,110] It is likely that the timing and specific nature of the maneuver (i.e., frequency, duration, etc.) will impact its effects in the clinical setting of surfactant administration.

Finally, given the promising, albeit early, results of HFO in patients with ALI, some comments regarding its potential in the setting of exogenous surfactant administration are warranted. Very few studies have been performed to date, and results are inconsistent. Froese et al demonstrated that HFO was superior to conventional modes of ventilation after surfactant administration in saline-lavaged adult rabbits, but relatively high mean airway pressures were required to maintain lung recruitment with HFO.[111] On the other hand, a study in saline-lavaged adult sheep showed that exogenous surfactant may obstruct conducting airways when delivered in association with HFO, and that a period of more conventional tidal ventilation during and immediately following administration may be required for optimal distribution before switching over to HFO.[112] Further studies are required to determine how HFO and recruitment maneuvers should be used in conjunction with exogenous surfactant administration in patients with ALI or ARDS.

NATURE OF THE UNDERLYING INJURY

As alluded to in previous sections, the efficacy of a particular surfactant treatment strategy may predominantly depend on the specific type of patient involved, and, in this regard, influence all of the factors previously described (Fig. 60-4). ALI and ARDS can be initiated by several different insults, including those directly affecting the lung, such as aspiration and pneumonia, as well as indirect causes, such as systemic sepsis and trauma. The results of a recent phase III clinical trial, involving the synthetic surfactant preparation Venticute administered to patients with various types of ARDS, suggested that patients with direct lung injuries initiating the development of the disease would benefit the most from surfactant therapy.[96] A follow-up study, however, specifically focused on patients with direct lung injuries failed to confirm those observations, although there was some question of inactivation of the surfactant before administration.[97]

Previous studies have shown that several host factors, as well as timing of the intervention may influence a patient's response to surfactant; thus predicting consistent outcomes can be a problem in this patient population. Unfortunately, animal models that accurately reflect the various types of patients who develop ARDS, and ultimately those who would

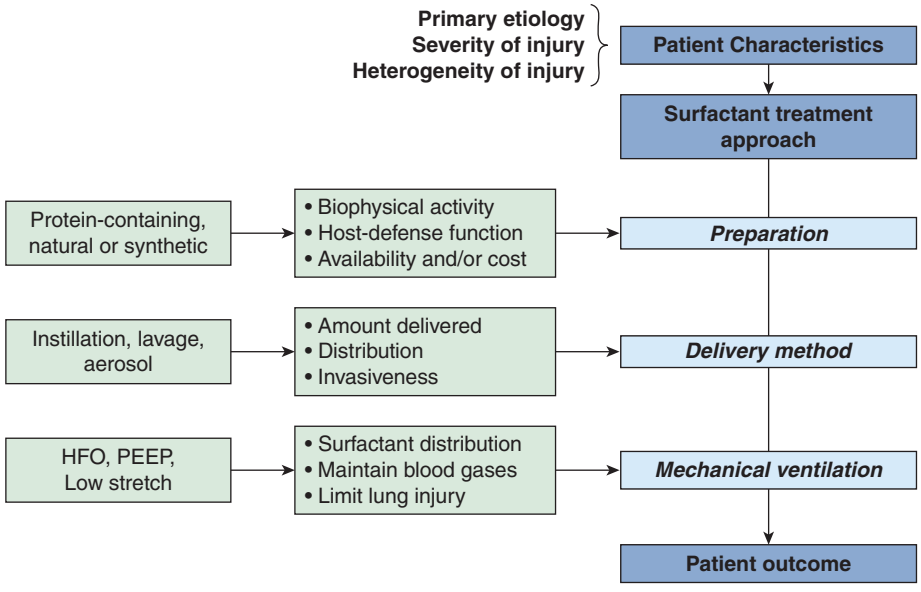

FIGURE 60-4 Various factors may influence a host's response to exogenous surfactant, including specific surfactant preparation, dosing and delivery method, mode of mechanical ventilation implemented during and after surfactant administration, and nature of the underlying injury. See text for details. *HFO*, high-frequency oscillation; *PEEP*, positive end-expiratory pressure.

respond to exogenous surfactant, are lacking. Patients with ARDS have a complex pathophysiology involving various types and severities of insults. As a result, we are left with the challenge of pursuing large, expensive, and time-consuming clinical trials with no guarantees that they will demonstrate beneficial results. It is imperative, therefore, that we gain as much insight as possible from the preclinical and clinical studies that have been conducted to date

FUTURE RESEARCH DIRECTIONS

Combination Therapies

The biophysical properties of surfactant make it a suitable candidate for combination therapies involving other agents.[113] For example, an effective surfactant adsorbs readily to the air–liquid interface and spreads rapidly across the alveolar space.[3,4,41] This puts the surfactant, as well as the added agent, in close proximity to alveolar epithelial cells as well as the pulmonary vasculature, ideally with a good distribution pattern. These particular characteristics would result in high local pulmonary concentrations of a therapeutic agent with minimal side effects or toxicity. Indeed, surfactant enhances the delivery as well as the expression of an adenoviral vector, and improves the peripheral distribution and activity of recombinant superoxide dismutases and antibiotics.[114–116] The combination of exogenous surfactant with other physiologically active compounds, such as nitric oxide and perfluorocarbons, also has been tested and shown to have synergistic effects.[117,118] Future applications for surfactant as a carrier vehicle and/or as part of a cocktail mixture for patients with lung injury require further investigation.

Role of Surfactant in Other Diseases

The vast majority of surfactant research that has focused on the mature lung has involved animal models and/or patients with ALI or ARDS. Recent evidence suggests, however, that alterations in the endogenous surfactant system also may be implicated in several other diseases of the lung, which potentially could lead to novel therapeutic approaches to these disorders in the future. One such disease reflecting alterations in endogenous surfactant metabolism is pulmonary alveolar proteinosis.[119] Increased synthesis and secretion together with decreased catabolism of surfactant results in excessive accumulation of surfactant lipids and proteins within the airspace. Removal of this excess material via whole-lung lavage has resulted in long-term benefits for most patients.

In addition, given the extensive *in vitro* and *in vivo* data showing that the various components of surfactant can affect immune-cell regulation, inflammatory cell responses, and bacterial and viral proliferation/killing, it is likely that surfactant also plays an important role in bacterial and viral pneumonia. Surfactant alterations have been consistently reported in these patients. A clinical trial involving children with respiratory syncytial virus showed improved lung function and shorter hospital stays in those receiving exogenous surfactant compared to non–surfactant-treated control subjects.[120,121] It is difficult, however, to separate the biophysical aspects of the improved lung function observed

from the immunomodulatory effects of surfactant on the development and progression of the infection itself. More animal studies and clinical trials evaluating early exogenous surfactant administration in this setting are necessary to determine if surfactant plays an important role in pulmonary infections.

Surfactant alterations also have been documented in patients with various interstitial lung diseases. These reports have shown decreased lipid and SP-A levels in the bronchoalveolar lavage fluid of patients with idiopathic pulmonary fibrosis, which in one study predicted 5-year survival.[122,123] SP-A levels were actually increased in the lungs of patients with sarcoidosis and hypersensitivity pneumonitis, suggesting that, similarly to the various types of ARDS, the role of surfactant may vary according to the specific type of interstitial disease and insult involved.[124]

Various studies suggest that surfactant plays an important role in obstructive lung diseases.[125] Surfactant facilitates ciliary function, downregulates some of the inflammatory processes implicated in these diseases (asthma and cystic fibrosis), and is important in maintaining the patency of conducting airways.[50,51] Although various studies report surfactant alterations in most obstructive diseases, only a few small studies have tested the efficacy of exogenous surfactant administration in this setting.[126] The results of these preliminary studies suggest that surfactant may be effective as therapy in asthma, although further research is required.

Finally, surfactant changes were demonstrated in the ischemia–reperfusion injury associated with lung transplantation. Exogenous surfactant, administered to the donor lung before storage, mitigated this injury, even in the setting of prolonged organ storage.[127] This indication for surfactant administration has not been tested in clinical trials to date.

SUMMARY AND CONCLUSIONS

Pulmonary surfactant is critical for maintaining alveolar stability and normal lung function. Although the composition of surfactant is relatively consistent among mammalian species, there is still much to be learned regarding the specific functions of the individual components of surfactant, particularly with respect to host defense. Most research to date involving surfactant perturbations in the mature lung has focused on the lung injury associated with ALI or ARDS, and has led to clinical trials evaluating the efficacy of exogenous surfactant administration in this setting. Unfortunately, results of these trials have been inconsistent, and somewhat disappointing. Careful analyses of these results, together with extensive preclinical studies, have provided important insight into the various factors that may influence a host's response to this therapy. Research conducted over the next few years should take advantage of the lessons learned from previous studies, and focus on the most important factors influencing a host's response to this therapy in various clinical settings, thereby optimizing patient outcomes.

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NITRIC OXIDE AS AN ADJUNCT

Klaus Lewandowski

As the saying goes, unexpected scientific discoveries are often the most important. The "principle of limited sloppiness," a term coined to describe fortuitous or accidental discoveries, hit in the 1970s, when Zawadski, a technician in the laboratories of Robert F. Furchgott, failed to follow his superior's directions correctly and did not remove the endothelium in a rabbit aorta preparation. In this preparation, acetylcholine caused potent relaxation whereas contraction was expected. Shortly thereafter, it was established that acetylcholine was acting on endothelial cell receptors to produce a substance that could diffuse to the vascular smooth muscle and initiate its relaxation.[1] This substance was called endothelium-derived relaxing factor. It took another 8 years for independent working groups to confirm that the chemical structure of endothelium-derived relaxing factor was identical to that of nitric oxide (NO).[2,3]

The scientific and global community honored the substance itself and its discovery by naming NO "Molecule of the Year" in 1992.[4] The Nobel Prize in Physiology or Medicine for 1998 was awarded jointly to Robert F. Furchgott, Louis J. Ignarro, and Ferid Murad, for their breakthroughs concerning "nitric oxide as a signaling molecule in the cardiovascular system."

NO is a colorless and odorless gas. It is a toxic air pollutant, present in motor vehicle exhaust and power plant effluent. The gas is found in the atmosphere in the range of 10 to 500 parts per billion (ppb), and locations with heavy vehicular traffic can exceed 1.5 parts per million (ppm). In the hot cone of a glowing cigarette, concentrations of 1000 ppm were measured in a 40-mL puff. NO is a free radical; it quickly reacts with oxygen (O_2) to form poisonous nitrogen dioxide.

In the 1980s it became evident that NO is an essential molecule that regulates a wide range of human physiologic processes. Early studies revealed that NO is produced in endothelial cells and diffuses to vascular smooth muscle cells, where it mediates relaxation. Further studies demonstrated that the substance controls several other physiologic systems, including the immune system, platelet aggregation, and neurotransmission. The focus of this chapter is the prominent role of NO in respiratory physiology and its therapeutic application by inhalation.

ENDOGENOUS NITRIC OXIDE IN THE RESPIRATORY SYSTEM

Endogenous Nitric Oxide Synthesis

Endogenous NO is produced by the enzyme system, nitric oxide synthase (NOS). In human subjects, NOS activity can be found in the epithelium of nasal and paranasal mucosa, the bronchial epithelium, type II alveolar epithelial cells, airway nerves, inflammatory cells, airway and vascular smooth muscle cells, and endothelial cells. Three isoforms of the enzyme have been identified: the constitutive neuronal NOS, the inducible NOS (iNOS) that is incited by cytokines, and the constitutive endothelial NOS. There is evidence that a fourth isoform, mitochondrial NOS exists, which has important functions in cellular metabolism.

NO generated by neuronal NOS in the peripheral nervous system acts as a neurotransmitter that modulates smooth muscle relaxation in the respiratory tract. Inflammatory cells express iNOS that enhances NO synthesis. It is supposed that NO plays a self-regulatory role in host-defense and inflammatory processes. Yet, there are conflicting results whether NO mediates proinflammatory or antiinflammatory effects. Concurrently, overproduction of NO may also be associated with the worsening of certain infectious diseases. NO formed by endothelial NOS in vascular endothelial cells regulates pulmonary and systemic vascular tone. Mitochondrial NOS is assumed to provide substantial amounts of cardiac NO responding to heart hypoxia. Figure 61-1 shows the schematic pathway of NO signal transduction.

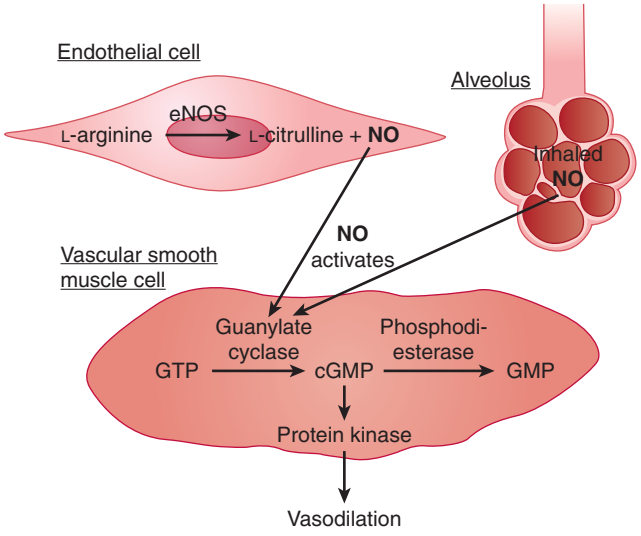

FIGURE 61-1 Endogenous or inhaled nitric oxide (*NO*) mediates vasodilation of vascular smooth muscle cells. NO is endogenously produced in endothelial cells of the pulmonary vasculature from the amino acid L-arginine, which is converted to L-citrulline and NO by the enzyme nitric oxide synthase. NO expressed by the endothelial cells, or inhaled NO, diffuses rapidly into the vascular smooth muscle cells, where it activates soluble guanylate cyclase, which converts guanosine triphosphate (*GTP*) into cyclic guanosine monophosphate (*cGMP*). The high intracellular concentration of cGMP relaxes the smooth muscle via cGMP-dependent protein kinase. cGMP is inactivated by the enzyme phosphodiesterase, which catalyzes the conversion of cGMP to guanosine monophosphate (*GMP*). *eNOS,* endothelial nitric oxide synthase.

Endogenous Nitric Oxide Concentrations in the Airways

The concentrations of NO in healthy human airways differ depending on the measurement site. Approximately 100 ppb were measured in the nasopharynx of healthy nonsmoking volunteers during nose breathing. During mouth breathing, even higher concentrations of 650 ppb were seen in the nasopharynx. The highest NO concentrations (1 to 30 ppm) were detected in the paranasal sinuses.[5] In the trachea of intubated patients the NO concentrations were markedly lower; they ranged between 5 and 10 ppb. The cilia of the epithelial cells of the maxillary sinuses contain high amounts of iNOS and can be viewed as a major production site of NO in the respiratory tract.[6]

Function of Endogenous Nitric Oxide in the Respiratory System

Endogenous NO was suggested to be an important signaling molecule in numerous physiologic processes. Autoinhaled NO from the paranasal sinuses is able to induce selective pulmonary vasodilation in ventilated areas. The blood flow through well-aerated lung areas with higher intraalveolar O_2 concentrations increases and ventilation–perfusion mismatch is antagonized.

Endogenous NO is also involved in host defense and has direct microbicidal effects. Especially the high levels of endogenous NO in the paranasal sinuses may be active in local nasopharyngeal host defense against bacterial or viral invaders. Other findings substantiate that endogenous NO increases airway mucus secretion. Ciliary beat frequency, responsible for microbial clearance, is also enhanced by iNOS stimulators.

Bronchodilation is suppressed by NOS inhibitors, indicating that endogenous NO modulates basal bronchial tone. There is evidence that endogenous NO may protect the airways of asthmatic patients from bronchoconstriction.[7] The high levels of NO, measured in the exhaled air of patients with asthma, however, are believed to mirror the stimulation of iNOS by proinflammatory cytokines and seem to have harmful effects, such as inflammation and increased vascular permeability.

NO is excreted by tumor and host cells and is a factor of promoting angiogenesis and tumor growth. The role of NO in cancer, however, is yet undetermined as it has been attributed both, tumoricidal as well as tumorigenic properties. There are indications that inhibiting iNOS may be beneficial in treatment of certain forms of cancer.

Furthermore, endogenous NO possibly regulates the coagulation system. Formation of endogenous NO also seems to be involved in mediating pulmonary vasodilation during transition of the pulmonary circulation at birth.

RATIONALE FOR THE USE OF INHALED NITRIC OXIDE AS AN ADJUNCT

Inhaled nitric oxide (iNO) acts as a selective pulmonary vasodilator. As a gas, it reaches only ventilated alveoli and produces relaxation of the accompanying pulmonary blood vessels. iNO acts by producing vasodilation in well-ventilated lung units and redistributing pulmonary blood flow from unventilated to ventilated regions of the lung. This results in improvement of ventilation–perfusion mismatch and oxygenation, in a decrease of pulmonary vascular resistance and pulmonary artery pressure (PAP), as well as in a lower right-ventricular afterload. The activity of iNO is mainly limited to the area of deposition when lower concentrations of iNO are applied because large amounts of the molecule are inactivated by binding to hemoglobin at the moment NO diffuses into the blood vessel. This explains why iNO has almost no systemic side effects and acts predominantly in the pulmonary circulation (Fig. 61-2).

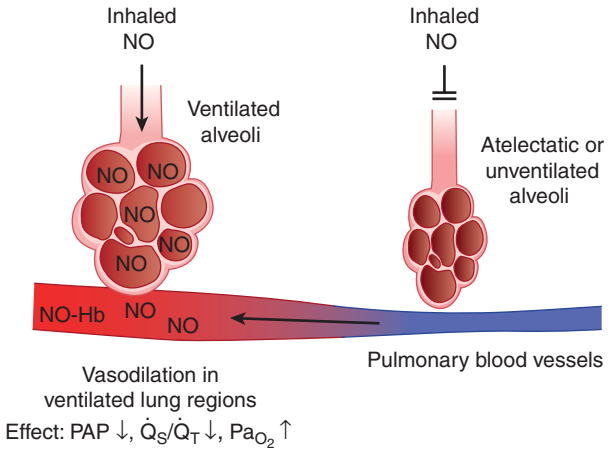

FIGURE 61-2 Inhaled NO selectively produces vasodilation in ventilated alveoli. iNO produces vasodilation in well-ventilated lung units and redistributes pulmonary blood flow from unventilated to ventilated lung regions. In patients with ventilation–perfusion mismatch (e.g., patients with acute respiratory distress syndrome), this leads to improvement in oxygenation and reduction of intrapulmonary right-to-left shunt. Selective vasodilation in the pulmonary circulation causes significant reduction of elevated pulmonary artery pressure; thus, iNO is a valuable therapy in patients with all kinds of pulmonary hypertension. Systemic vasodilation does not occur to a noteworthy extent because large amounts of NO rapidly bind to hemoglobin and are thereby inactivated. *Hb,* hemoglobin; *iNO,* inhaled nitric oxide; *NO,* nitric oxide; Pa_{O_2}, arterial partial pressure of oxygen; *PAP,* pulmonary arterial pressure; $\dot{Q}_S/\dot{Q}_T$, intrapulmonary right-to-left shunt.

INDICATIONS AND OUTCOME OF INHALED NITRIC OXIDE THERAPY

Adults and Older Children

Inhaling low concentrations of NO causes rapid and safe reduction of an elevated PAP, and improves the impaired oxygenation in many patients without causing systemic hypotension. In the early 1990s, iNO became an innovative treatment option for patients with acute respiratory failure and pulmonary hypertension.

In patients with acute respiratory distress syndrome (ARDS), improvement of oxygenation and reduction of PAP is an important therapeutic goal. iNO selectively enhances perfusion in ventilated lung areas and counteracts the ventilation–perfusion mismatch typical of this condition. Because NO works only in aerated lung tissue, measures that recruit previously collapsed alveoli can enhance the beneficial effect of NO. The overall effect of iNO is often an impressively increased arterial partial pressure of oxygen (PA_{O_2}) and a reduction of the elevated PAP. Several enthusiastic reports encouraged the hope that iNO would prove to be the promising new therapy that would ultimately improve the low survival rates in ARDS. Disappointingly, an improved outcome of ARDS patients could not be observed. A meta-analysis of twelve randomized controlled trials that included 1237 patients revealed that iNO significantly improves oxygenation during the first days of inhalation, although no benefit on survival could be detected. Treatment with iNO was further burdened with an increased risk of renal dysfunction.[8]

The significant improvements in oxygenation and reduction of elevated PAP by iNO, however, could not be denied, and prompted scientists to study the effect of iNO in other diseases associated with severe hypoxia or pulmonary hypertension. Table 61-1 presents a literature survey, focusing on iNO therapy in several diseases or conditions in adults or older children. It further provides expert recommendations for the application of iNO in the respective patient collectives. Synopsis of the information compiled in the table allows for the conclusion, that in most cases of severe oxygenation impairment or high PAP, iNO is effective. When considering iNO as a possible therapeutic option in adult patients, it is important to recognize that certain pathophysiologic variables may significantly improve, although in no instance was survival clearly enhanced.

What are still suitable indications for iNO in adults or older children? It may be indicated in patients who are in a phase of severely impaired gas exchange that is unresponsive to maximal medical therapy. In such settings, application of iNO can significantly enhance pulmonary gas exchange and thereby prevent hypoxic organ damage. Moreover, iNO can be tried in all patients suffering from severe pulmonary hypertension. In most cases, elevated PAP drops and relieves the right heart. When considering possible iNO treatment,

TABLE 61-1: iNO TREATMENT IN ADULTS AND OLDER CHILDREN: BENEFIT AND EXPERT RECOMMENDATIONS

Diagnosis	Effect of NO Inhalation	Expert Recommendations
Heart disease, heart failure (iNO for diagnostic purposes)	Pulmonary vascular reactivity testing with O_2 and iNO can identify patients with pulmonary hypertension suitable for corrective cardiac surgery or heart transplantation.[52] Patients with severe heart failure may experience pulmonary edema with inhalation of NO, probably because of increased left atrial filling after pulmonary vasodilation.[53]	iNO trial for identification of patients suitable for cardiac surgery or heart/lung transplantation is recommended. iNO testing in patients with left-heart dysfunction is dangerous, heart function should be optimized before iNO testing.[20]
Pulmonary arterial hypertension (iNO for diagnostic purposes)	iNO decreases PAP effectively in some patients. The acute decrease of PAP with iNO is the best predictor of long-term response to oral vasodilator treatment.[54] iNO can identify responders for a long-term treatment with calcium-channel blockers.[55]	iNO is recommended for acute vasodilator testing in a dosage of 10 to 20 ppm.[20] Insufficient data to recommend long-term inhalation of NO.[20]
Thromboembolism	In four cases of pulmonary embolism, iNO led to improvement of pulmonary hemodynamics and oxygenation.[56] In four further patients with acute massive pulmonary embolism, inhaled NO rapidly improved pulmonary and systemic blood pressures, heart rate, and gas exchange.[57]	No routine use of iNO in thromboembolic disease recommended because of insufficient data. In patients with severe right-ventricular failure or severe hypoxemia, iNO may be beneficial.[20]
Sickle cell disease	Most common complications of sickle-cell disease are the vasoocclusive pain crisis and the acute chest syndrome, a form of lung injury, as well as hemolysis. Hemolytic anemia is associated with pulmonary hypertension.[58] Results from two small randomized, placebo-controlled trials suggested that in severe vasoocclusive crisis, inhalation of 80 ppm NO decreased pain scores and morphine use.[59,60]	No routine use of iNO recommended because of insufficient data.[20]
Chronic obstructive pulmonary disease (COPD)	Effects of iNO in patients with COPD are contradictory. In one study, iNO improved oxygenation and reduced PAP while right-ventricular ejection fraction increased.[61] In another study, iNO reduced PAP but did not improve right-ventricular ejection fraction or arterial oxygenation in patients with acute respiratory failure caused by acute exacerbation.[62] In a third study, however, addition of iNO to inhaled oxygen did not improve or worsen arterial partial oxygen pressure, but caused a significant decrease in mean PAP. Cardiac output increased. Long-term use of iNO was effective.[63] In ten volunteers with very severe COPD iNO in concentrations of 40 to 40,000 ppb did not improve oxygenation.[64]	No evidence of a clinical benefit of iNO in patients with COPD.[20]
High-altitude pulmonary edema (HAPE)	In mountaineers prone to HAPE, iNO produced a marked decrease in PAP. In subjects with radiographic evidence of pulmonary edema, iNO improved oxygenation.[65] In fourteen patients with severe HAPE, iNO reduced PVR by 36% compared with room air. PVR fell by 54% when iNO was combined with 50% oxygen. Pa_{O_2} increased by 14% when iNO was applied.[66] In a rat model of HAPE, iNO improved survival.[67]	No recommendation because of insufficient data.
Myocardial infarction and cardiogenic shock	In thirteen patients with right ventricular myocardial infarction and cardiogenic shock iNO significantly decreased PAP and PVR, and increased CI by 24%.[68] Application of iNO before and during coronary reperfusion is able to reduce infarct size (animal experiment).[69]	No recommendation because of insufficient data.
Right-ventricular failure (RVF)	RVF responds favorably to afterload reduction. In RVF after myocardial contusion or after right-ventricular myocardial infarction with cardiogenic shock, iNO rapidly improved hemodynamics.[68,70]	No recommendation because of insufficient data.

Perioperative pulmonary hypertension and RVF in cardiac surgery	Cardiopulmonary bypass reduces NO production in pulmonary tissue that leads to pulmonary vasoconstriction and right-ventricular dysfunction postoperatively (animal experiment).[71] Inhalation of NO during and after cardiopulmonary bypass diminishes the release of markers of myocardial injury. Left ventricular dysfunction during and immediately after cardiopulmonary bypass is antagonized.[72] In twenty-three patients with pulmonary hypertension, treated with iNO immediately after cardiopulmonary bypass, iNO significantly reduced PAP and PVR and lead to increased cardiac output.[73]	In patients with perioperative acute right-ventricular dysfunction and pulmonary hypertension, RVF should be optimized first by conventional measures before a trial of iNO should be undertaken. iNO doses >20 ppm have no advantage.[20]
Left-ventricular assist devices (LVADs)	Pulmonary hypertension is frequent in patients treated with LVADs and may lead to right-ventricular dysfunction. Eleven patients with LVADs and pulmonary hypertension were randomized to iNO (20 ppm) and control therapy. iNO precipitated significant reductions in PAP and increased LVAD flow. In control patients, no hemodynamic improvement was recorded.[74] A recent randomized controlled trial studied the effect of iNO in forty-seven patients with implanted LVADs. Only in the iNO group did PVR decrease significantly, from 311 ± 35 to 225 ± 17 dyn sec cm^{-5} ($p < 0.01$).[75]	Expert panel believes that iNO improves pulmonary hemodynamics in patients with inadequate left-sided flow during use of LVADs and pulmonary hypertension refractory to conventional maneuvers. In this situation, they recommend application of iNO among other vasodilator therapies.[20]
Heart transplantation	Pulmonary hypertension is a frequent problem during heart transplantation and may contribute to life-threatening right-heart failure. In heart transplant recipients with pulmonary hypertension, iNO given in the postoperative period selectively reduced PVR and enhanced right-ventricular stroke work. Compared with a historical cohort, the NO treated group had better survival rates.[76] Fourteen patients with either heart transplantation or lung transplantation received iNO in the operating room when pulmonary hypertension, refractory hypoxemia, or right-ventricular dysfunction were present. Inhalation of 20 ppm NO lowered PAP and central venous pressure, increased cardiac index, and improved mixed venous oxygen saturation.[77]	iNO is used by several institutions with experience in cardiac transplantation. They recommend it as standard therapy for heart transplantation complicated by an elevated PVR.[20]
One-lung ventilation (OLV)	Hypoxia is a frequent complication during OLV. Sixteen patients who developed hypoxemia during OLV were randomized to iNO (20 ppm) or control groups (nitrogen). iNO when administered to the dependent lung was not superior to nitrogen.[78] In patients with pulmonary hypertension during OLV, iNO caused a significant reduction of mean PAP and improved oxygenation in patients with severe hypoxemia.[79] A combination of iNO with almitrine significantly improved oxygenation during OLV.[26]	Expert panel does not recommend routine use of iNO during OLV. Only in case of severe hypoxemia, refractory to conventional therapy, iNO may beneficial.[20]
Major lung resection	Postpneumonectomy pulmonary edema is a severe complication of lung resection and afflicted with high mortality rates. In a patient with major lung resection iNO was successfully applied to treat postpneumectomy pulmonary edema (case report).[80]	No recommendation because of lack of data.
Lung transplantation	There remains controversy whether iNO can prevent ischemia–reperfusion injury in lung-transplant recipients. Some studies performed in the 1990s reported that iNO reduced reperfusion injury in transplanted lungs. Another study, however, showed that prophylactic iNO does not prevent reperfusion injury. During reperfusion, however, patients with reperfusion injury experienced improved oxygenation and reduction of PAP.[81] Contrary to earlier studies, a large randomized, controlled trial could also not detect a significant effect on physiologic variables or outcomes in the group of iNO-treated patients, in whom iNO was initiated 10 minutes after reperfusion.[82] The occurrence of acute graft rejection, however, was less frequent in the iNO group in comparison with historical controls.[83] Recent randomized clinical trials could not detect a benefit of a prophylactic administration of iNO for prevention of primary graft failure, however, in case of development of a hypoxic phase during primary graft failure, iNO may reduce the need for extracorporeal membrane oxygenation in lung transplant patients.[84]	No evidence that iNO prevents reperfusion injury after lung transplantation.[20]

(*continued*)

TABLE 61-1: iNO TREATMENT IN ADULTS AND OLDER CHILDREN: BENEFIT AND EXPERT RECOMMENDATIONS (*CONTINUED*)

Diagnosis	Effect of NO Inhalation	Expert Recommendations
Acute lung injury (ALI)/ acute respiratory distress syndrome (ARDS)	iNO was found to reduce elevated PAP, improve oxygenation, and decrease intrapulmonary right-to-left shunt during the first days of treatment.[31] A meta-analysis of twelve randomized controlled trials that included 1237 patients revealed that iNO improves oxygenation during the first days of inhalation. No benefit on survival could be detected. Risk of renal dysfunction was increased in the iNO patients.[8] These findings were confirmed by a large systematic review of the Cochrane Collaboration.[29]	No routine use of iNO in ALI/ARDS. Trial of iNO as a rescue treatment in case of life-threatening hypoxemia.[20]
Influenza	Patients with H1N1 influenza very rapidly develop respiratory failure. Thirty-two patients of the H1N1 influenza epidemic 2009 in Spain were evaluated and 25% received iNO as a rescue therapy.[85] In Canada, 168 critically ill patients with influenza A (H1N1) were admitted to thirty-eight intensive care units and prospectively evaluated; 13.7% of the patients received iNO as a rescue therapy.[86]	ICUs treating influenza patients should provide advanced ventilatory support and rescue therapies including iNO.[87]
Inhalation injury	There are only few reports on use of iNO in burn patients with inhalation injury.[88–90] All studies reported an improved oxygenation with iNO therapy. An immediate and stronger early response to NO inhalation may eventually predict recovery, however, all studies were only performed in a small series of patients with the respective weakness of the reported results.	No routine use of iNO in inhalation injury. Trial of iNO as a rescue treatment in case of life-threatening hypoxemia after conventional treatment has been optimized. In case of early response to iNO, the inhalation should be continued.[91]
Asthma	Inhalation of NO results only in a minor relaxation of airway tone in adults.[92,93] In children with asthma, iNO has no apparent bronchodilatory effect.[94] In case of severe status asthmaticus, however, iNO might have a bronchodilatory effect (case report).[95] In five children with life-threatening status asthmaticus who required MV and did not respond to maximal medical management, iNO decreased Pa_{CO_2} significantly. Four children survived.[96]	No recommendation as to date no controlled studies on this topic have been performed.

Abbreviations: CI, cardiac index; *ICU,* intensive care unit; *iNO,* inhaled nitric oxide; *PAP,* pulmonary artery pressure; *PVR,* pulmonary vascular resistance.

however, it is strongly recommended to optimize conventional treatment before a trial of iNO is undertaken.

Infants

Application of iNO yielded the best results in critically ill infants. In 1999, the use of iNO was approved by the United States Food and Drug Administration (FDA) for the treatment of term and near-term newborns (>34 weeks of gestation) with hypoxic respiratory failure associated with pulmonary hypertension.

In neonates with respiratory failure, persistent pulmonary hypertension of the newborn (PPHN) is common. PPHN is characterized by elevated pulmonary resistance, pulmonary vasoconstriction, and altered vascular reactivity. Desaturated blood circulates partly through an extrapulmonary right-to-left shunt, across the foramen ovale and ductus arteriosus. Since 1970, extracorporeal membrane oxygenation (ECMO) has been the treatment of choice if PPHN is present. Survival rates of up to 80%[9] were achieved with ECMO therapy whereas survival with conservative therapy was approximately 50%.[10] In hypoxemic newborns with PPHN, clinical studies indicate that iNO increases systemic O_2 levels, decreases PAP, and mitigates ventilation–perfusion mismatch. Randomized, placebo-controlled trials of iNO in neonates with PPHN failed to show a significant decrease in mortality rates in the iNO group; iNO therapy did, however, reduce the requirement for ECMO.[11,12]

Some years ago, a large, randomized, controlled trial documented the effectiveness of iNO in 207 preterm neonates with respiratory failure. iNO decreased the incidence of chronic lung disease and death.[13] These encouraging findings, however, were not supported by further studies. A recent systematic review of fourteen randomized controlled trials that studied iNO therapy in preterm neonates unveiled a disappointing picture. iNO was not able to significantly decrease mortality rates and early rescue treatment is probably associated with a higher risk of intraventricular hemorrhage.[14] In a selected patient collective of premature infants with a birth weight between 1000 and 1250 g, however, early inhalation of NO might reduce the incidence of bronchopulmonary dysplasia.[15]

Perioperative pulmonary hypertension in infants with congenital heart defects is harmful and compromises their chance of survival. iNO, however, has not proven to reduce mortality or the number of pulmonary hypertensive crises.[16] A trial with iNO could only be recommended in infants with severe pulmonary hypertension in the perioperative setting of congenital heart surgery.[17,18]

From a pathophysiologic point of view, iNO therapy may be harmful for newborns with congenital heart disease dependent on right-to-left shunts and its routine use is not recommended in this setting.[11] Newborns with congestive heart failure and lethal congenital anomalies should also be excluded from iNO therapy.[11]

Table 61-2 presents an overview of the literature on the effect of iNO therapy in several diseases or conditions in infants together with expert recommendations. In a nutshell, physicians caring for infants with hypoxic respiratory failure and PPHN should be familiar with the use of iNO. In newborns it should be used liberally if these indications are present, because ECMO therapy can be avoided in many cases. In preterm infants, however, routine use of iNO is not recommended.[17]

TECHNIQUE OF NITRIC OXIDE INHALATION

It is strongly recommended to use a delivery device for iNO that is approved for clinical use.[11] The FDA has published a guidance document for approval of NO delivery systems that specifies the technical requirements for safe administration of iNO.[19] Important specifications are that the gas be supplied in a constant concentration during inspiratory flow; administered iNO concentrations should not vary with flow fluctuation within the inspiratory phase of the respiratory cycle; for regulation of iNO concentrations, a range of 0 to 80 ppm should be allowed; the system should be specified for connection with pharmaceutical grade NO gas cylinders containing 400 to 800 ppm NO in nitrogen; contact time of NO and O_2 should be short to limit NO_2 formation; the system should further be equipped with NO, NO_2, and O_2 gas analyzers and alarm functions to warn the intensivist against too low or too high levels of NO and O_2 concentrations, discontinuation of gas flow, or accumulation of NO_2;[11,19] NO analyzers should be able to measure iNO concentrations as low as 1 ppm;[19] and a manual back-up NO supply device for emergency or transport reasons should be available near the ventilator to ensure continuous delivery of the therapeutic gas.[20]

In clinical practice, iNO delivery devices are generally connected to anesthesia and intensive care ventilators, to high-frequency ventilators, to transport ventilators, and manual ventilation systems. In spontaneously breathing, nonintubated infants, iNO therapy is also established by nasal cannula and continuous positive airway pressure systems. It is recommended to check the manufacturers' specifications before connecting the iNO system to any ventilation device.[11]

DOSAGE OF INHALED NITRIC OXIDE

Dose–response studies in patients with ARDS show that very low concentrations of iNO, only 10 ppb, are able to enhance oxygenation; higher concentrations are necessary to decrease the elevated PAP. The respective effective doses whereby 50% of individuals will show the expected response to iNO are 100 ppb and 2 to 3 ppm. Improvement in oxygenation reached a maximum at 10 ppm and

TABLE 61-2: iNO TREATMENT IN INFANTS: BENEFIT AND EXPERT RECOMMENDATIONS

Application of iNO/ Diagnosis	Effect of NO Inhalation		Expert Recommendations
Assessment of the reversibility of pulmonary hypertension	When evaluating a patient for corrective heart surgery or heart transplantation, an iNO trial may be useful in determining operability. One hundred twenty-four patients with heart disease complicated by pulmonary hypertension received 100% oxygen and iNO to test pulmonary vascular reactivity. Test results could identify proper candidates for corrective surgery.[52] A recent retrospective trial studied children with pulmonary hypertension who underwent vasodilator testing before heart transplantation. Children who did not respond had increased rates of right-ventricular failure (RVF) and death from RVF. Preemptive use of iNO might decrease frequency of RVF.[97]		Pulmonary reactivity testing with iNO and oxygen is recommended in infants with heart disease complicated by pulmonary hypertension to identify proper candidates for corrective surgery.[18]
Hypoxia in term and near-term neonates	In 1999, use of iNO was approved by the FDA for treatment of hypoxic respiratory failure and pulmonary hypertension in term and near term neonates. The Cochrane Collaboration performed an analysis of fourteen randomized, controlled studies in term and near-term newborns with hypoxia. Use of iNO reduced the need for extracorporeal membrane oxygenation (ECMO) and improved oxygenation. Reduction of mortality was not evident. There were, however, indications that outcome of infants with diaphragmatic hernia was worsened.[12]		A trial of iNO is favored in newborns ≥34 weeks gestation, <14 days of age and with Pa_{O_2}/FI_{O_2} <100 mm Hg and/or an oxygenation index >25. iNO therapy should begin early in the course of the disease.[11]
Hypoxia in preterm neonates	Despite some encouraging early reports, iNO has not proven to be beneficial in preterm neonates. A recent systematic review performed by the Cochrane Collaboration analyzed fourteen randomized, controlled trials investigating iNO therapy in preterm neonates. Rescue therapy with iNO in case of severe hypoxia did not reduce mortality. Routine application of iNO in infants with pulmonary disease also could not reduce mortality. Although early rescue treatment was associated with a 20% higher incidence of intraventricular hemorrhage, this finding was not significant.[14]		Routine use of iNO in preterm infants (<34 weeks gestation) is not recommended.[17]
Persistent pulmonary hypertension of the newborn (PPHN) caused by lung parenchyma diseases leading to abnormally constricted pulmonary vasculature[98]	Meconium aspiration syndrome, Respiratory distress syndrome, Pneumonia	In 1999, use of iNO was approved by the FDA for treatment of hypoxic respiratory failure and pulmonary hypertension in term and near-term neonates. A recent systematic review for the development of evidence based clinical practice guidelines for use of iNO in newborns, presenting with hypoxemic respiratory failure associated with pulmonary hypertension, revealed the following results[11]: analysis of nine studies that reported mortality detected no significant effect of iNO on this parameter; eight studies evaluated long-term outcomes. Neurodevelopmental outcomes were similar in neonates treated with iNO and controls. Pulmonary outcomes in both groups were also similar. Eight studies reported requirement for ECMO. Meta-analysis of these data revealed less need of ECMO in the iNO groups.	A trial of iNO is recommended in newborns ≥34 weeks gestation, <14 days of age and with Pa_{O_2}/FI_{O_2} <100 mm Hg and/or an oxygenation index >25. iNO therapy should begin early in the course of the disease.[11] iNO therapy should start with 20 ppm. If there is no response to a 30- to 60-minute trial of iNO, iNO therapy should be terminated. In parenchymal lung disease optimal recruitment of lung tissue should be achieved before NO inhalation. Lowest effective dose of iNO and O_2 should be applied.[11]
PPHN due to abnormally remodeled pulmonary vasculature with normal lung parenchyma[98]	Idiopathic PPHN		

PPHN caused by hypoplastic pulmonary vasculature[98]	Congenital diaphragmatic hernia (CDH)	Patients with CDH seem to gain almost no benefit from iNO treatment. A randomized study in fifty-three term and near-term infants with CDH reported no significant improvement in oxygenation in the iNO group. Although patients of the iNO group needed more ECMO treatment and had a higher death rate than control patients, these findings were not significant.[99] Controversial results were offered by further studies. Early surgery and iNO improves the outcome and reduces the requirement for ECMO in the treatment of antenatally diagnosed congenital diaphragmatic hernia.[100] Retrospective data from sixty-one newborns with CDH give evidence that survival rates of infants with CDH have improved over the last 10 years, which was attributed by the study team to new therapies, including iNO.[101] This result is not concordant with data from a similar study in twenty-seven Norwegian neonates with CDH. The patient collective treated with novel therapeutic measures including iNO had a higher mortality than that treated before 1997, when these therapy options were not available.[102]	No convincing benefit for newborns with congenital diaphragmatic hernia. Routine use of iNO in these patients is not indicated.[11]
Bronchopulmonary dysplasia (BPD)	BPD is a chronic lung disease mainly of preterm infants, that often develops after postnatal injury by therapeutic measures, such as mechanical ventilation and high inspiratory oxygen concentrations.[98] Pulmonary hypertension and reduction of alveolar–capillary surface area are significant contributors to high mortality in these patients. There are no convincing results that support prophylactic inhalation of NO for prevention of BPD in preterm neonates. Only one study described a markedly lower incidence (30% vs. 60%) of BPD with iNO therapy in premature infants with a birth weight between 1000 and 1250 g.[15]		No recommendation because of a lack of data.
Perioperative pulmonary hypertension in congenital heart patients	Pulmonary hypertensive crises postoperatively after congenital heart surgery are dangerous and afflicted with high mortality. One hundred twenty-four infants with congenital heart defects were randomized to iNO or placebo therapy from heart surgery and postoperatively until extubation as a prophylaxis for prevention of pulmonary hypertension. Frequency of pulmonary hypertensive crises was less in infants receiving iNO (RR = 0.66).[103] These findings differ from that of a Cochrane review of four randomized trials that analyzed the effects of postoperative iNO versus placebo. No differences in several outcome variables (i.e., mortality, number of pulmonary hypertensive crises, oxygenation, etc.) between the two groups could be detected.[16]		No routine use of iNO in the postoperative management of hypoxic term or near-term infants with congenital heart disease.[11] More data from clinical trials are necessary to recommend routine prophylactic iNO administration in children who are at risk for pulmonary hypertension after congenital heart surgery.[17] A trial of iNO, however, is proposed in patients with significant pulmonary hypertension in the perioperative setting.[17,18]
Cavopulmonary circulations, Fontan-type procedures	iNO may be of use in the setting of cavopulmonary circulations. iNO administered in thirteen patients postoperatively after total cavopulmonary connection significantly decreased transpulmonary pressure gradient and improved oxygenation.[104] These findings were confirmed by a prospective randomized trial in forty-six patients with high PVR and impaired oxygenation after Fontan-type procedure. iNO significantly decreased the transpulmonary pressure gradient and improved the oxygenation, however, the combination of iNO with milrinone was even more effective.[105]		After cavopulmonary procedures a trial of iNO could be considered when a high transpulmonary gradient is present in the postoperative period.[18]

Abbreviations: iNO, inhaled nitric oxide; *PVR,* pulmonary vascular resistance; *RR,* relative risk.

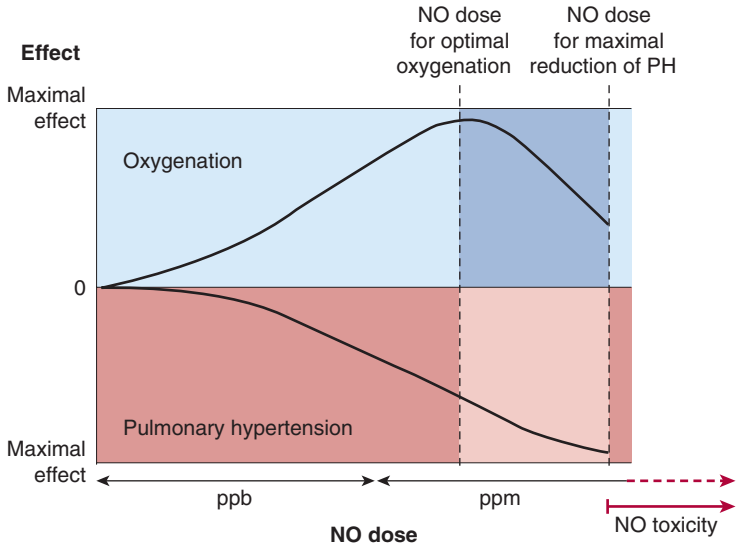

FIGURE 61-3 Schematic dose–response curve for patients with ARDS treated with iNO. Low doses of iNO (in the parts per billion range) are able to improve oxygenation whereas higher levels of iNO are necessary to significantly decrease the elevated PAP. Oxygenation improves to a maximum and then deteriorates at higher NO concentrations. Maximal reduction of PAP needs even higher doses of NO. It is recommended to verify the dose–response characteristics for each individual patient starting before NO treatment. *iNO,* inhaled nitric oxide; *NO,* nitric oxide; *PAP,* pulmonary arterial pressure; *PH,* pulmonary hypertension; *ppb,* parts per billion; *ppm,* parts per million.

deteriorated at higher NO doses; PAP further decreased with higher NO concentrations. Studies were stopped at 100 ppm.[21] Data suggest that higher doses of NO reach blood vessels supplying partially or nonventilated lung areas. For exact dosage, the registration of an individual dose–response curve for each patient is indispensable (Fig. 61-3). This approach is also desirable in patients with indications other than ARDS.

For improvement of oxygenation in adult patients with ARDS, iNO concentrations ranging from 1 to 20 ppm are effective, for reduction of mean PAP a dose in the range of 1 to 40 ppm is required.[22] Concentrations of 80 to 100 ppm should not be exceeded.

For neonates, it is recommended to start with a dose of 20 ppm iNO. If an improvement with iNO therapy is observed, the iNO concentration should be reduced to the lowest dose that sustains the response.[11]

RESPONDERS AND NONRESPONDERS

Regarding oxygenation and PAP, about a third of critically ill patients are nonresponders and do not react favorably to NO.[22] Reasons include persistent pulmonary blood flow to dorsal edematous lung areas; physical barriers, such as the presence of exudate or fibrosis; molecular mechanisms, such as increased activity of phosphodiesterase; unfavorable ventilator settings; and, most likely, a number of currently unknown factors. It appears sensible to evaluate a patient's response to iNO on a daily basis because initial nonresponders may convert to responders over time, and vice versa.

ADJUNCTIVE THERAPY

When the clinician faces a patient in acute respiratory failure who does not respond to iNO at all or the patient's response is very weak, adjunctive measures can positively change the situation.

Nonresponse to iNO may be related to lack of aerated lung tissue. Measures ensuring that the lungs inflate adequately and therapeutic options maintaining a sufficient end-expiratory lung volume, applied before NO inhalation, may lead to a satisfying NO response.

Re-evaluation of the level of positive end-expiratory pressure represents one of these measures. Recruiting additional alveoli may increase the number of alveoli, whereby NO can easily flow in and exert its beneficial effects. This idea has been tested in experimental and clinical trials. It was shown that when positive end-expiratory pressure led to alveolar recruitment, a rise in $P_{A_{O_2}}$ of more than 100 mm Hg could be achieved.[23,24]

Ventilating critically ill patients in the prone position may dramatically enhance oxygenation by antagonizing ventilation–perfusion mismatch. Exploiting this mechanism in patients receiving iNO therapy can further enhance oxygenation as compared with iNO in the supine position.[25]

Almitrine bismesylate acts as a pulmonary vasoconstrictor mainly in pulmonary vessels supplying hypoxic lung regions and reduces their perfusion. Theoretically, it was hoped that NO, a selective pulmonary vasodilator, and almitrine, a selective pulmonary vasoconstrictor, would act additively on oxygenation. iNO combined with almitrine was studied in patients with ARDS and during one-lung ventilation.[26,27] Addition of almitrine to iNO may lead to a further improvement in oxygenation, although a rise of

mean PAP of about 3 to 8 mm Hg has to be accepted. Given the potentially harmful effects of this strategy, its routine use is not advisable.

SIDE EFFECTS AND TOXICOLOGY

An adage attributed to the physician, astrologer, and theologian, Philippus Theophrastus Bombastus of Hohenheim, better known as Paracelsus (1493–1541), reads: "All substances are poisons; there is none which is not. The right dose differentiates a poison from a remedy." Regarding NO, this is surely true. Only a narrow margin exists between an effective and a toxic dose. Direct NO toxicity at clinically relevant doses, however, is uncommon, whereas exposure to NO_2 is potentially toxic.

Formation of Nitrogen Dioxide

NO reacts with O_2 and forms toxic nitrogen dioxide (NO_2). High O_2 concentrations combined with high NO concentrations react with the formation of that toxic by-product. Inhaled NO_2 at 2 ppm already affects alveolar permeability and NO_2 concentrations above 10 ppm may induce pulmonary edema, alveolar hemorrhage, methemoglobinemia, hypoxemia, changes in surfactant activity, hyperplasia of type II alveolar cells, intrapulmonary accumulation of fibrin, neutrophils, and macrophages, and eventually death.[28]

Synthesis of harmful concentrations of NO_2 is uncommon, especially when therapeutic doses of NO are inhaled. A study presented by the Cochrane Collaboration that analyzed fourteen randomized trials on acute lung injury/ARDS found no elevated risk for NO_2 formation associated with iNO therapy.[29] In clinical practice, it is recommended to limit the iNO concentration to 10 ppm or less when long-term application is necessary, to reduce possible genesis of toxic NO_2.[20] Alarm levels should be set to 2 ppm NO_2.[11]

Rebound after Nitric Oxide Withdrawal

During weaning from NO, its rapid withdrawal can cause marked rebound pulmonary vasospasm,[30] high intrapulmonary right-to-left shunt, and decreased PA_{O_2}.[31] Twenty-six percent of patients receiving iNO for acute hypoxemic respiratory failure (responders) exhibited only minimal changes in PA_{O_2} or hemodynamics after abrupt discontinuation of iNO, whereas 48% exhibited worsening of gas exchange. Another 26% of the patients reacted primarily with hemodynamic side effects. Reapplication of iNO immediately reversed the hemodynamic and oxygenation deterioration.[32] This phenomenon can be explained by downregulation of NO synthase activity in the presence of exogenous NO. In pediatric patients after cardiac surgery, longer continuation of iNO and its lower final concentration are factors that contribute to its successful weaning. Consequently, it seems prudent to slowly wean a patient from iNO. Rebound phenomena may be mitigated when iNO is not discontinued until a considerable clinical improvement is accomplished and the iNO dose is progressively reduced to 1 ppm before the gas is switched off. It is further recommended to increase FI_{O_2} before iNO cessation.[11]

Alternatively, the clinician can exchange NO for a different pulmonary vasodilator, or wait until the patient's endogenous production recommences. The drug sildenafil, given before discontinuation of iNO, has shown to effectively prevent rebound pulmonary hypertension in children.[33,34]

Systemic Vasodilation

For many years, a key characteristic of NO seemed to be its selectivity as a pulmonary vasodilator. This characteristic was explained by its rapid binding to the heme moiety of hemoglobin and its very short duration of action. Indeed, in many clinical trials and animal experiments, substantial effects on arterial blood pressure or other systemic circulation variables have not been observed. In some instances, however, reductions in systemic blood pressure and systemic vascular resistance were documented.[35,36] A new insight helps explain this phenomenon: NO can bind reversibly with albumin and hemoglobin and thereby enter the systemic circulation.[37–39] Circulating erythrocytes may be the vehicles that distribute NO to peripheral vascular beds. In areas of low O_2 tension, erythrocytes offload O_2 and NO, thereby inducing hypoxic vasodilation.[40] Furthermore, nitrite and nitrate, the oxidative end products of NO metabolism, exert systemic NO effects because they can be recycled to NO in blood and tissues.[41]

Methemoglobinemia

iNO can combine with hemoglobin to form nitrosyl hemoglobin, which is rapidly oxidized to methemoglobin. High iNO doses are associated with methemoglobin formation. In numerous clinical studies, however, severe methemoglobinemia was not observed with inhalation of NO. Two recent systematic reviews on the use of iNO in acute lung injury, revealed that methemoglobinemia is not a major concern when usual concentrations of iNO are applied.[8,29] It is recommended to measure methemoglobin level 4 hours after initiation of iNO and then once daily.[20] iNO is contraindicated in patients with methemoglobin reductase deficiency.[20] The patient, especially the neonate, should be weaned from iNO if methemoglobin level exceeds 5%.[11]

Interference with Surfactant

Analyses of surfactants recovered from experimental animals that had received 80 to 120 ppm iNO revealed reduced

quality, in terms of capacity to lower surface tension. It is unclear whether this is a consequence of the toxic actions of various NO by-products, such as peroxynitrite and NO_2, or if it is mediated by hemoglobin found in the alveoli when there is high-permeability lung edema.[42,43] Further experiments in preterm rabbits revealed that hyperoxia without iNO reduced large surfactant aggregates and surface activity. Addition of low-dose iNO (14 ppm per nose cannula) prevented or mitigated these deleterious effects on surfactant.[44]

Effects on Coagulation

Inhibition of human platelet aggregation by iNO has been reported in several studies. In addition, prolongation of bleeding time and inhibition of P-selectin expression with decreased binding of fibrinogen to the platelet glycoprotein IIb/IIIa receptor was demonstrated. Results from a randomized experimental animal study in twelve healthy piglets, however, do not support the hypothesis of an increased risk of bleeding associated with iNO. All coagulation variables including bleeding time were unaffected by iNO.[45] In healthy human volunteers, NO may[46] or may not[47] prolong bleeding time and exert effects on various coagulation variables. In patients with ARDS, iNO did not increase the risk of bleeding.[29] In infants with acute hypoxic respiratory failure, most randomized controlled trials did not report an increase in bleeding disorders with iNO therapy.[11] In premature infants with respiratory distress syndrome, however, a risk of intracranial hemorrhage may be considered.[14]

Nephrotoxicity

In the kidney, NO controls glomerular and tubular function, the tubuloglomerular feedback, renin release, and the extracellular fluid volume. Large amounts of NO may contribute to progression of renal disease, although NO may have protective qualities in acute renal failure.[48] Two large meta-analyses evaluated the adverse effects of iNO therapy.[8,29] Up to fourteen randomized, controlled trials of iNO treatment in children and adults with acute lung injury and ARDS were identified. Both meta-analyses reported a risk of renal impairment associated with iNO treatment in adults.[8,29] As the analysis of renal impairment was based only on four of all randomized, controlled trials, although the four studies enrolled 72% of the entire study collective, this result has to be interpreted with caution.[8]

A conclusive explanation for this observation cannot be offered. Inhibition of mitochondrial and enzymatic function, membrane damage or alterations of deoxyribonucleic acid have been discussed.[8] Renal failure in association with iNO treatment has not yet received much attention and needs further investigation.

SAFE INHALED NITRIC OXIDE THERAPY AND CONTRAINDICATIONS

Safe iNO therapy requires continuous analysis of NO and NO_2 concentrations, closely integrated respiratory and hemodynamic monitoring of the patient, periodic analyses of methemoglobin levels, use of certified NO delivery systems and tanks, and administration of the lowest concentration required. Rebound problems after withdrawal of iNO demand skill and endurance during weaning of the drug.

Contraindications to iNO therapy are based on its toxicology. In clinical practice, methemoglobin formation and elevated NO_2 levels are of interest, although both are uncommon during iNO therapy with normal therapeutic doses. These complications may become clinically important when patients are receiving higher doses of iNO. In patients with high levels of methemoglobin, additional iNO therapy may not be indicated and in patients with methemoglobin reductase deficiency, iNO therapy is contraindicated. The clinical risks of bleeding problems may be neglected. Data from large-scale meta-analyses in adults, children and infants did not reveal an elevated risk of coagulopathy associated with iNO. In patients with a hemorrhagic diathesis or coagulation or bleeding problems, however, iNO therapy should be well considered. There are indications that iNO might compromise renal function in adults with acute lung injury or ARDS. To date, this issue remains open.

THE FUTURE

What are upcoming scientific challenges in studying this extraordinary substance? What about the development of alternative NO therapies for the respiratory system?

First, more high-quality studies of diseases in which iNO therapy is of benefit are needed. These studies should evaluate not only survival rates with iNO therapy, but also outcome variables such as quality of life, cognitive impairment, and lung function. Dose–response studies for the different indications of iNO therapy are needed, and safety of long-term application of iNO should be investigated. The responder–nonresponder problem also needs to be probed.

Basic scientific work is needed to investigate the problem of the physiologic autoinhalation of endogenous NO from the paranasal sinuses, which is excluded in intubated and ventilated patients. It is assumed that some concentration of autoinhaled NO in the airways is necessary and protective against infection. During intubation and mechanical ventilation, low doses of iNO may restore the physiologic airway concentration of NO and protect against ventilator-associated pneumonia. It is possible that a patient's own nasal NO may be redirected into the inspiratory limb of the ventilatory circuit.

Therapy with iNO is expensive and technically demanding. Future research may yield cheaper, alternative drugs that selectively supply NO in ventilated lung regions. Inhalation

of prostacyclins, which also produces selective pulmonary vasodilation, may be a cheaper alternative, although further studies are necessary to advocate inhaled prostaglandins as a promising therapeutic option.

Is sildenafil the new iNO? In neonates with PPHN, sildenafil, administered orally or intravenously yielded promising results.[49,50] In most cases oxygenation improved significantly, and a randomized controlled trial of fifty-one term infants with PPHN reported a decrease in mortality.[50] It's a moot question, however, whether sildenafil is of benefit in adult patients with hypoxic respiratory failure. Limited data, however, suggest that sildenafil, does decrease PAP, but increases shunt fraction, which may make the drug unsuitable for treatment of patients with ARDS.[51]

The suspense continues. Will iNO survive in the long run or will it be replaced by intelligent, selective intravenous vasodilators?

SUMMARY AND CONCLUSION

NO is an important signaling molecule in the respiratory system. It modulates perfusion of lung units and it can prevent inflammatory processes. Administered by inhalation, low doses of NO selectively dilate pulmonary blood vessels in ventilated lung areas and redistribute blood flow from atelectatic to aerated lung units. When lower concentrations of iNO are applied, almost no systemic vasodilation can be observed because most of the NO rapidly binds to hemoglobin and is thus inactivated. The overall effect of NO inhalation is a sustained reduction of elevated PAP and improvement in oxygenation if a ventilation–perfusion mismatch of the lung is present. iNO is used to treat several cardiopulmonary disorders that are associated with hypoxia or pulmonary hypertension; its main application, however, is in neonatology. In infants with PPHN, iNO significantly reduces the need for ECMO. In no instance, however, was NO clearly shown to enhance long-term survival. There is no end in sight for the future role of NO inhalation. What we urgently need are more high-quality studies of the diseases in which iNO therapy is effective, and, hopefully, to demonstrate higher survival rates or at least improved secondary outcome variables, for example, reduced need of extrapulmonary oxygenation, fewer neurodevelopmental sequelae, or improved quality of life.

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62 DIAPHRAGMATIC PACING

Anthony F. DiMarco

Chronic respiratory failure requiring ventilatory support is usually caused by severe derangements in the function of the lungs, chest wall, and/or respiratory muscles. Mechanical ventilation is the only feasible option for most patients with these disorders. In certain patients, however, the function of the respiratory apparatus is completely intact except for lack of adequate nervous output from the respiratory centers in the medulla (central hypoventilation syndrome [CHS])[1–3] or interruption of electrical signals from the medulla to the respiratory motoneurons in the spinal cord, which innervate the major inspiratory muscles (cervical spinal cord injury). These patients can be offered an alternative means of respiratory support by diaphragmatic pacing (DP), a more natural and physiologic form of breathing.[3–12]

Although straightforward in concept, DP required several significant scientific developments before becoming a clinically useful modality. A brief historical perspective provides some insight into the evolution of DP and understanding of its clinical utility.

It was more than two centuries ago that Caldani[13] first observed that diaphragm movement could be achieved by electrical stimulation of the phrenic nerve in animals. In the first human demonstration (1818), Ure[14] stimulated the phrenic nerve and restored breathing in a criminal immediately following execution. In the latter portion of the nineteenth century, the application of moistened sponges over the outer borders of the sternocleidomastoid muscles resulted in activation of the phrenic nerves, and this technique became an accepted method of restoring ventilation.[15,16] Duchenne found phrenic nerve stimulation to be the best method of producing natural respiration[17] and is credited to have placed electrophrenic stimulation on a solid physiologic foundation.[18] In the 1940s, Sarnoff et al[19,20] demonstrated that ventilation could be maintained in an acute setting in patients with bulbar poliomyelitis utilizing percutaneous electrodes. The lack of implantable devices that were safe and reliable, however, limited the long-term usefulness of DP to support ventilation. Consequently, the technique of phrenic nerve stimulation was supplanted by the development of the more reliable mechanical ventilators.

In the 1960s, the critically important work of Glenn et al resolved major technological issues, which led to the development and implementation of modern-day pacing systems.[21–23] These investigators defined the appropriate patient selection criteria, preoperative assessment methodology, surgical methods including optimal electrode placement, and appropriate stimulation parameters necessary to achieve full-time ventilatory support.[8–12,23,24] Further refinements to this early design were made by other investigators with regard to improved electrode design[25,26] and less-invasive methods of electrode placement.[27–30] As a consequence, DP

TABLE 62-1: POTENTIAL BENEFITS OF DIAPHRAGMATIC PACING

A. Improved quality of life
   1. Subjective sense of more normal breathing
      a. Utilization of breathing muscles
      b. Negative-pressure respiratory support
   2. Improved comfort level
      a. Elimination of pull of ventilator tubing
      b. Negative-pressure breathing
   3. Improved speech
   4. Restoration of olfactory sensation
   5. Increased mobility
      a. Easier transport outside the home
      b. Easier transfer to and from bed
   6. Reduced anxiety and embarrassment
      a. Elimination of ventilator noise
      b. Elimination of fear of ventilator disconnection
      c. Elimination of ventilator tubing
      d. Daytime closure of tracheostomy
B. Reduced overall costs
   1. Reduction or elimination of ventilator supplies
   2. Reduced level of nursing and respiratory therapy services

Source: Used, with permission, from Dimarco.[31]

has evolved into a safe and practical method of providing ventilatory support in select patient groups.

RATIONALE FOR DIAPHRAGMATIC PACING

For patients requiring chronic ventilatory support, DP provides several advantages compared to mechanical ventilation (Table 62-1).[5,6,11,31–35] Although the realized benefits of DP are subjective and vary between individuals, most patients describe an improved sense of well-being and overall health. This impression can be attributable to one or more factors. Because patients are utilizing their own breathing muscles, patients relate the sensation of more normal breathing. Negative pressure ventilation also has the potential to reduce the incidence of barotrauma and may have beneficial cardiovascular effects.[36] Because ventilator tubing is unnecessary, tension on the tracheostomy tube by attached tubing is eliminated, improving patient comfort.

Although the volume of speech may be less with DP than with mechanical ventilation, quality of speech is often improved because ventilator interference is eliminated. Speech can also be enhanced by use of an abdominal binder.[37] Olfactory sensation is also restored with DP contributing to improvement in life quality.[38] There is some evidence that the incidence of respiratory tract infections is less with DP compared to mechanical ventilation. In a prospective clinical trial of sixty-four patients over a 20-year period, there were significantly fewer respiratory infections in DP patients compared to those on mechanical ventilaton.[39] The patients on mechanical ventilation, however, were significantly older compared to those on DP (mean: 53 vs. 29 years old).[39]

A life-support system that requires attachment to a mechanical ventilator by connecting tubing is extremely restrictive. Patient mobility and patient transport therefore is usually enhanced by DP. Simple daily maneuvers such as transfer from bed to chair are less cumbersome and eventful. Transport of patients outside the home is also easier. Improved mobility may allow patients to acquire gainful employment, become eligible for participation in specific rehabilitation programs, and participate in more social events.[31,34,40–42] In a recent study, improved mobility and sense of freedom were described as the main benefits of DP.[38]

Other concerns for many patients include social embarrassment because of ventilator noise, attached tubing, and being tethered to a machine. Many patients cannot support themselves off the ventilator and live in constant fear of disconnection. By comparison, DP is virtually indistinguishable from normal breathing by observers, and the fear of ventilator disconnection is eliminated.

The institution of DP is very expensive. With direct phrenic nerve stimulation systems, total costs can easily exceed $100,000. Although substantially less, the total costs of the intramuscular DP system can be expected to exceed $40,000. Once in place, however, servicing and maintenance costs are minimal.[33,43] Despite the high initial cost, it can be argued that DP is cost effective. Many patients are transferred to less intensive and less expensive care settings.[31,32,44] The high cost of maintenance supplies necessary with mechanical ventilators is reduced. Because most patients who undergo DP are young and require respiratory support for many years, these cost savings can be substantial.[44–46]

EQUIPMENT

There are two basic types of commercially available DP pacing systems. In the first, electrodes are implanted directly on the phrenic nerves (direct phrenic nerve stimulation system). In another, more recently developed system, electrodes are implanted within the diaphragm (intramuscular DP system).

Direct Phrenic Nerve Stimulation Systems

Each of these systems is very similar in design, consisting of both implanted materials and external components (Fig. 62-1A). The electrodes and radiofrequency receivers comprise the surgically implanted components. An external power supply, radiofrequency transmitter, and antenna wires comprise components outside of the body.

With each system, a single stimulating electrode is surgically positioned on each phrenic nerve. With unipolar systems, an indifferent electrode is also implanted subcutaneously.[10] Wires are tunneled subcutaneously to connect each electrode to a radiofrequency receiver that is

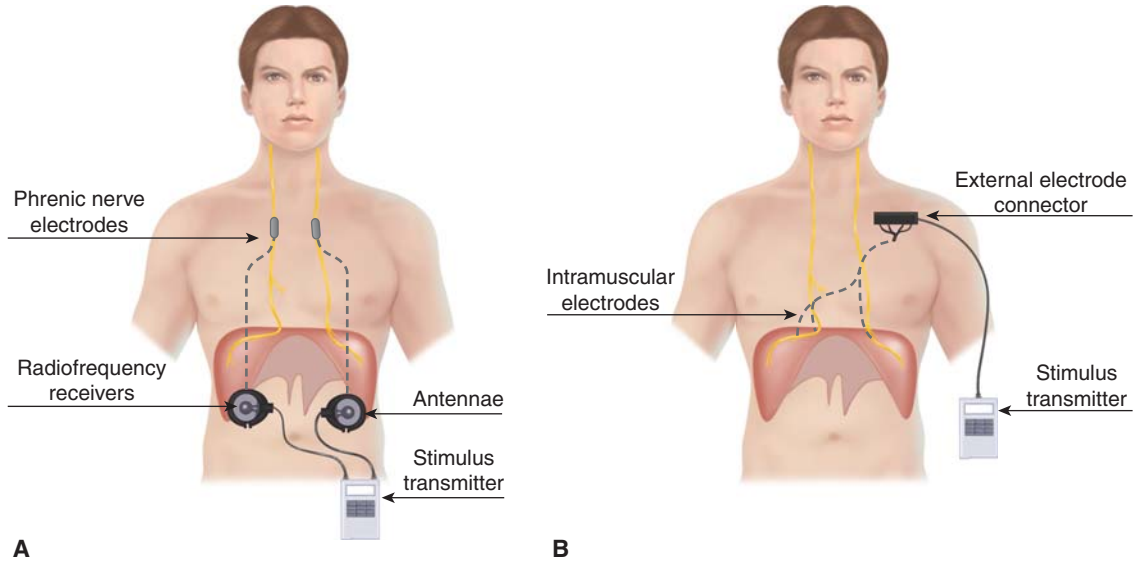

FIGURE 62-1 Basic design of commercially available diaphragmatic pacing systems. Direct phrenic nerve stimulation system (**A**) and intramuscular diaphragmatic pacing system (**B**). With the direct phrenic nerve stimulation system, the internal components consist of a single electrode implanted on each phrenic nerve in the thorax with a wire connected to each implanted radiofrequency receiver. The external components consist of a stimulus transmitter and attached rubberized antennae, which must be positioned over the radiofrequency receivers. The receiver converts radiofrequency signals from the transmitter into electrical signals, which stimulate the phrenic nerves to activate the diaphragm. With the intramuscular diaphragmatic pacing system, two wires are implanted into the body of each hemidiaphragm near the phrenic nerve motor points. These wires are tunneled subcutaneously to a site over the chest wall where they exit the skin and are attached to an external electrode connector.

positioned over the anterior chest wall, usually over the lower rib cage.[10] The external battery-powered transmitter generates radiofrequency signals, which are inductively coupled to the receivers via circular rubberized antennas. Each antenna must be positioned directly over each receiver and secured in place to ensure proper transmission of the signal. The transmitter signal is demodulated by the receivers, converting the radiofrequency signals to electrical signals, which are transmitted to the electrodes to stimulate the phrenic nerves and activate the diaphragm.[10,20]

The transmitter allows adjustment of stimulus amplitude (milliamperes [mA]) and stimulus frequency (Hertz [Hz]) to modulate the magnitude of tidal volume. Respiratory rate can be adjusted by altering the train rate. Inspiratory time and inspiratory flow rate can be adjusted, in tandem, by alterations of stimulus on-time. Sigh breaths can also be provided.

Surgical techniques have been developed for both cervical and thoracic placement of phrenic nerve electrodes.[8–12] Although less invasive from a surgical standpoint, the cervical approach has significant disadvantages. First, an accessory branch from a lower segment of the cervical cord may join the main trunk of the phrenic nerve low in the neck or in the upper thorax.[9] Activation of the cervical portion of the phrenic nerve may therefore lead to incomplete activation of the phrenic nerve and reduce the chance of successful pacing. Second, other nerves in close proximity to the phrenic nerve may also be activated, resulting in pain and/or unwanted movement.[41] Finally, neck movement may displace the electrode, resulting in incomplete diaphragm activation and/or place significant mechanical stress on the nerve increasing the risk of injury. Consequently, the thoracic approach is the preferred method of implantation.[26,32,48]

Phrenic nerve electrodes have been successfully placed thoracoscopically.[30,48] This procedure involves placement of trocars in several intercostal spaces and is technically quite demanding. Successful pacing was achieved for 12 to 14 hours/day while awake in a small group of children, primarily for management of congenital CHS. Moreover, although less invasive than thoracotomy, these patients also developed complications of pneumonia, atelectasis, and pneumothorax postoperatively. Additional studies are necessary to determine the long-term success of this procedure and its applicability to patients with cervical spinal cord injury.

Of the three commercially available DP systems, only the Avery system is available worldwide. Table 62-2 lists the technical characteristics of each device.

AVERY LABORATORIES MARK IV

Glenn et al performed the basic science and clinical studies that led to the commercial application of the Avery (Commack, NY) system in the 1960s.[49,50] The electrode consists of a semicircular platinum-iridium ribbon embedded in molded silicone rubber. The electrode contains a shallow trough for placement of the phrenic nerve. Monopolar and bipolar electrodes (recommended for patients with

TABLE 62-2: TECHNICAL FEATURES OF DIAPHRAGMATIC PACING SYSTEMS

Manufacturer	Avery Laboratories	Atrotech OY	Medimplant
Transmitter (stimulus generator)	Mark IV[a]	PX 244	Medimplant 8-channel stimulator
Size (mm)	146 × 140 × 25	185 × 88 × 28	170 × 130 × 51
Transmitter/battery weight (kg)	0.54	0.45 + 0.6 (12V) 0.45 + 0.046 (9V)	1.42
Rate (breaths/min)	6 to 24	8 to 35	5 to 60
Amplitude (mA)	0 to 10	0 to 6	0 to 4
Pulse width (μs)	150	200	100 to 1000
Battery life (hours)	400	160-320 (12V) 8 (9V)	24
Sigh possible	Yes	Yes	Yes
Antenna	902A	TC 27-250/80	RF transmission coil
Receiver	Model I-110A	RX 44-27-2	Implantable receiver
Size (mm)	30 (diam) × 8	49 (diam) × 8.5	56 × 53 × 14
Electrodes	Monopolar, bipolar	Quadripolar	Quadripolar
No. of receivers to stimulate both hemidiaphragm	2	2	1

[a]The Mark IV supersedes all earlier versions manufactured by Avery Laboratories. Most patients implanted with earlier models have been upgraded to the Mark IV without surgery.

Source: Used, with permission, from DiMarco.[31]

cardiac pacemakers) are available.[9] The recent Avery Mark IV transmitter is lighter and provides a wider range of stimulus amplitudes than previous models.[33] An optional interface also allows biofeedback control from pulse oximetry and CO_2 monitoring.[33] Transtelephonic monitoring is available, which allows the electronic output and neurophysiologic response of the pacing system to be monitored by telephone.[51]

ATROTECH OY

The unique feature of the Atrotech (Tampere, Finland) system lies in its electrode technology, which consists of a four-pole electrode design.[25,52] The electrode consists of two identical strips of Teflon fabric with two platinum buttons mounted onto each strip. Theoretically, when appropriately placed, the phrenic nerve is divided equally into four stimulation compartments. Each quadrant of the nerve, which supplies a specific set of diaphragm motor units, is stimulated sequentially. During one stimulus sequence, which consists of four current combinations, one pole in turn acts as a cathode and one pole on the opposite side as an anode. The result is four excitation compartments around the nerve. Combined stimulation of all quadrants of the nerve (each at 5 to 6 Hz) results in activation of the diaphragm near its optimum fusion frequency of 20 to 25 Hz, resulting in smooth contraction of the diaphragm.[25,52]

By this method, the stimulation frequency of individual axons is less than with monopolar stimulation. The slower stimulus frequency should provide more time for recovery, improve the endurance characteristics of the diaphragm, and shorten the conditioning process, compared to conventional unipolar stimulation.[25,52,53] This technique had been approved by the FDA through an investigational device exemption. As of October 2005, however, the investigational device exemption study has been terminated. Therefore, this device is no longer available in the United States.

MEDIMPLANT BIOTECHNISCHES LABOR

The Medimplant Biotechnisches Labor (Vienna, Austria) system is also differentiated by a unique electrode design.[26] A complex microsurgical technique involving placement of four electrode leads around each phrenic nerve is required. The nerve tissue between each electrode lead comprises different stimulating compartments, only one of which is stimulated during any single inspiration. The various compartments are stimulated in sequence during subsequent inspirations (carousel stimulation).[54] Sixteen different electrode combinations can be adjusted individually for each nerve. Similar to the Atrotech device, only a portion of the nerve is stimulated at any given time, allowing more recovery time and therefore less chance for the development of fatigue compared to the unipolar design. Availability of this system is limited predominantly to Austria and Germany.

Intramuscular Diaphragmatic Pacing System

The phrenic nerves can also be activated via placement of electrodes directly into the diaphragm (Fig. 62-1B).[27,28,55,56] The major advantage of this method compared to direct phrenic nerve stimulation systems is that electrode placement does not require a thoracotomy. A thoracotomy

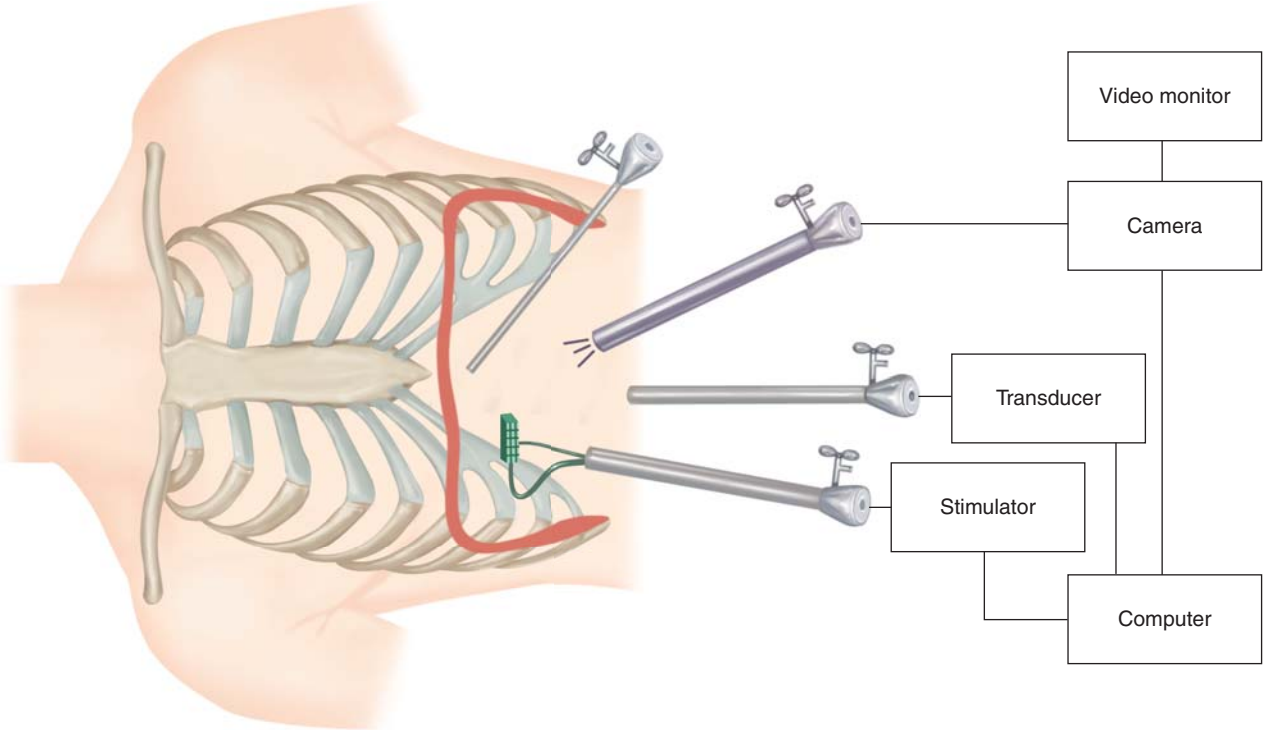

FIGURE 62-2 Schematic of laparoscopic implant materials required for implantation of intramuscular diaphragmatic electrodes. Four laparoscopic ports are necessary to provide access to the abdominal cavity. Ports are necessary for visualization, insufflation of the abdominal cavity, diaphragmatic mapping, and insertion of the electrode implant tool. (Reprinted with permission of the American Thoracic Society. Copyright © 2012 American Thoracic Society. DiMarco AF, Onders RP, Kowalski KE, et al. Phrenic nerve pacing in a tetraplegic patient via intramuscular diaphragm electrodes. *Am J Respir Crit Care Med.* 2002;166:1604–1606. Official Journal of the American Thoracic Society.)

is associated with significant perioperative morbidity, requiring an inpatient hospital stay and high cost. These disadvantages have limited the number of patients undergoing this procedure and are significant obstacles for patients undertaking phrenic nerve pacing. Intramuscular diaphragm electrodes can be positioned using minimally invasive laparoscopic techniques. This procedure can be performed on an outpatient basis or with an overnight observational stay, significantly reducing costs.[27,28,56,57] The risk of nerve injury is virtually eliminated because this procedure does not require manipulation of the phrenic nerve. Postoperative pain is less for patients with CHS and recovery times are reduced significantly.

SYNAPSE BIOMEDICAL

Conventional laparoscopy is employed for electrode placement of the Synapse Biomedical (Oberlin, OH) system.[58] Four laparoscopic ports are required to provide access to the abdominal cavity for visualization, insufflation of the abdominal cavity, diaphragm mapping, and insertion of the implant tool (Fig. 62-2). Specially designed surgical tools and intramuscular electrodes are required for implantation.[27–29,59–61] Two intramuscular electrodes are implanted into each hemidiaphragm near the phrenic nerve motor points (Fig. 62-3).[62,63] A mapping procedure is required for appropriate electrode placement.[27,28] By this method, full-time respiratory support can also be maintained in ventilator-dependent tetraplegic patients (both children and adults) with success rates similar to those of direct phrenic nerve stimulation.[19,27,28,34,64] It is important to note that despite the fact that electrodes are positioned within the diaphragm muscle, the mechanism of diaphragmatic activation by this method is stimulation of the phrenic nerve motor points. This technique, therefore, represents a form of phrenic nerve stimulation, rather than direct diaphragm muscle stimulation.

Combined Intercostal and Diaphragmatic Pacing

Many patients with cervical spinal cord injury have damage to one or both phrenic motor neuron pools in the spinal cord and/or phrenic rootlets, and therefore cannot be offered DP.[31,65,66] By placing electrodes epidurally on the ventral surface of the upper thoracic spinal cord, however, the inspiratory intercostal muscles of the upper rib cage can also be stimulated to produce large inspired volumes.[67–69] Moreover, gas exchange during intercostal breathing alone is comparable to diaphragmatic breathing.[70]

In initial clinical trials, in patients with absent diaphragmatic function, stimulation of the intercostal muscles alone produced inspired volumes of similar magnitude to those

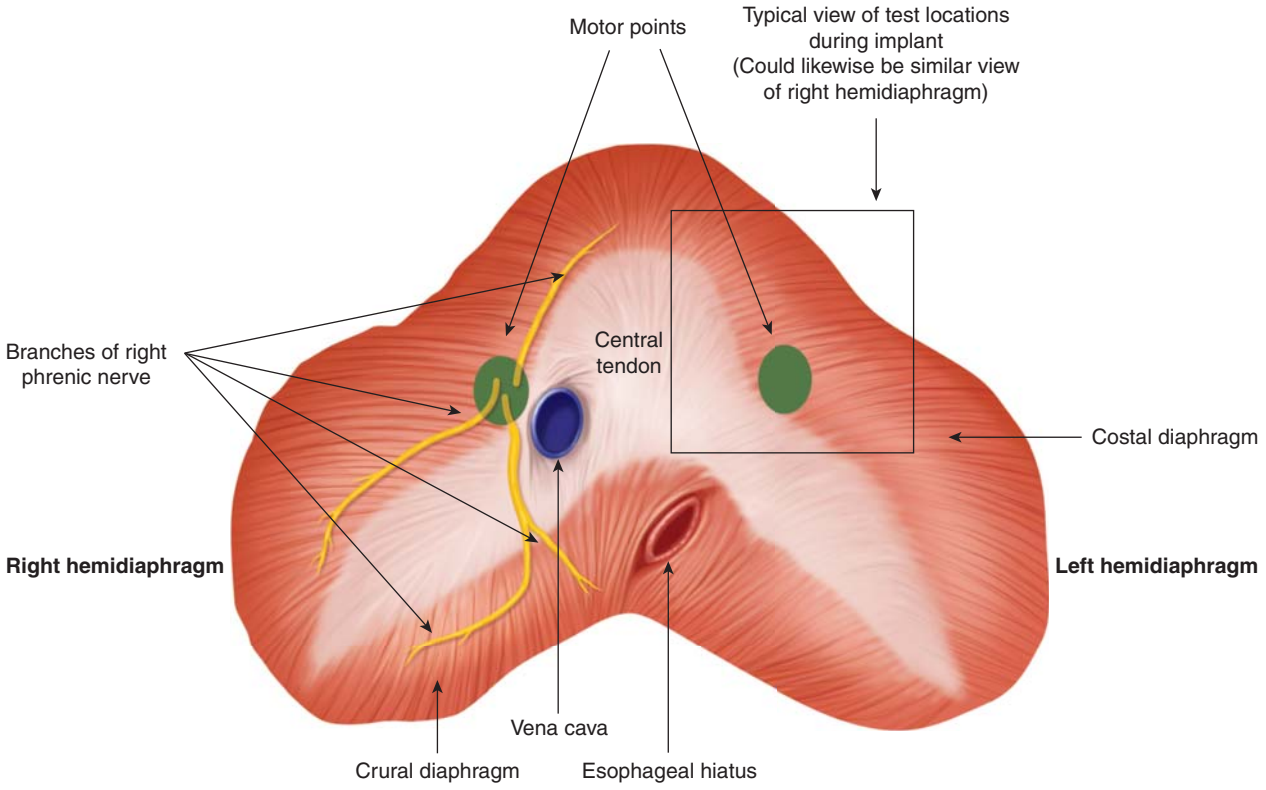

FIGURE 62-3 Schematic of the anatomy of the diaphragm from the abdominal surface and entrance points of each phrenic nerve into each hemidiaphragm (phrenic nerve motor points). (Reprinted with permission of the American Thoracic Society. Copyright © 2012 American Thoracic Society. DiMarco AF, Onders RP, Kowalski KE, et al. Phrenic nerve pacing in a tetraplegic patient via intramuscular diaphragm electrodes. *Am J Respir Crit Care Med.* 2002;166:1604–1606. Official Journal of the American Thoracic Society.)

resulting from activation of a single hemidiaphragm.[69] Inspired volume, however, was not sufficient to support ventilation for prolonged periods. In subsequent trials in tetraplegic patients with unilateral diaphragm function, however, stimulation of the intercostal muscles in combination with unilateral phrenic nerve stimulation was successful in providing long-term ventilatory support.[71]

Side effects of intercostal muscle stimulation included mild flexion of both hands and contraction of the muscles of the upper torso, which was well tolerated.[69,71] Intercostal pacing may be a useful adjunct to enhance tidal volume in patients whose inspired volume with phrenic nerve pacing is suboptimal.

This technique is not yet commercially available but has received approval by the FDA through an investigational device exemption.

PATIENT SELECTION

As mentioned, DP provides clinical benefit in two patient groups: ventilator-dependent tetraplegics[8,11,34] and patients with CHS.[5,6,72] Although phrenic nerve pacing has been tried in patients with chronic obstructive pulmonary disease to prevent ventilatory depression associated with oxygen administration,[73] noninvasive ventilator support is of equal or greater effectiveness.

In all patients, significant lung, chest wall, cardiac, or primary skeletal muscle disease must be excluded because these conditions may preclude successful pacing.[40,47,74]

Ventilator-Dependent Tetraplegia

Respiratory failure is common following acute cervical spinal cord injury.[65,66] Fortunately, most patients achieve significant recovery following their initial presentation and are able to breathe spontaneously. Nonetheless, approximately 4% require lifelong respiratory support.[57] Although the time course of recovery is variable, the degree of impairment is likely permanent 12 to 15 months following injury.[66,75] Given the high cost and the invasive procedure required, direct phrenic nerve DP should not be considered before this time. However, given the minimally invasive nature of intramuscular DP, and the significant advantages of DP compared to mechanical ventilation, much earlier placement of this system should be considered. In the event that the clinical status of the patient improves to the point that spontaneous breathing is restored, the DP system can be removed.

Vigorous attempts should be made to wean tetraplegic patients from mechanical ventilation. Vital capacity measurements of less than 10 mL/kg suggest inadequate inspiratory muscle function to maintain spontaneous breathing.[66] In some patients with sufficient inspiratory muscle strength,

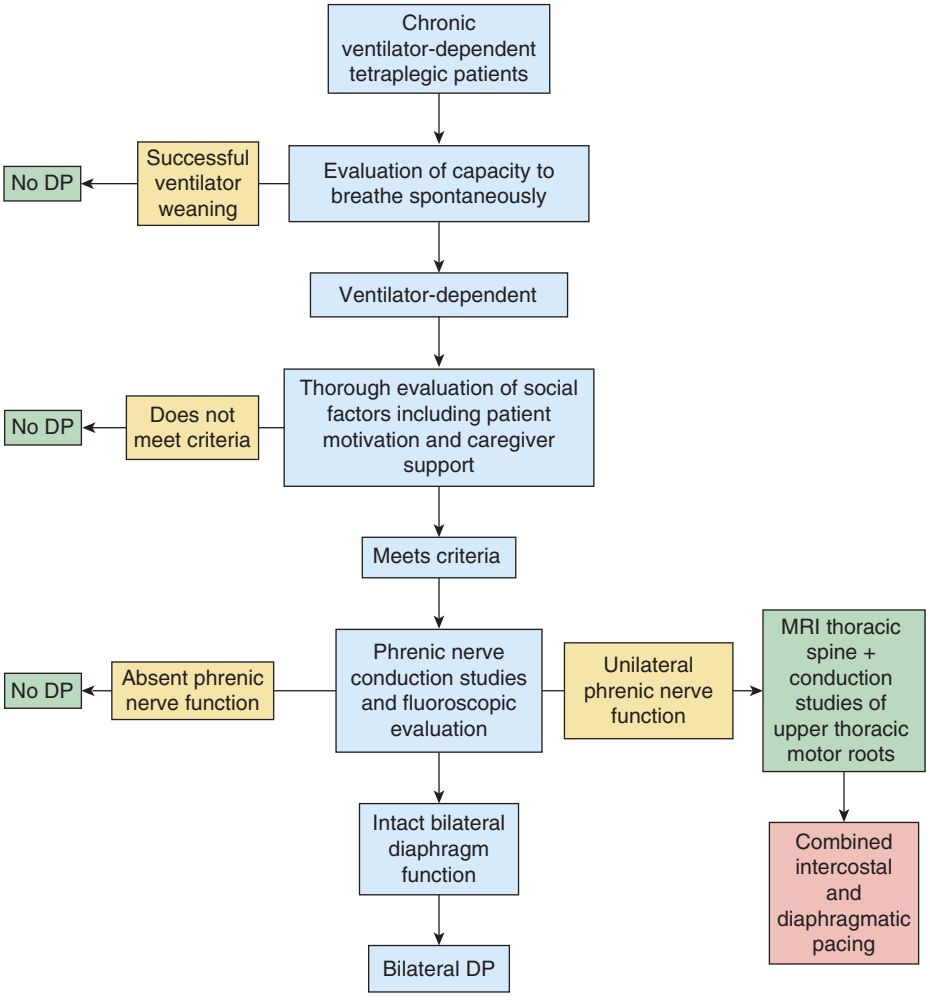

FIGURE 62-4 Evaluation of potential candidates with cervical spinal cord injury for diaphragmatic pacing.

however, noninvasive ventilator support may be a suitable alternative to DP.[76,77]

Individual psychosocial conditions are important factors in the ultimate success of phrenic nerve pacing.[27,31,34,49] A high level of motivation and cooperation of the patient and family members is imperative. A home situation in which the family unit is anxious to improve the mobility, social interaction, occupational potential, and ability of the patient to function independently is optimal. Consequently, a psychosocial evaluation should be conducted before any technical evaluation. Figure 62-4 shows the evaluation process of potential candidates for DP.

Central Hypoventilation Syndromes

Patients with CHS consist mainly of infants and children. Pacing is not instituted before 6 to 12 months of age to allow time to identify other potential abnormalities and determine the full extent of the ventilatory deficit.[4] CHS can be congenital[1–3] or secondary to brainstem injury from injury, bleeding, tumor, encephalitis, or Arnold-Chiari malformations.[4,11] To assess the presence and degree of hypoventilation, arterial blood gases, nocturnal polysomnograms, and ventilatory responses to hypercarbia and hypoxia should be performed.

The diagnosis of congenital CHS is usually made shortly after birth. Many of these patients have normal wake ventilation and therefore require DP only during sleep.[3–5] Patients who require full-time ventilator support are paced during the day and maintained on mechanical ventilation during sleep. A psychosocial evaluation of these patients should also be performed.

Evaluation of Phrenic Nerve Function

Before instituting DP, a thorough evaluation of phrenic nerve function is mandatory in all patients.[10,23,27,72] Phrenic nerve function can be assessed by measurements of nerve conduction times.[45,78,79] Diaphragmatic action potentials are monitored by surface electrodes positioned between the

seventh and ninth intercostal spaces. The phrenic nerves can be electrically stimulated by surface electrodes or monopolar needle electrodes at the posterior border of the sternocleidomastoid muscle at the level of the cricoid cartilage. Electrical current is applied with single pulses of gradually increasing intensity until a supramaximal M wave is seen. With stimulation, the abdominal wall expands outward. Phrenic nerve conduction time can be determined by measuring the time interval between the applied stimulus and onset of the compound muscle action potential (CMAP). Phrenic nerve function can also be assessed by cervical magnetic stimulation of the phrenic nerves.[80,81] Mean onset latency is 7 to 9 milliseconds in normal adults.[45,78,79] Mild prolongation of conduction times (up to 14 milliseconds), however, does not preclude successful pacing.[12] In children, latencies are significantly shorter at 2.2 milliseconds at 6 months of age, but increase to 4.2 milliseconds between 5 and 11 years of age.[7,82] The magnitude of the CMAP is a less reliable indicator of phrenic nerve function compared to conduction time.[32,78]

Fluoroscopy is also a useful method to assess phrenic nerve function. The diaphragm should descend at least 3 to 4 cm following stimulation.[10,31,45] In children with CHS, diaphragmatic descent of at least two rib spaces following spontaneous effort indicates adequate phrenic nerve function.[4] In this population, phrenic nerve stimulation is reserved for patients in whom the fluoroscopic results are questionable.

A recent study[83] evaluated the use of diaphragmatic compound muscle action potentials (CMAPs) to evaluate phrenic nerve function. The investigators found that diaphragmatic CMAPs were recorded only when the diaphragm was observed to move on fluoroscopic examination. These results suggest that assessment of the presence of diaphragmatic CMAPs can be used interchangeably with fluoroscopic evaluation to assess phrenic nerve integrity. Because of false-positives and false-negatives associated with conduction time measurements, and technical challenges associated with this test, fluoroscopy should be performed on all patients being evaluated for DP (personal observation).

Phrenic nerve function can also be assessed by measurements of transdiaphragmatic pressure (Pdi) (i.e., the pressure difference across the diaphragm).[43] By this method, small balloon-tipped catheters are placed into the esophagus and stomach to determine intrathoracic and intraabdominal pressures, respectively. Single-shock stimulation results in Pdi values of approximately 10 cm H_2O for each side in normal subjects.[84] Because of diaphragmatic atrophy, this value may be reduced significantly in ventilator-dependent patients. In spontaneously breathing individuals, diaphragmatic strength can be assessed by measuring Pdi during a maximal sniff maneuver.[84]

IMPLEMENTATION

The various surgical techniques to implant electrodes necessary for DP have been described elsewhere[9,12,85] and are beyond the scope of this chapter.

DP should not commence until 10 to 14 days postoperatively to allow resolution of inflammation and edema at the electrode–nerve interface and initial healing of surgical wounds.[10] In patients who have been maintained on mechanical ventilation for prolonged periods, the transition to DP requires a gradual conditioning period, because of diaphragmatic atrophy.[11,23,24,86] Too rapid institution of pacing carries the risk of diaphragmatic fatigue and possible injury.

Determination of Stimulus-Output Values

Ideally, several parameters should be determined initially and then monitored regularly.[12,32] These include stimulus threshold values (minimum stimulus amplitude that results in visible or palpable diaphragmatic contraction) and supramaximal amplitudes and frequencies (lowest stimulus parameters that result in maximum inspired volume production). Changes in airway pressure during airway occlusion also provide a useful assessment of diaphragmatic force. The magnitude of inspired volumes and force generation gradually increase during the conditioning phase. Plateaus in these indices over time suggest that the conditioning phase is complete and optimum diaphragmatic function has been achieved. Assessment of diaphragmatic action potentials may also be useful in the determination of maximum stimulus amplitude.[4]

Determination of Stimulus Parameters to Achieve Adequate Ventilation

Utilizing supramaximal amplitudes, tidal volume is adjusted by changing stimulus frequency. With respiratory rates (stimulus train rates) between 8 and 14 breaths/min, stimulus frequency is adjusted to achieve inspired volumes resulting in partial pressure of carbon dioxide (P_{CO_2}) values in the low normal range. Stimulus frequency should be set at the lowest level possible and should not exceed 20 Hz. Respiratory rate and tidal volume are further adjusted for patient comfort. Inspired volume measurements should be made both in the supine and upright postures. While sitting, spinal cord-injured patients should wear a snug fitting abdominal binder because of the shorter diaphragm length and higher resting lung volume associated with this posture. Higher stimulus parameters may be required in this posture to achieve adequate ventilation.

Institution of Diaphragmatic Pacing

The methods of transition from mechanical ventilation to pacing are somewhat arbitrary. With the objective of achieving full-time DP as quickly as possible, but without the development of diaphragmatic fatigue, the following protocol is suggested. Utilizing the above-mentioned stimulus parameters, continuous bilateral DP is initially provided

until significant blood gas derangements (reductions in oxygen saturation or elevations in end-tidal P_{CO_2}), reductions in inspired volume generation (monitored every 5 to 10 minutes), or patient discomfort related to air hunger are observed. Pacing is then initiated for a somewhat shorter time period (approximately 5 minutes) every hour during the day, for the first week. This assessment is repeated weekly and a new pacing schedule is applied accordingly. After full-time pacing is achieved during wakefulness, pacing is provided during sleep. Most patients cap their cuffless tracheostomy tube while pacing during the daytime. During sleep, however, airflow through the tracheostomy should be maintained to prevent upper airway obstruction. This occurs secondary to the dyssynchrony between upper airway and diaphragmatic contraction during sleep.[5,23]

Previous studies have demonstrated that chronic diaphragmatic stimulation at high frequencies can be associated with myopathic changes and consequent reductions in force generation.[8,34,87] Consequently, it is important that DP occur at low stimulus frequencies (<20 Hz), which convert the diaphragm from a mixed-fiber-type population to predominantly high-oxidative, slow-twitch fatigue-resistant type I fibers.[8,88] As the conditioning phase progresses, stimulation frequencies and respiratory rates should be gradually reduced to the lowest values that maintain adequate ventilation and patient comfort. With the Avery system, stimulation frequency can usually be reduced to 7 to 9 Hz with respiratory rates of 6 to 12 breaths/min in the supine position.[8] Less adjustment is usually required with the Atrotech device secondary to the initial application of low frequencies via sequential nerve stimulation. With intramuscular stimulation, stimulation is initiated with four electrodes at 20 Hz. Stimulation frequency can be reduced to as low as 11 Hz with stimulation of only two electrodes.[27] Infants and young children require higher respiratory rates in the range of 20 breaths/min, but can be maintained with lower inspiratory times of 0.6 to 0.9 second compared to the requirement of 1 to 1.4 second in adults.[5,89] Conditioning time can vary between 4 weeks and several months. In most instances, however, conditioning is accomplished within 6 to 10 weeks.

In patients with CHS who employ DP only during sleep, DP should be adjusted in a sleep laboratory.[4] Given the high compliance of the rib cage and higher ventilatory requirements, bilateral pacing is always necessary to support ventilation in infants and young children.[4,5] In patients undergoing daytime pacing, pacing parameters must be reevaluated because ventilatory requirements are typically higher during wakefulness.

Combining Pacing with Mechanical Ventilation

Full-time pacing is generally not advisable in infants and small children to avoid fatigue and the risk of permanent injury to the diaphragm and phrenic nerves.[3–5,89] Consequently, children with tetraplegia and those with CHS who require full-time ventilator support utilize DP during the day and are maintained on mechanical ventilation at night.[3] Likewise, adult patients who do not achieve inspired volumes sufficient to maintain full-time pacing can be maintained on ventilator support at night. Because the major advantages of DP are realized during the day and most patients still require a tracheostomy, part-time DP does not detract significantly from the benefits of this device.

In some instances, patients cannot tolerate significant time off mechanical ventilation and initial inspired volumes achieved by pacing are insufficient to maintain adequate ventilation for even short periods.[59] In these patients, the initial phase of muscle reconditioning can be performed in conjunction with mechanical ventilation. This can be accomplished by setting the ventilator in the assist mode. The negative inspiratory pressure generated at the tracheal opening by pacing can be used to trigger the ventilator.

EFFECT OF DIAPHRAGMATIC PACING ON PATIENT OUTCOME

Clinical studies reveal that DP is a feasible and effective means of providing ventilatory support in patients with tetraplegia and CHS. In most patients requiring full-time ventilatory support, DP can be utilized as the sole mode of respiration.[8,11,27,34]

The actual success rate of DP, however, is difficult to ascertain because most patients have undergone this technique at centers where patient numbers are small.[35,41,90] Moreover, previous large series have evaluated the outcome of DP while technology was still in development.[23,91–93] Consequently, these results are not applicable to systems available today.

In a recent report, the clinical outcome of patients whose DP systems were implanted before 1981 was compared to patients implanted between 1981 and 1987.[34] The earlier group underwent high-frequency DP; the success rate in terms of achieving full-time pacing was small because of the development of diaphragmatic fatigue. The latter group underwent low-frequency stimulation at low respiratory rates; DP was successful in each of the twelve patients, stressing the importance of current pacing regimes. Six patients continued pacing for a mean duration of 14.8 years. The other six patients did not achieve sustained long-term pacing because of lack of adequate financial and social support or concomitant medical conditions. The results of this analysis indicate that the long-term success of DP depends heavily on adherence to strict criteria for patient selection. High success rates have also been observed in infants and children in whom a more modest goal of part-time pacing (<15 hours/day) was achieved.[4]

The more recently developed quadripolar electrode design and receiver (Atrotech OY) is associated with high success rates. Based on analysis of sixty-four patients, successful pacing was achieved in 94% of pediatric and 86% of

adult patients.[53] At the time of study, however, the average duration of pacing was approximately 2 years.

COMPLICATIONS AND SIDE EFFECTS

Technical developments and clinical experience with DP over the past 20 years have markedly reduced the incidence of complications and side effects. With modern-day equipment, appropriate patient selection, proper use of stimulus paradigms, and adequate patient monitoring, complications are few. As with any life-support system, patients must be carefully monitored because pacemaker failure can have catastrophic consequences. For this reason, all patients who are unable to maintain adequate spontaneous ventilation for prolonged periods should have emergency access to mechanical ventilation.

Several technical problems can cause reductions in volume production (Table 62-3). The most common cause of mechanical failure is loss of battery power. With current pacing systems, however, routine maintenance requires regular battery changes and recharging schedules. Low-battery alarms are also present. Breakage of the external antenna wires at stress points, either near the connection to the transmitter or more commonly at the connection to the antennae, can occur. With the intramuscular DP system, wire breakage can occur at the skin exit site.

Concerning the internally implanted components with direct phrenic nerve stimulation systems, failure of the radiofrequency receiver was a fairly common problem with older systems, secondary to leakage of body fluid through the epoxy encapsulation. Wire breakage within the receiver was also an issue.[91] With older systems, this problem often occurred within 5 years of implantation.[23,47,91] With improvement in housing materials, receiver life has been extended significantly and reports of receiver failure are much less common.[53] Electrode wire malfunction or breakage is also much less common but can occur unpredictably at variable time periods following implantation. The most recent analysis of the quadripolar electrode system in patients who had undergone DP for approximately 2 years, demonstrated an electrode failure rate of 3.1%.[53] Failure rates were similar in tetraplegics and patients with CHS, and in adults and children. Failure of one or more of the four electrode combinations was fairly common, but usually did not interfere with successful pacing.[53]

Iatrogenic injury of the phrenic nerve can occur secondary to mechanical trauma during electrode implantation or secondary to subsequent tissue reaction and fibrosis around the electrode.[11,23,88] When performed at centers, however, by surgeons with expertise in DP and use of monopolar or quadripolar electrodes, rather than the older bipolar cuff electrodes that encircled the nerve, phrenic injury is infrequent.[53]

As with any foreign body, implantation of the internal components carries some risk of infection. Since the institution of this technique in the 1970s, infection rates have been relatively constant in the range of 3% to 5%.[22,53,91] The higher infection rate observed in active children with CHS is thought to occur as a result of the greater likelihood of local trauma in this population.[53] The development of infection usually requires the removal of all implanted materials.

Although there are some reports of successful tracheostomy closure following institution of DP, these are very uncommon. During the daytime, the state of wakefulness is associated with synchronous activation of the upper airway muscles and diaphragm during DP. During sleep, however, there is reduced activation of the upper airway dilator muscles and a greater tendency toward asynchronous upper airway muscle contraction resulting in upper airway obstruction, a form of obstructive sleep apnea.[5,94,95] With few exceptions, therefore, patients undergoing DP require a patent tracheostomy for nocturnal use. Maintenance of a tracheostomy also facilitates application of mechanical ventilation in the event of pacemaker malfunction or instances of increased respiratory demand such as acute infections.

With direct phrenic nerve pacing systems, monopolar stimulation may interfere with demand-type cardiac pacemakers. For this reason, if a cardiac pacemaker is present, it is advisable to use bipolar electrodes for DP.[96] The electrodes should be at least 10 cm from the cardiac pacemaker.[96,97] The presence of cardiac pacemakers, however, is not a contraindication for use of the intramuscular DP system. In twenty tetraplegic subjects with cardiac pacemakers and DP, there were no device-to-device interactions.[98]

In young children, paradoxical movement of the rib cage may occur as a result of the high chest wall compliance, resulting in reduced inspired volume generation. Consequently, bilateral pacing is required because of the paradoxical movement of the contralateral diaphragm and chest wall during DP.[4,23]

TABLE 62-3: COMPLICATIONS AND SIDE EFFECTS OF DIAPHRAGMATIC PACING

A. Technical malfunction
   1. External components
      a. Battery failure
      b. Breakage of antenna wires
   2. Implanted components
      a. Receiver failure
      b. Electrode malfunction
      c. Breakage of implanted connecting wires
B. Infection
   1. Receiver site
   2. Electrode site
C. Mechanical injury to the phrenic nerve
   1. Iatrogenic injury at the time of surgery
   2. Late injury as a result of scar formation and/or tension on the nerve
D. Upper airway obstruction after tracheostomy closure
E. Paradoxical movement of the upper rib cage, particularly in children

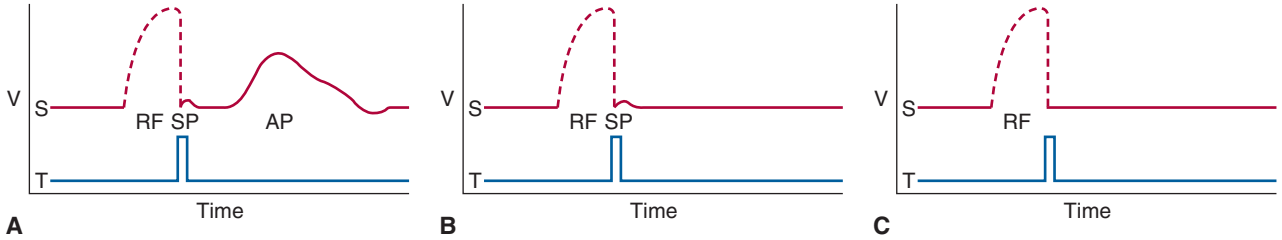

FIGURE 62-5 **A.** Schematic of an oscilloscopic tracing showing a properly functioning diaphragmatic pacing system. The lower tracing *T* represents the output from an extra receiver that was used to trigger the oscilloscope sweep. The upper trace (*S*) represents the signal obtained from the percutaneous leads on the chest. Shown in sequence are the radiofrequency signal (*RF*) from the transmitting antenna, the stimulus pulse (*SP*) from the electrode on the phrenic nerve, and the compound action potential (*AP*) from the diaphragm. **B.** Schematic of a malfunctioning pacing system. The tracing is the same except for the absence of the action potential. Breakage of wire insulation, lack of adequate phrenic nerve/electrode contact, or phrenic nerve damage are consistent with this finding. **C.** Schematic of another type of malfunctioning pacing system. In this case, the action potential and radiofrequency signal are absent. This finding suggests receiver malfunction. (Used, with permission, from Weese-Mayer et al.[94])

Finally, strong magnetic fields, such as those that occur with magnetic resonance imaging scanning, can override the electronic circuitry of pacing systems. The substantial energy transmission associated with this scanning could be transmitted to the electrode resulting in phrenic nerve injury. The pacing system's internal components would also be attracted to the magnet. Exposure to electrotherapeutic devices that generate strong radiofrequency fields should also be avoided because they may interfere with the pacing system.

MONITORING

Unlike mechanical ventilators, DP systems have no alarm systems that reflect inadequate levels of ventilation. When not receiving direct attendance by caregivers, patients should employ a pulse oximeter as a monitor for possible pacemaker malfunction or inadequate tidal volume generation secondary to patient-related issues.

Bedside Evaluation

For all patients supported by DP, breathing should be comfortable and effortless. Caregivers should evaluate pacemaker function on a routine basis and also in situations that give rise to dyspnea. On palpation of the chest wall, inspiration should be associated with vigorous lateral expansion of the lower rib cage and anterior abdominal wall, bilaterally. Attachment of a spirometer to the tracheostomy tube allows easy measurement of tidal volume. The transmitter enables separate stimulation of each hemidiaphragm, allowing evaluation of each side independently. Adequacy of ventilation should be assessed with pulse oximetry and end-tidal CO_2 measurements.[31,32,43,70]

TROUBLESHOOTING

If inspired volume is inadequate, the function of the external components should be evaluated first. Initially, the batteries should be replaced because this is the most common cause of pacemaker malfunction. Subsequently, the antenna should be replaced. If function is not restored, the back-up transmitter should then be changed.[4]

The occurrence of abnormal lung mechanics can also cause reductions in inspired-volume generation during DP. For example, most tetraplegics have a markedly reduced ability to cough and consequently accumulate airway secretions that require regular evacuation. Retained secretions cause increases in airway resistance and the development of atelectasis with secondary reductions in lung compliance. These mechanical derangements will reduce inspired-volume generation. Removal of secretions usually results in prompt improvement. Likewise, bronchitis and pneumonia will also result in reductions in inspired volume. If reductions in inspired volume are persistent, therefore, chest radiography may be necessary. This test is also useful to evaluate for wire breakage and electrode position.

With the direct phrenic nerve stimulation systems, evaluation of the internal components can be performed according to previously described techniques.[91] Surface electrodes are placed at the costal margin to record the pacemaker stimulus pulse and diaphragmatic action potential. The signals are amplified and recorded on an oscilloscope. Figure 62-5 is a schematic of the signals obtained from the chest leads. The DP system is functioning properly if the radiofrequency signal from the transmitting antenna, stimulus pulse from the phrenic nerve electrode, and diaphragmatic action potential are seen on the oscilloscope. If the radiofrequency signal and stimulus pulse are observed without the action potential, this indicates that the wire insulation is no longer intact, the phrenic nerve is not in contact with the electrode, or the phrenic nerve has been damaged. If the stimulus pulse and action potential are both not seen, the receiver is not functional.

IMPORTANT UNKNOWNS

The impact of DP, compared to mechanical ventilation, on long-term survival is unknown. Carter et al,[99] however, compared survival rates in a retrospective analysis.

Overall survival rates were similar between groups, but the patients on mechanical ventilation expired earlier than did patients maintained on DP. In a more recent clinical trial of sixty-four patients over a 20-year period, there was no significant difference in longevity between use of DP and mechanical ventilation.[39] Respiratory tract infections, however, were a more common cause of death in the mechanical ventilation group.

In the absence of depressed mental status and weakness of oropharyngeal muscles, some investigators have demonstrated that direct airway pressure methods, including mouth and nasal intermittent positive-pressure ventilation, can maintain adequate ventilation in tetraplegic patients.[74,75] These modalities offer the significant advantage of tracheostomy closure. Given the high cost and invasive nature of phrenic nerve implantation, these modalities may be better suited for some individuals. Newer methods of electrode placement, however, may swing the advantage in favor of DP.[27,28]

THE FUTURE

Although existing DP systems provide substantial lifestyle advantages to patients compared to mechanical ventilation, current systems are somewhat cumbersome and have significant disadvantages and limitations. With the ultimate goal of complete restoration of normal respiratory system function, several refinements are needed.

Perhaps most significant is the future development of systems that synchronize upper-airway muscle and diaphragmatic contraction, which would eliminate upper-airway obstruction during DP.[94,95] One option is to use an upper-airway muscle signal to trigger diaphragm activation. Such a device would not only eliminate the need for a tracheostomy but also provide ventilation on demand, allowing for changes in ventilatory requirements. A totally implantable system has not yet been developed, in part because of the high energy requirements of phrenic nerve pacing. A totally implantable system, similar to cardiac pacemakers, would eliminate the need for attachment of materials to the body surface, connection to a transmitter box, and battery changes. This development would further improve patient convenience and mobility.

DP in tetraplegic patients often requires a long reconditioning program because of disuse atrophy. Implantation of less-invasive intramuscular electrodes soon after injury would allow more tetraplegic patients to use DP in place of mechanical ventilation. In patients in whom weaning is possible, electrodes can subsequently be removed without injury. Using this technique, it is also conceivable that intensive care unit patients who require prolonged mechanical ventilation with the expectation of eventual recovery may benefit from DP to prevent diaphragmatic atrophy and consequent difficulty in weaning.

Finally, in patients with bilateral phrenic nerve injury, intercostal to phrenic nerve transfer may restore phrenic nerve viability and provide patients with the option of DP.[100]

SUMMARY AND CONCLUSIONS

In patients with ventilator-dependent tetraplegia and CHS, DP represents a practical method of ventilatory support with significant health and lifestyle advantages compared to mechanical ventilation. Advantages include increased mobility and level of independence, improved speech, improved sense of smell, and reduced anxiety and embarrassment associated with mechanical ventilation. The DP systems are smaller and more portable than ventilators and require less maintenance. Patients, however, must be carefully screened for social factors, including level of patient motivation and caregiver support, as well as coexisting medical conditions. Adequacy of phrenic nerve function must also be thoroughly evaluated preoperatively. In some patients, other means of support such as noninvasive ventilation may be more appropriate. Clinical studies examining methods of activating the inspiratory intercostal muscles are underway. These new techniques are likely to increase the number of eligible patients and expand the clinical indications for DP.

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DISCLOSURES

Dr. DiMarco is a founder and owner of Synapse Biomedical, LLC, a manufacturer of DP systems.

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63 BRONCHODILATOR THERAPY

Rajiv Dhand

Bronchodilators relax constricted airway smooth muscle in vitro. Because of this property, bronchodilators reverse airway obstruction, prevent bronchoconstriction and provide protection from constrictor stimuli.[1] In this chapter, bronchodilators employed in mechanically ventilated patients are discussed with a special emphasis on inhalation therapy.

RATIONALE

Ventilator-dependent patients with acute exacerbations of chronic obstructive pulmonary disease (COPD) and acute severe asthma routinely receive bronchodilators to relieve bronchoconstriction. By reducing airway resistance, bronchodilators reduce the pressure required to ventilate the lung. This reduction in pressure may protect the lung against injury and enhance patient comfort. A general population of ventilated patients in a medical intensive care unit (ICU)[2,3] and patients with acute respiratory distress syndrome[4,5] showed improvement in expiratory airflow and airway resistance after bronchodilators. Infants with bronchopulmonary dysplasia, and children with asthma, or bronchiolitis also receive bronchodilators on a routine basis.[6–10] In ventilated patients with COPD, elevated airway resistance and intrinsic positive end-expiratory pressure are major causes for weaning failure.[11] In these patients, bronchodilators may facilitate weaning.[12] Therapy with bronchodilators is, therefore, routinely and commonly employed for many indications in ventilator-dependent patients.[13]

PHARMACOLOGIC AGENTS

β-adrenergic agonists, anticholinergic drugs, and methylxanthines are the three major classes of bronchodilators employed in the ICU. β-adrenergic agonists and anticholinergics are usually administered by the inhaled route, whereas methylxanthines can only be administered enterally or parenterally. Although they are not bronchodilators in the classic sense, corticosteroids, both inhaled and systemic, are commonly employed in acutely ill patients to reduce airway inflammation and increase airway caliber.[14–16]

TABLE 63-1: DOSES AND DURATION OF ACTION OF COMMONLY USED BRONCHODILATORS IN VENTILATED PATIENTS[a]

Agents	Dose	Time Course (Onset, Peak, Duration)	Frequency of Dosing
Albuterol (Salbutamol)	SVN: 0.083% solution, 3 mL (2.5 mg), pMDI: 90 mcg/puff, 4 puffs	5 to 15 minutes, 30 to 60 minutes, 5 to 8 hours	4 to 6 times daily
Levalbuterol	SVN: 0.63 mg, or 1.25 mg	15 minutes, 30 to 60 minutes, 5 to 8 hours	3 to 4 times daily
Formoterol	SVN: 20 mcg/2 mL solution	1 to 3 minutes, 1 to 3 hours, 8 to 12 hours	2 times daily
Arformoterol	SVN: 15 mcg/2ml solution	1 to 3 minutes, 1 to 3 hours, 8 to 12 hours	2 times daily
Ipratropium	pMDI: 18 mcg/puff, 4 puffs SVN: 0.02% solution, 2.5 mL (0.5 mg)	15 minutes, 90 to 120 minutes, 6 to 8 hours	4 to 6 times daily
Albuterol + Ipratropium	pMDI: 90 mcg + 18 mcg/puff, 4 puffs SVN: 2.5 mg + 0.5 mg/dose	5 to 15 minutes, 30 to 60 minutes, 6 to 8 hours	4 to 6 times daily

Abbreviations: pMDI, pressurized metered-dose inhaler; *SVN*, small-volume nebulizer.

[a]Dry powder inhalers are not routinely employed in ventilated patients.

β-Agonists

The pharmacology of the β-agonists was extensively reviewed in the second edition of this textbook,[17] and other excellent reviews are available.[18]

ROUTE OF ADMINISTRATION OF β_2-ADRENERGIC AGONISTS

β-agonists have been given by oral, subcutaneous, intravenous, and inhaled routes. Table 63-1 lists doses for individual drugs. Inhaled therapy is preferred because the drug is delivered directly to its site of action in the airways, a smaller quantity of drug produces an effect comparable to that observed with systemic administration, onset of effect is rapid, and systemic absorption of the drug is limited, thus minimizing side effects. The oral approach has been all but abandoned, and there appears to be no advantage to the intravenous route even in severe asthma with hypercapnia.[19] A meta-analysis found no evidence of benefit for the intravenous use of β-agonists in patients who are refractory to inhaled β-agonists.[20]

INDIVIDUAL AGENTS

Albuterol. Albuterol is today's standard short-acting bronchodilator. Its pharmacokinetics depend on the dose administered, the formulation of albuterol used (dry powder, pressurized metered-dose inhaler [pMDI], or nebulized) and the clinical situation (mechanically ventilated or ambulatory). Although increasing doses of albuterol produce greater bronchodilation, the optimum dose is difficult to predict. Peak bronchodilator response after 10 puffs of albuterol in ventilated patients was seen within 5 minutes and sustained for 60 minutes.[12] Duration of action of 6 puffs of albuterol delivered from a pMDI to ventilated patients ranged from less than 2 hours to more than 4 hours.[21] Systemic effects are dose related, usually appearing within an hour of administration with a return to baseline within 4 hours.[22]

Levalbuterol. Commonly available racemic albuterol is a 50-50 mixture of R-albuterol and S-albuterol. Levalbuterol, the R-enantiomer, was formulated to avoid possible adverse effects of the S-enantiomer. For doses that produce similar increases in forced expiratory volume in 1 second (FEV_1), increases in heart rate are less with levalbuterol (2 to 4 beats/min) than with albuterol,[23] and the bronchodilator effect is greater in patients with acute asthma.[24,25] In patients receiving long-term mechanical ventilation, levalbuterol produced an increase in secretion volume but the effect dissipated rapidly.[26]

Salmeterol. Salmeterol is a long-acting β_2-agonist. Its onset of action is slower than that of albuterol in vitro (mean: 6.4 vs. 1.9 minutes)[27] and in vivo (mean: 10 vs. 4 minutes).[28] With salmeterol, peak bronchodilator response was seen at 5 hours versus 1 hour with albuterol, and FEV_1 was higher than predose FEV_1 levels for 12 hours.[28] Systemic effects of salmeterol are dose related, manifest later, and last longer; maximum effects on heart rate occur within 75 to 135 minutes and are still evident after 4 hours.[22] In ventilated patients with acute exacerbations of COPD, four doses of salmeterol by pMDI (100 mcg) produced a bronchodilator effect within 30 minutes that was maintained for approximately 8 hours, with significant variability in the magnitude and duration of the response among patients.[29]

Formoterol. Formoterol is a long-acting agent like salmeterol but is distinguished by its relatively quicker onset of action.[30] Duration of effect is approximately 12 hours. Because of its rapid onset of effect, formoterol is effective during acute exacerbations.[31] Stereoselective formoterol (arformoterol) is available as a nebulized solution.

Once-Daily Long-Acting β-Agonists. Indacaterol, vilanterol, and carmoterol have duration of action of 24 hours or more and are in various stages of clinical development.[32]

Anticholinergics

ANTICHOLINERGIC ACTION AND AIRWAY SMOOTH MUSCLE RELAXATION

The principal mechanism of action of muscarinic antagonists is to block vagally mediated bronchoconstriction. In patients with COPD, a greater bronchodilator response occurs after atropine than after albuterol. The bronchodilator response to atropine in patients with COPD is greater than that in normal subjects. These data suggest enhanced parasympathetic activity in COPD.[33,34] Patients with chronic asthma do not show as much benefit with anticholinergic agents, although patients with acute asthma exacerbations benefit from inhaled anticholinergic agents.

OTHER EFFECTS OF ANTICHOLINERGIC ACTION IN THE LUNGS

The quaternary ammonium-containing muscarinic antagonists in current use have no significant effects on mucus secretion or the rheologic properties of mucus,[35] although some reports do suggest a decrease in sputum volume.[36] Mucociliary clearance is unchanged with inhaled ipratropium.[37,38]

Acetylcholine can stimulate alveolar macrophages to release chemotactic factors.[39] Long-acting anticholinergics may thus decrease airway inflammation by blocking the actions of acetylcholine.[40]

SIDE EFFECTS OF ANTICHOLINERGICS

Although muscarinic receptors are widespread in the body, the quaternary ammonium group in modern antimuscarinic agents (ipratropium and tiotropium) results in poor systemic absorption allowing higher doses to be inhaled with few systemic effects.

Dryness of the mouth is a common side effect of anticholinergics, whereas blurring of vision occurs infrequently. Unilateral mydriasis is believed to result from direct contact of the nebulized solution with the eyes.[41,42] Ipratropium inhalation does not worsen arterial oxygenation,[43] and tolerance to the bronchodilator or bronchoprotective effects of anticholinergics does not occur. Systemic side effects (tachycardia, palpitations, urinary hesitancy, constipation, blurred vision, or glaucoma) are more common with tertiary ammonium compounds, such as atropine, than with ipratropium or tiotropium. In the Lung Health Study, Anthonisen et al found a higher incidence of supraventricular arrhythmias as well as significant increases in hospitalization and mortality rates in the ipratropium group as compared to the placebo group.[44] A slightly higher risk of developing cerebrovascular accidents was suggested for patients receiving tiotropium (http://www.fda.gov/medwatch/safety/2008/safety08.htm#Tiotropium), and a metaanalysis found a higher risk of cardiovascular events in patients with COPD receiving ipratropium or tiotropium,[45] although these have not been observed in a recently concluded large randomized controlled trial.[46] Nevertheless, ipratropium and tiotropium should be used with caution in patients with renal failure, prostatic hypertrophy, urinary retention, or glaucoma.

INDIVIDUAL AGENTS

Ipratropium. The usual dose is 36 mcg (2 puffs from a pMDI) every 4 to 6 hours. There is a plateau in the achievable improvement in FEV_1 with increasing doses with no significant improvement beyond a dose of 72 mcg.[47] In patients with severe airway obstruction, however, the amount of drug delivered to the site of action may vary and higher doses may be needed. The usual nebulized dose is 500 mcg every 6 hours. The onset of action is within 30 minutes of an inhaled dose and the effects last for about 4 to 6 hours.

Tiotropium. Tiotropium is a long-acting bronchodilator that has equal binding affinity for M_1, M_2, and M_3 receptor subtypes. It dissociates much more slowly from M_3 receptors than from M_2 receptors.[48] In view of the role of M_2 receptors in inhibiting acetylcholine release, this may represent a beneficial aspect of its action. Tiotropium is inhaled once daily. Onset of action is within 30 minutes. An increase in FEV_1 from baseline is present at 24 hours.[49]

Corticosteroids

Corticosteroids have no direct action on contraction of airway smooth muscle; hence, they are not bronchodilators in the classic sense. Corticosteroids, however, offer bronchoprotection, and they improve airway obstruction by reducing airway inflammation and via vasoconstrictor effects.[16,50] Corticosteroids reduce airway inflammation by several mechanisms,[51–54] decrease airway hyperresponsiveness and reduce the predilection to acute episodes of airflow obstruction. Corticosteroids also upregulate β-receptor expression on cell membranes, increase the proportion of β receptors in a high-affinity binding state, and inhibit the release of inflammatory mediators such as phospholipase A_2, which could destabilize membrane support of the β receptor.[55]

Several corticosteroids, such as hydrocortisone, cortisone, prednisone, prednisolone, and methylprednisolone are given parenterally or orally for treatment of inflammation in asthma and COPD. Agents with high topical activity are employed as inhaled corticosteroids (ICSs), such as beclomethasone, triamcinolone, flunisolide, fluticasone, budesonide, mometasone, and ciclesonide, because they produce direct antiinflammatory effects while minimizing unwanted systemic side effects.

Systemic administration of corticosteroids is associated with several adverse side effects.[56] The use of ICSs is attractive mainly to reduce the side effects observed with systemic therapy.[57,58] Side effects of therapy with ICSs include oropharyngeal fungal infections, hoarseness, hypothalamic–pituitary–adrenal axis suppression, reduction in bone mass, growth restriction in children, skin bruising, and increased propensity to develop pneumonia.[57–60]

Clinical Use of Bronchodilator Drugs

Patients presenting with acute severe asthma and acute exacerbations of COPD are in urgent need of bronchodilation. Inhalation is the preferred route of administration of bronchodilator agents because it produces a rapid onset of action, requires smaller doses than those needed orally or parenterally, and minimizes systemic side effects.[61] For administration of short-acting β-agonists the use of pMDI and holding chamber (a chamber spacer that incorporates a valve, so that aerosol is retained within the chamber for a finite time after pMDI actuation) is a convenient and cost-effective option and provides efficacy similar to that achieved with a jet nebulizer.[62]

β-AGONISTS IN ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

In general, repeated administration of short-acting β-agonists at frequent intervals is recommended for relief of symptoms in patients with acute asthma.[50,63] There is a dose–response relationship with increasing doses of β-agonists resulting in increasing bronchodilation.[64,65] Rodrigo and Rodrigo, however, noted that 2.4 mg of albuterol every hour (400 mcg every 10 minutes) delivered via a pMDI/holding chamber produced clinically significant bronchodilation, and higher doses increased the incidence of adverse effects without enhancing bronchodilation.[66,67] Other investigators have concluded that the cumulative dose, and not the dosage regimen, influences the bronchodilator response (i.e., the same response was obtained when 5 mg was given as a single dose as when it was given as two doses of 2.5 mg).[68,69] The usual dose necessary to produce bronchodilation in severe asthma is between 5 and 10 mg of albuterol.[70] Use of higher doses during the initial phase of an acute exacerbation of asthma may have clinical utility. A faster response may be seen, and, because most patients respond to 5 to 10 mg of albuterol, nonresponders could be identified. Nonresponders, defined as those requiring admission, not discharge, to an emergency department, were found to have a flatter dose–response curve to albuterol, with peak expiratory flow remaining below 45% despite administration of high doses of albuterol.[68,71,72]

The logistical problem in repeatedly administering doses of nebulized albuterol (intermittent therapy) stimulated interest in continuous nebulization. Various investigators have reported conflicting findings with continuous nebulization.[73,74] Two meta-analysis of published trials also reached different conclusions.[75,76] Overall, it appears that patients with more severe airway obstruction could benefit from continuous nebulization,[4,77] especially if they do not respond to therapy within the first hour in the emergency department.

Both formoterol and arformoterol are effective for treatment of patients with COPD.[78–81] There is not much published experience with their use during acute exacerbations of asthma or COPD.

In summary, the severity of an individual episode is better measured as response to bronchodilator therapy rather than by baseline pulmonary function. Continuous nebulization may be employed in patients with acute severe asthma in whom pulmonary function does not improve by the end of the first hour of intensive bronchodilator therapy.

CHOICE OF DELIVERY SYSTEM

In clinical studies evaluating bronchodilator administration through pMDI/holding chamber versus nebulizers, equivalent changes in FEV_1 were produced by 6 mg/hour of albuterol given by the nebulized route and 2.4 mg/hour of albuterol given by pMDI/holding chamber, an equivalent dose ratio of 2.5:1. A higher incidence of tremor and anxiety and higher serum albuterol was seen in the nebulizer group.[82] Improvement in pulmonary function is similar[70,83,84] or slightly better[85,86] with pMDI/holding chamber than with nebulizers, while increases in heart rate are more frequent with nebulizers.[70]

ANTICHOLINERGICS IN ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

The ideal bronchodilator and optimal regimen for acute exacerbations of COPD have not been established. A pooled analysis comparing the effects of β-agonists (fenoterol and metaproterenol) and anticholinergics (ipratropium) found no significant differences in improvement in FEV_1.[87] If response to β-agonists is suboptimal or the exacerbation is severe, ipratropium can be added.[88]

CORTICOSTEROIDS IN ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

A short course of systemic corticosteroids may be necessary to gain control of asthma symptoms. ICS may be started at the same time and the systemic steroid tapered slowly. Subsequent adjustments in ICS dose are based on assessments of symptoms, rescue use of short-acting β-agonists, and measurement of peak expiratory flow rates.

High-dose ICSs administered by pMDI to patients with acute asthma exacerbations achieve similar improvements in symptoms and pulmonary function as systemically administered corticosteroids.[89–91]

Corticosteroids for Chronic Obstructive Pulmonary Disease. In patients with COPD, regular use of ICSs produces a small increase in pulmonary function and

improves health status.[92–94] ICSs, however, do not alter the rate of decline in FEV_1 and they do not reduce mortality.[95] In acute exacerbations, oral or parenteral corticosteroids are often employed with some benefit for patients who are admitted to the hospital.[96,97] Current evidence favors moderate over high doses, and short courses of oral corticosteroids over intravenous therapy for treating acute exacerbations.[98–100]

Risk-to-benefit considerations have prompted investigation of ICS use for treatment of acute exacerbations of COPD. Several investigators have shown that the efficacy of nebulized budesonide is comparable to that observed with systemic corticosteroids, except in the most severely ill patients.[101–104]

In patients receiving long-term ventilation for severe COPD, Nava et al observed a small, but statistically significant, reduction in airway resistance with fluticasone.[105] The optimal methods of administering ICS and the appropriate doses in ventilated patients have not been determined, but are likely to be higher than those used for maintenance therapy in COPD.[16,101–104] Moreover, many ventilated patients receive systemic corticosteroids for acute exacerbations of asthma and COPD, and it is unclear if patients derive additional benefits from ICSs in the presence of high-dose therapy with oral or parenteral corticosteroids. Finally, regular use of ICSs in ambulatory patients with COPD is associated with a higher risk of pneumonia.[60] Because ventilated patients are already vulnerable to developing pneumonia for a variety of reasons, the potential to add another risk factor by administering ICSs requires serious consideration. In summary, ICSs may have a limited role in ventilated patients, but further investigations are needed to determine the appropriate dosing regimen and risk-to-benefit ratio of using ICSs in this group of patients.

Combination Therapy

β-AGONISTS AND ANTICHOLINERGICS

In acute asthma, some investigators found additional benefits with combined anticholinergic and β-agonist therapy over β-agonists alone,[106–108] whereas others[109,110] found no difference. A meta-analysis that compared albuterol alone to albuterol with ipratropium found an overall improvement of 7.3% in FEV_1 and 22.1% in peak expiratory flow rates, and reduction in hospitalization rates for studies in which data were available.[111] A more recent meta-analysis by Rodrigo and Rodrigo[112] found benefit for a combination of anticholinergics with albuterol in severe asthma (FEV_1 <50%).

In patients with acute exacerbations of COPD, adding an anticholinergic to a β-agonist may[113] or may not[114–116] provide greater bronchodilation. Fernandez et al[117] found an improvement in airway pressures in ventilated patients with the combination of ipratropium and fenoterol in comparison to ipratropium; ipratropium alone achieved no benefit.

BRONCHODILATORS AND INHALED CORTICOSTEROIDS

There is little doubt that combinations of ICSs plus long-acting β-agonists (Advair Diskus; Advair pMDI; Symbicort pMDI) are the most effective and widely used treatments currently available for treatment of asthma. A combination of formoterol and budesonide, used as a reliever as well as maintenance therapy, may be employed for treatment of mild to moderate acute asthma exacerbations that could be managed at home. This management strategy significantly reduces the frequency of more severe exacerbations.[118] Currently, there is limited experience with bronchodilator and ICS combination therapy for treatment of acute exacerbations of COPD, especially in ventilated patients.

Methylxanthines

Theophylline is an inexpensive and commonly employed bronchodilator in many developing countries. The reader is referred to the second edition of this book[17] for details on its pharmacology and mechanisms of action.

Theophylline administration requires empiric loading and maintenance dosing with frequent measurement of serum levels and dose adjustment.[119] Plasma theophylline levels should be maintained between 5 and 15 mg/L because adverse effects frequently occur with higher levels.[120–122] At concentrations less than 15 mg/L, theophylline is a relatively weak bronchodilator and its beneficial effects are more likely explained by its antiinflammatory action, particularly in synergy with corticosteroids.[123]

In acute asthma, theophylline does not confer additional bronchodilation in patients receiving intensive therapy with inhaled β-agonists and intravenous corticosteroids.[124–126] Likewise, routine use of theophylline in acute exacerbations of COPD is not supported by randomized controlled trials.[114] Theophylline may have a role in reducing hospitalization among patients receiving emergency department treatment for asthma and COPD,[127] and in promoting corticosteroid activity in patients with acute exacerbations of COPD.[128] Few investigators have reported on the use of theophylline in ventilated patients.[117,129,130] In the neonatal ICU, theophylline is employed to prevent apneas.[131] In adults, loading doses of intravenous theophylline produced significant bronchodilation, comparable to that achieved with two inhalations of either albuterol or ipratropium bromide.[117,129,130] The increased respiratory muscle strength with theophylline[132–134] may help in weaning.

Frequent side effects with theophylline, especially nausea and vomiting, are a major drawback. Older patients and those with a low serum albumin are particularly susceptible to serious theophylline toxicity, such as cardiac arrhythmias and seizures.[135–137] In summary, the high frequency of side effects, its relatively low efficacy, frequent drug interactions, complicated dosing regimens, and the need for repeatedly monitoring serum levels have significantly limited theophylline use in the ICU.

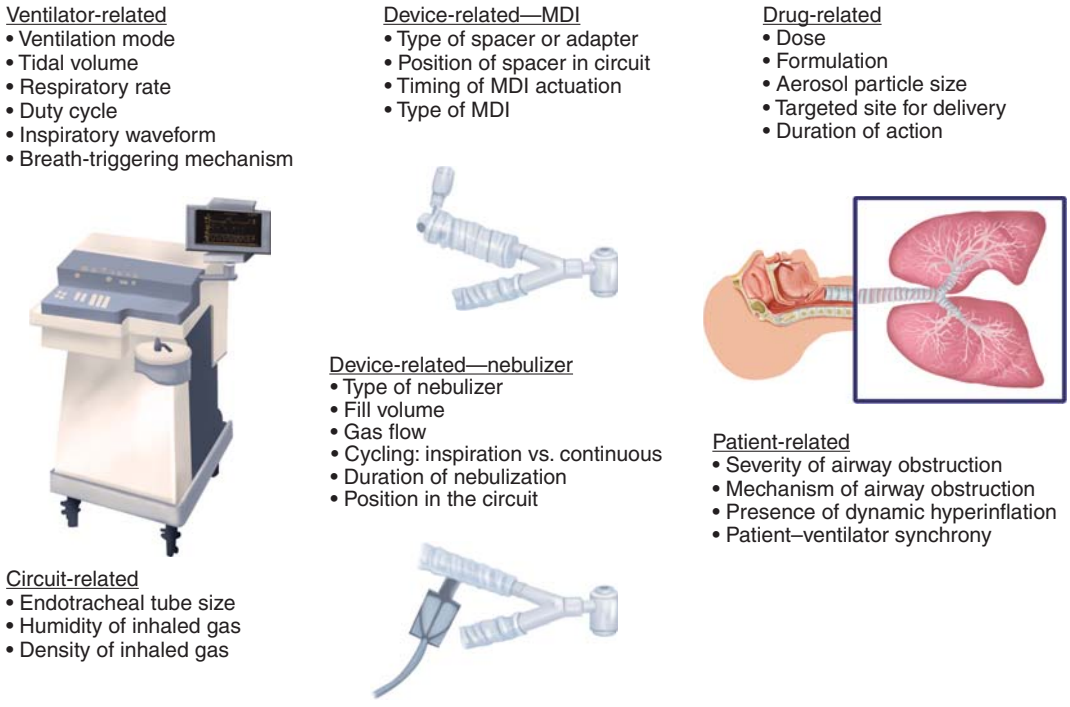

FIGURE 63-1 Factors influencing aerosol delivery in mechanically ventilated patients. *MDI*, metered-dose inhaler. (Modified with permission from Dhand R. Basic techniques for aerosol delivery during mechanical ventilation. *Respir Care.* 2004;49(6):611–622.)

Selective Phosphodiesterase E_4 Inhibitors

Phosphodiesterase E_4 (PDE_4) is the predominant isozyme responsible for metabolizing cyclic adenosine monophosphate in airway smooth muscle, and in immune and inflammatory cells.[138,139] Elevation of cyclic adenosine monophosphate by selective PDE_4 inhibition has a wide variety of pharmacologic effects. Orally administered selective PDE_4 inhibitors have bronchodilator and antiinflammatory effects in patients with asthma and COPD.[140–145] Unlike theophylline, these agents do not exhibit significant drug interactions.[146,147] Side effects, such as nausea and headache, are generally mild to moderate, but could limit the use of these agents in critically ill patients.

Leukotriene-Modifying Agents

Leukotrienes are formed by the action of 5-lipoxygenase on cell membrane-derived arachidonic acid. Zileuton blocks 5-lipoxygenase and inhibits leukotriene synthesis, whereas zafirlukast, montelukast, and pranlukast all block the final step in the action of leukotrienes on the leukotriene receptor. The leukotrienes are mainly employed in patients with chronic asthma as adjuncts to ICSs. In acute asthma, intravenous montelukast achieves modest early gains in lung function without significant improvement in rates of hospital admission.[148]

FACTORS INFLUENCING AEROSOL DELIVERY DURING MECHANICAL VENTILATION

Several factors influence aerosol delivery during mechanical ventilation, including variables related to the aerosol-generating device, the ventilator and ventilator circuit, the inhaled drug or agent, and the patient (Fig. 63-1). Aerosol delivery during mechanical ventilation depends to a great extent on the type of aerosol-generating device employed.

Aerosol-Generating Devices

NEBULIZERS

Several types of nebulizers, jet, ultrasonic, vibrating mesh, and soft-mist inhalers convert liquids into aerosols for inhalation (Fig. 63-2).[61]

Jet Nebulizers. Aerosol particle size is influenced by nebulizer design, solution characteristics (density, viscosity, and surface tension) and volume, gas pressure and flow, baffle design, and ratio of liquid to gas flow.[149–151] Droplet size decreases when gas flow increases, whereas droplet size increases with increase in the ratio of liquid to gas flow. A certain volume of solution (dead or residual volume)

cannot be nebulized. Residual volume varies from 1 to 3 mL; it can be reduced by using a nebulizer with a conical shape, improving the wetness of the plastic surfaces, and reducing the internal surface area of the nebulizer.[149,151] During operation, the solution concentration increases and its temperature decreases secondary to evaporative losses.[152,153] Both increased solution concentration and cooling influence nebulizer output and particle size.[151,154] Significant disadvantages of jet nebulizers are the requirement for a power source, inconveniently long treatment time, need for equipment setup and cleaning, and significant variations in the performance of various nebulizers, both within the same brand and across different brands.[155–157]

Ultrasonic Nebulizers. Most ultrasonic nebulizers have a higher rate of nebulization and require a shorter time of operation than jet nebulizers (see Fig. 63-2). Generally, the aerosol particle size is larger with ultrasonic nebulizers compared to jet nebulizers. The cost and bulk of ultrasonic nebulizers and their relative inefficiency in nebulizing drug suspensions are major limitations to their use, although smaller ultrasonic nebulizers are available and have been employed during mechanical ventilation.[158–162]

Vibrating Mesh Nebulizers. Newer-generation nebulizers employ a vibrating mesh or plate with multiple apertures to produce an aerosol.[163,164] Because the frequency of vibration of the plates is lower than that in ultrasonic nebulizers, these devices can be operated with a battery pack and or electrical source. As a result, these devices are portable and less noisy. Moreover, these devices have negligible residual volume, and this property significantly improves the drug output. The Aeroneb Pro (Aerogen Inc., Mountain View, CA) is specifically designed as an inline nebulizer (see Fig. 63-2); a breath-synchronized version of the Aeroneb Pro—the Pulmonary Drug Delivery System (PDDS, Nektar Therapeutics, San Francisco, CA)[165]—has been successfully employed in ventilated patients.[166] The vibrating mesh nebulizers have a high rate of nebulization, and drug output is two to four times higher than with jet nebulizers.[167] Unlike ultrasonic nebulizers, the temperature of the solution does not change during operation of the vibrating mesh nebulizers,

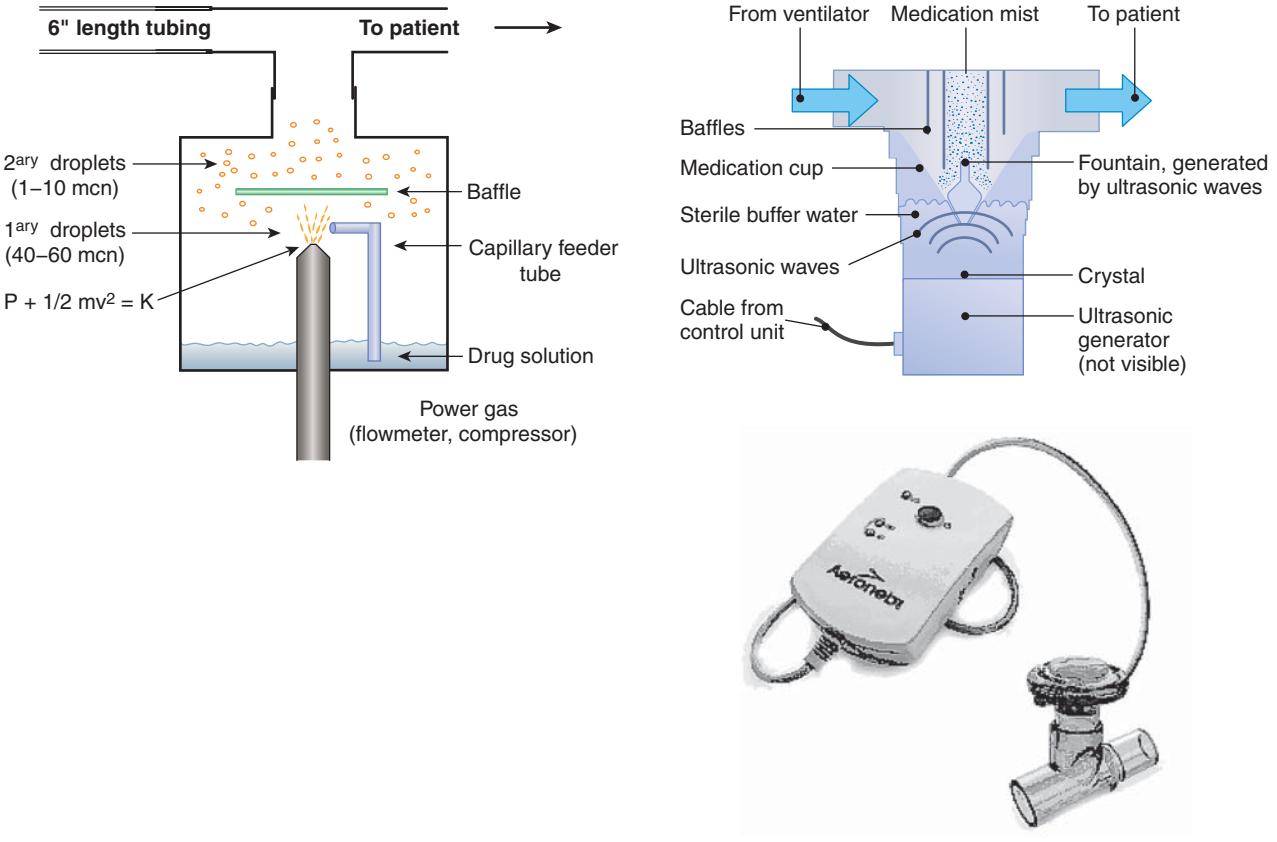

FIGURE 63-2 Several types of nebulizers are available for clinical use, including jet nebulizers (*left*), ultrasonic nebulizers (*upper right*), and vibrating mesh nebulizers (*lower right*). The jet nebulizers employ compressed gas or air to generate an aerosol. In ultrasonic nebulizers, aerosol is generated by vibration of a piezoelectric crystal at ultrasonic frequencies. In the vibrating mesh nebulizers, aerosol is produced by high-frequency vibration of a plate with multiple apertures. Vibration of the aperture plate pushes the liquid to be nebulized through the apertures and generates a fine particle mist. *mcn*, micron.

and proteins and peptides can be nebulized with minimal risk of denaturation.

Intratracheal Catheter. The intracorporeal nebulizing catheter (Aeroprobe; Trudell Medical International, London, Ontario, Canada) is a novel, investigational device that produces an aerosol in the trachea.[168,169] Preliminary data suggest that lung deposition is improved with its use compared to more conventional forms of aerosol administration.[170,171]

PRESSURIZED METERED-DOSE INHALERS

The pMDI canister contains a pressurized mixture of propellants, surfactants, preservatives, flavoring agents, and active drug, the latter comprising approximately 1% of the total contents.[172,173] This mixture is released from the canister through a metering valve and stem, which fits into an actuator boot.[172,173] Previously, most pMDIs used chlorofluorocarbon (CFC) propellants, but a newer generation of pMDIs contain hydrofluoroalkane (HFA) propellants.[174] The formulation, metering valve, and actuator design of HFA-pMDIs are different from those of CFC-pMDIs.[61]

The efficiency of drug delivery with a pMDI depends on how well the canister stem fits into the spacer adapter. In bench models of mechanical ventilation, HFA-pMDIs used with an AeroVent spacer provided lower drug delivery than that achieved with CFC-pMDIs.[175] In contrast, beclomethasone HFA-pMDIs employed with an AeroChamber HV MV spacer (Monaghan Medical, Plattsburgh, NY) had a higher efficiency of drug delivery than the beclomethasone CFC-pMDI.[176] Likewise, HFA-pMDIs were shown to achieve drug delivery similar to CFC-pMDIs in pediatric and neonatal bench models of mechanical ventilation.[177,178] To improve drug delivery with HFA-pMDIs during mechanical ventilation, actuators that better fit the stem of the HFA-pMDI canister must be employed.

DRY POWDER INHALERS

Dry powder inhalers could be employed inline in ventilator circuits either by employing the ventilator's inspiratory airflow to generate an aerosol or by first producing an aerosol and then entraining the drug particles into the airflow from the ventilator. Everard et al[179] employed a modified Turbuhaler in a dry ventilator circuit, and found that approximately 20% of the nominal dose was delivered to a filter placed at the distal end of the endotracheal tube. Humidity reduces drug delivery from dry powder inhalers,[180] and because ventilated patients routinely receive warm and humidified gas, the feasibility of administering dry powders during mechanical ventilation needs further evaluation.

FACE MASKS

Aerosol deposition in nasal passages significantly reduces drug delivery to the lung[181–183] and could reduce bronchodilator efficacy;[184] however, face masks may be necessary for treatment of acutely dyspneic or uncooperative patients. For optimal efficacy, the face mask should produce a tight seal[185–187] to avoid aerosol leakage and increased aerosol deposition around the eyes.[188]

The orientation of the nebulizer with respect to the face mask influences the pattern of aerosol deposition. In "front-loaded" masks the nebulizer is inserted directly into the face mask, whereas in "bottom-loaded" masks the aerosol enters the mask from below. Front-loaded masks provide greater inhaled mass but also produce greater facial and ocular deposition.[189] Deposition of aerosol on the face and eyes could be minimized by employing masks that incorporate vents and have cut outs in the region of the eyes.[189,190]

HIGH-FLOW NASAL CANNULAE

Humidified high flow nasal cannulae are increasingly employed in the ICU to enhance gas exchange and avoid mechanical ventilation.[191] In a bench study, the inhaled mass of aerosol and aerosol particle size with high-flow nasal cannulae were comparable to those obtained with mouthpiece inhalation from a continuously operating jet nebulizer.[192]

Methods to Assess Aerosol Delivery during Mechanical Ventilation

In the past, pMDIs and nebulizers[193,194] were shown to have poor efficiency during mechanical ventilation, mainly because of drug deposition in the ventilator circuit and artificial airway.[195,196] Both in vitro and in vivo studies have helped in understanding the complex factors governing aerosol delivery during mechanical ventilation.[196–198]

Whereas in vitro methods measure *drug delivery* to the lower respiratory tract, in vivo methods measure the amount of *drug deposition* in the lung. This distinction is important because a variable portion of inhaled particles do not deposit in the lung and are exhaled. A "mass balance" technique that matches ventilator circuits and ventilator parameters has been employed to determine the correlation between the results of in vitro tests and those in ventilator-supported patients.[199,200] With such techniques, it was estimated that approximately 5% of the nominal dose of albuterol administered by a pMDI is exhaled by ventilated patients,[175] compared to less than 1% exhaled by ambulatory patients.[201] The mean exhaled fraction (7%) with nebulizers in ventilated patients is similar to that with pMDIs, but there is considerable variability (coefficient of variation: 74%) among patients.[199]

The particle size of the aerosol is an important determinant of aerosol delivery to the lung. Devices that produce aerosols with mass median aerodynamic diameter less than 2 μm are more efficient during mechanical ventilation than devices that produce aerosols with larger particles.[199,200] Nebulizers that produce smaller particle size have been employed, but they require a considerably greater time to deliver a standard dose.[200,202] Moreover, a significant

TABLE 63-2: DETERMINATION OF LOWER RESPIRATORY TRACT DEPOSITION OF AEROSOL DELIVERED BY A PRESSURIZED METERED-DOSE INHALER USING IN VITRO MODELS

Type of model and Ref.	Type of Adapter	Breath Type	Measurement	Results
ETT (6.0, 7.5 and 9.0 mm) in trachea[204]	Swivel adapter	Continuous flow or MDI actuation then flow	Filter weight	Greater efficiency with larger ETT and actuation into continuous flow
ETT and laser spectrometer[205]	Three different adapters inline or cylindrical spacer	V_T 800 mL; flow 60 L min^{-1}	Particle volume 1 to 5 μm	Adapters produced lower volume of particles than standard actuator
Ventilator circuit; ETT (8 mm)[209]	Swivel adapter at ETT or cylindrical spacer	V_T 800 mL; flow 48 L min^{-1}	Albuterol assay	Greater deposition with cylindrical spacer
ETT and laser spectrometer[206]	Nine different MDI spacers or adapters	–	Particle volume 0.7 to 5.0 μm	Chamber spacers delivered greater volume than other adapters
Ventilator circuit[207]	MDI with large chamber or small chamber spacer	V_T 700 mL; flow 50 L min^{-1}	Radioactivity	Similar delivery with the devices
Plastic syringe and simulated carina[210]	MDI with catheter	–	Albuterol assay	≈90% of dose delivered beyond ETT
ETT (6 mm) and swivel adapter[211]	Catheters placed in ETT (13 or 22 cm long)	Flow 30 L min^{-1}	Albuterol assay	Longer catheters delivered greater dose than shorter catheters
Model of trachea and main bronchi[195]	Cylindrical spacer 8 mm ETT	Flow 40 L min^{-1}	Albuterol assay	Decreased deposition with humidification and CMV breaths

Abbreviations: CMV, controlled mechanical ventilation; *ETT*, endotracheal tube; *pMDI*, pressurized metered dose inhaler; V_T, tidal volume.

proportion of submicronic particles (<1 μm) are exhaled.[199] For optimal pulmonary deposition, the size of the particles in the aerosol should be small enough to allow maximum penetration through the artificial airway, yet large enough to avoid being carried back out into the atmosphere with the exhaled breath.

IN VITRO STUDIES

Carefully performed in vitro tests that simulate the conditions of actual clinical use have played an important role in determining the optimal techniques for administering aerosols to ventilated patients.[175,176,199,200,202–209] Table 63-2 shows various bench models that were used. Models that employ a tracheobronchial model and directly measure the amount of drug deposited on a filter placed distal to the endotracheal tube[175,176,195,209–211] have produced the most reproducible results.

For any given aerosol-generating device, the efficiency of drug delivered varies widely; for pMDIs, it varies from 0.3% to 97.5% and for nebulizers from 0% to 42%. These variations in drug delivery underscore the need for optimizing the techniques of administration with each device. With pMDIs, the type of pMDI propellant formulation[176] and the drug formulation[203] also influence drug delivery.

Configuration of the Device with Metered-Dose Inhalers. For a pMDI to be employed in a ventilator circuit, the canister must be removed from the actuator (supplied by the manufacturer) and connected to the ventilator circuit with another different adapter, thereby making it a unique device with different aerosol characteristics and performance. Several types of adapters, including elbow adapters, inline devices that may be unidirectional or bidirectional, and chamber or reservoir adapters, are commercially available (Fig. 63-3).[162,212] The adapter efficiency could have a significant influence on the dose required to produce a therapeutic effect.[213] Several investigators have shown that employing a chamber spacer with a pMDI in a ventilator circuit results in fourfold to sixfold greater aerosol drug delivery compared with either an elbow adapter or a unidirectional inline spacer.[202,205,209,214] A pMDI and chamber spacer placed at a distance of approximately 15 cm from the endotracheal tube provides efficient aerosol delivery and elicits a significant bronchodilator response.[12,197,215] The efficiency of a bidirectional inline spacer was higher than that of a unidirectional inline spacer[203] and was comparable to that achieved with chamber spacers,[203] although the performance of the bidirectional spacer has not been established in clinical studies.

Configuration of the Device with Nebulizers. Both jet and ultrasonic nebulizers are connected in the inspiratory limb of the ventilator circuit or at the patient Y. Placing a jet nebulizer at a distance from the endotracheal tube improves its efficiency compared with placing it between the patient Y and endotracheal tube.[208,216,217,218] Placement of the continuously operating jet nebulizer before the humidifier (i.e., between the humidifier and ventilator) had

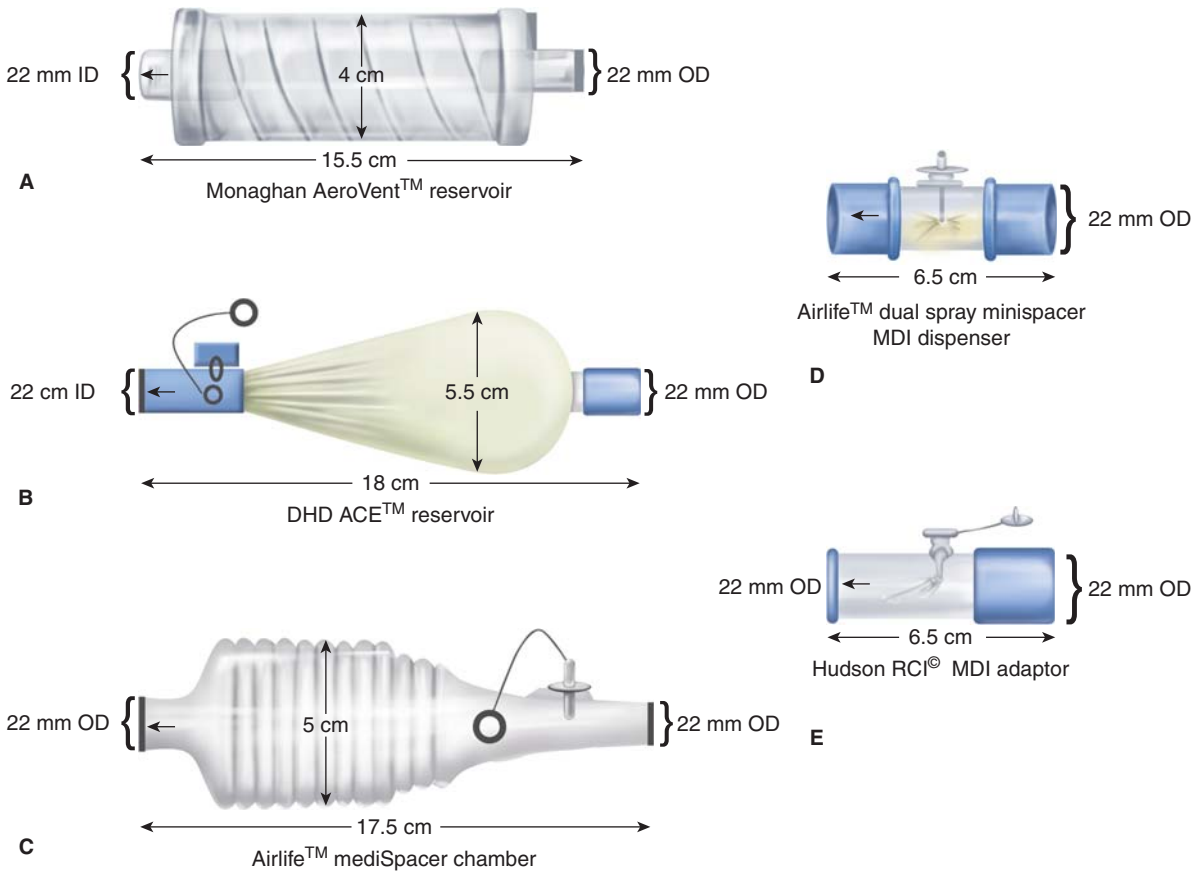

FIGURE 63-3 Commercially available spacers and adapters that are used to connect a metered-dose inhaler (*MDI*) canister in the ventilator circuit. *Top left:* Collapsible spacer chamber. *Middle left:* Aerosol cloud enhancer, wherein the aerosol flume is directed away from the patient. *Bottom left:* Noncollapsible spacer chamber. *Top right:* Bidirectional actuator (mini spacer). *Bottom right:* Inline adapter. *OD*, outside diameter. (Used, with permission, from Rau et al.[203])

a higher efficiency of aerosol delivery than placement closer to the endotracheal tube,[218] probably because the inspiratory limb of the ventilator circuit acts as a reservoir for the aerosol during the exhalation phase. For the same reason, addition of a reservoir between the nebulizer and endotracheal tube also modestly increases efficiency of drug delivery.[219] The nebulizer brand,[157,208] diluent volume, operating pressures and flows, and duration of treatment,[149,157] influence the efficiency of aerosol generation.

Ultrasonic nebulizers are infrequently employed for bronchodilator therapy during mechanical ventilation and there is scant published information about drug delivery with these devices.[160] Moreover, the particle size of aerosols produced by ultrasonic nebulizers in ventilator circuits has not been well characterized. The newer vibrating mesh nebulizers deliver twofold to fourfold higher drug dose than jet nebulizers. In the absence of bias flow, a vibrating mesh nebulizer was most efficient for drug delivery when it was placed 15 cm from the endotracheal tube, whereas in the presence of bias flow (2 L/min) the efficiency of the device was enhanced by placing it at the inlet of the humidifier (i.e., between the humidifier and ventilator).[218]

Synchronizing Aerosol Generation with Inspiratory Airflow. The actuation of a pMDI must be synchronized with the precise onset of inspiratory airflow from the ventilator.[220,221] As short as a 1- to 1.5-second delay between pMDI actuation and a ventilator breath can profoundly reduce the efficiency of drug delivery.[202]

In a ventilator circuit, nebulizers can be operated continuously or intermittently by airflow from the ventilator. Continuous aerosol generation requires a pressurized source of gas (from a wall outlet, pressurized tank, or an air compressor), whereas intermittent operation that is synchronized with inspiratory airflow requires a separate line to conduct inspiratory airflow from the ventilator to the nebulizer. Intermittent operation of the nebulizer is more efficient for aerosol delivery compared with continuous aerosol generation because it minimizes aerosol wastage during the exhalation phase of the breathing cycle.[200,217] The lower driving pressure provided by the ventilator (<15 pounds per square inch [psi]) than that provided by pressurized gas (≥50 psi) could decrease the efficiency of some nebulizers.[222] Aerosol generated by a nebulizer operating at the lower pressure may generate particles whose diameter is larger than the 1 to 5 μm that is optimal for aerosol deposition. When intermittent nebulizer operation is employed, the specific ventilator and nebulizer brand should be tested to determine the characteristics of the aerosol generated and the efficiency of drug delivery.[200]

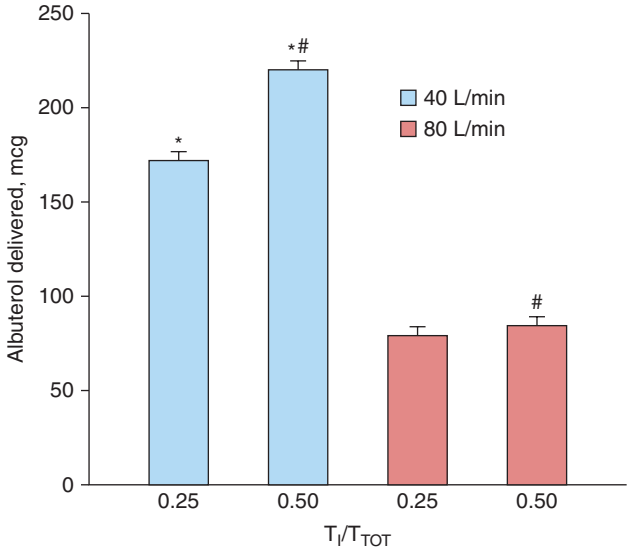

FIGURE 63-4 Comparison of aerosol delivery at different inspiratory airflows and duty cycles (T_I/T_{TOT}) in a bench model of mechanical ventilation. The ventilator delivered a tidal volume of 1000 mL with a constant inspiratory flow of 40 or 80 L/min, and the frequency of breathing was varied to achieve T_I/T_{TOT} values of 0.25 or 0.50 at each inspiratory flow setting. Albuterol delivery to the bronchi was greater with a T_I/T_{TOT} of 0.50 than of 0.25 at inspiratory flows of 40 L/min and 80 L/min. For each value of T_I/T_{TOT}, drug delivery with a slower inspiratory airflow (40 L/min) was almost twice that at the faster inspiratory airflow (80 L/min). *, $p < 0.01$, 40 L/min versus 80 L/min at T_I/T_{TOT} of 0.25 and T_I/T_{TOT} of 0.50; #, $p < 0.01$ T_I/T_{TOT} of 0.5 versus T_I/T_{TOT} of 0.25 at 40 L/min and 80 L/min. (Dhand R. Aerosol delivery during mechanical ventilation: from basic techniques to new devices. *J Aerosol Med Pulm Drug Deliv.* 2008;21:45–60.)

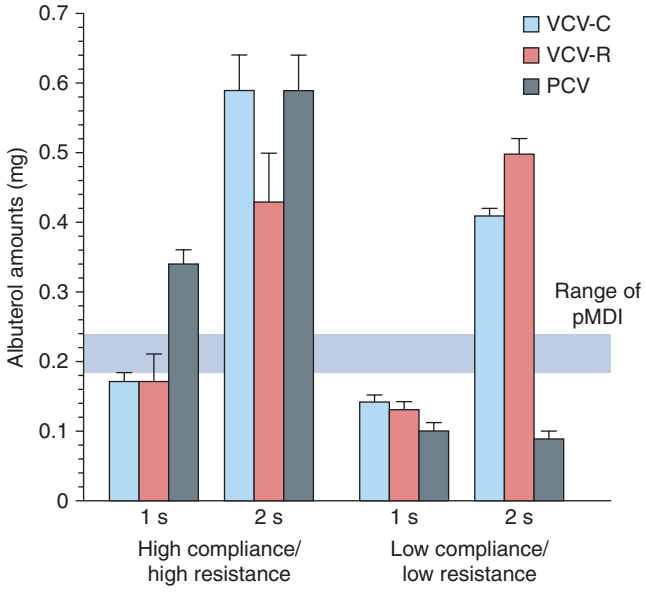

FIGURE 63-5 Comparison of aerosol delivery from a pressurized metered-dose inhaler (*pMDI*) and jet nebulizer in bench models of pressure-controlled and volume-controlled ventilation. The lung mechanics were varied by selecting two settings of resistance and compliance to achieve high or low time constants. For each condition, the amounts of aerosol delivered during inspiratory times of 1 second or 2 seconds were measured. Increasing the duration of inspiration from 1 second to 2 seconds improved the nebulizer efficiency. In the high-compliance/high-resistance setting with 1-second inspiration, nebulizer efficiency was higher during pressure-controlled than during volume-controlled ventilation, whereas the converse occurred in the low-compliance/low-resistance setting with 2 seconds inspiratory time. In contrast, the efficiency of a pressurized MDI (*horizontal purple area*) remained fairly constant under the various conditions simulated in the bench model. Thus, several factors, such as inspiratory time, pattern of inspiratory flow, and lung mechanics, that could influence drug delivery from a nebulizer have minimal influence on drug delivery from a pMDI. *PCV*, pressure-controlled ventilation; *VCV-C*, volume-controlled ventilation with a constant inspiratory flow; *VCV-R*, volume-controlled ventilation with a descending ramp flow pattern. (With kind permission from Springer Science and Business Media: Hess DR, Dillman C, Kacmarek RM. In vitro evaluation of aerosol bronchodilator delivery during mechanical ventilation: pressure-control vs. volume control ventilation. *Intensive Care Med.* 2003;29:1145–1150.)

Ventilator-Related Factors. The characteristics of the ventilator breath have an important influence on aerosol drug delivery. A tidal volume of 500 mL or more (in an adult),[195] longer inspiratory time, and slower inspiratory flows improve aerosol delivery[195,223,224] (Fig. 63-4). An inspiratory flow rate of 30 to 50 L/min is optimal for aerosol delivery; however, slow inspiratory flow rates may increase inspiratory time and by reducing the time for exhalation may have the unintended consequence of increasing auto–positive end-expiratory pressure.[225] Drug delivery is linearly correlated with a longer duty cycle (inspiratory time-to-total time [T_I/T_{TOT}]) for both pMDIs and nebulizers.[175,195,208] Moreover, drug delivery is improved when a pMDI is synchronized with a simulated spontaneous breath compared with a controlled ventilator breath of similar tidal volume.

The inspiratory waveform influences drug delivery from nebulizers, but has much less influence on drug delivery from a pMDI.[226] Unlike pMDIs, nebulizer efficiency could be different during pressure-controlled ventilation than during volume-controlled ventilation (Fig. 63-5).

The breath-triggering mechanism does not significantly influence drug delivery from a pMDI, but use of a flow trigger with a nebulizer could dilute the aerosol and increase the washout of the aerosol into the expiratory limb between breaths.[195,208]

Circuit-Related Factors. Several investigators found that drug delivery to the lower respiratory tract from both pMDIs and nebulizers is reduced by 40% or more in a humidified circuit when compared to a dry circuit (Fig. 63-6).[158,175,200,202,207,208] Circuit humidity increases the size of drug particles generated by a nebulizer.[227] When a pMDI is employed in a ventilator circuit, humidity probably interferes with propellant evaporation so that drug particles remain of a larger size and impaction losses are increased.[212,228]

Heat and moisture exchangers (HMEs) are employed as an alternative to heated humidifiers.[229] The filter in the HME captures the heat and moisture in the exhaled breath and transfers part of it to the air in the following inspiration. The HME filter captures drug particles in the aerosol and

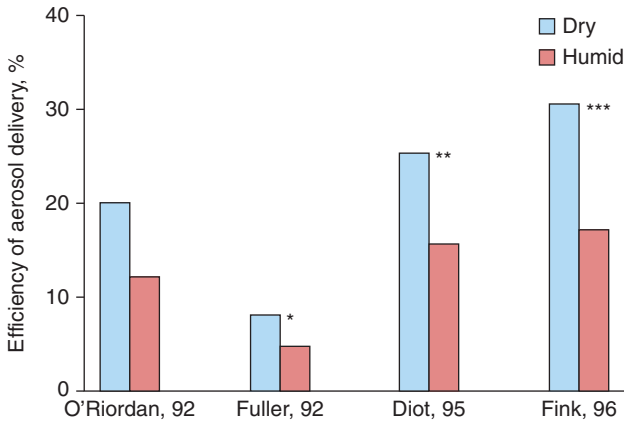

FIGURE 63-6 Effect of humidity on aerosol delivery. The delivery of aerosol to the lower respiratory tract in bench models of mechanical ventilation is reduced by approximately 40% when the circuit is humidified instead of dry. *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$. Studies: O'Riordan et al. 1994, Fuller et al. 1992, Diot et al. 1995, and Fink et al.1996, (Reprinted with permission of the American Thoracic Society. Copyright © 2012 American Thoracic Society. From Dhand R, Tobin MJ. Inhaled bronchodilator therapy in mechanically ventilated patients. *Am J Respir Crit Care Med.* 1997;156:3–10. Official Journal of the American Thoracic Society.)

markedly reduces the efficiency of drug delivery. Therefore, the HME must be removed from the circuit during aerosol treatments. Although placement of a nebulizer between the HME and endotracheal tube could provide adequate drug delivery, backflow of aerosol from the nebulizer could deposit on the HME filter, increase its airflow resistance, and increase the work of breathing for the patient.[230]

The density of the inhaled gas also influences drug delivery. High inspiratory flows employed during mechanical ventilation are associated with turbulence. Inhalation of a less-dense gas, such as a helium-oxygen 70/30 mixture, makes airflow less turbulent and more laminar. The use of helium-oxygen mixtures improved aerosol drug delivery in a pediatric model of mechanical ventilation.[231] In a bench model of adult mechanical ventilation, drug delivery from a pMDI was noted to be 50% higher with a helium-oxygen 80/20 mixture than with oxygen alone (Fig. 63-7A).[232] In contrast, nebulizer operation with helium-oxygen reduced drug output and respirable mass (Fig. 63-7B).[232,233] A practical method to achieve maximum pulmonary deposition of aerosol from a nebulizer during mechanical ventilation is to operate the nebulizer with oxygen at a flow rate of 6 to 8 L/min and to entrain the aerosol generated into a ventilator circuit containing helium-oxygen (Fig. 63-8).[233] Before employing helium-oxygen in ventilated patients, it is important to ensure that the ventilator is compatible with the use of such gas mixtures.[234]

Aerosol impaction on the endotracheal tube poses a significant barrier to effective drug delivery in infant and pediatric mechanical ventilation (endotracheal tube internal diameter 3 to 6 mm),[204,235] with aerosol delivery efficiency being lower with narrower endotracheal tube tubes.[236] In adult mechanical ventilation, there was no difference in nebulizer efficiency with endotracheal tubes of internal diameter 7 mm versus internal diameter 9 mm.[208] Drug losses within the endotracheal tube could be minimized by placing the aerosol generator at a distance from the endotracheal tube instead of being directly connected to it.[196] Removing the right angled elbow connector between the patient Y and endotracheal tube improves aerosol delivery.[175,237] Some investigators attached a long catheter to the nozzle of an pMDI and delivered aerosol directly into the trachea (i.e., beyond the endotracheal tube).[211] With this delivery system, concerns have been raised about catheter blockage and mucosal damage induced by propellants, surfactant, or other constituents of the pMDI formulation.[238]

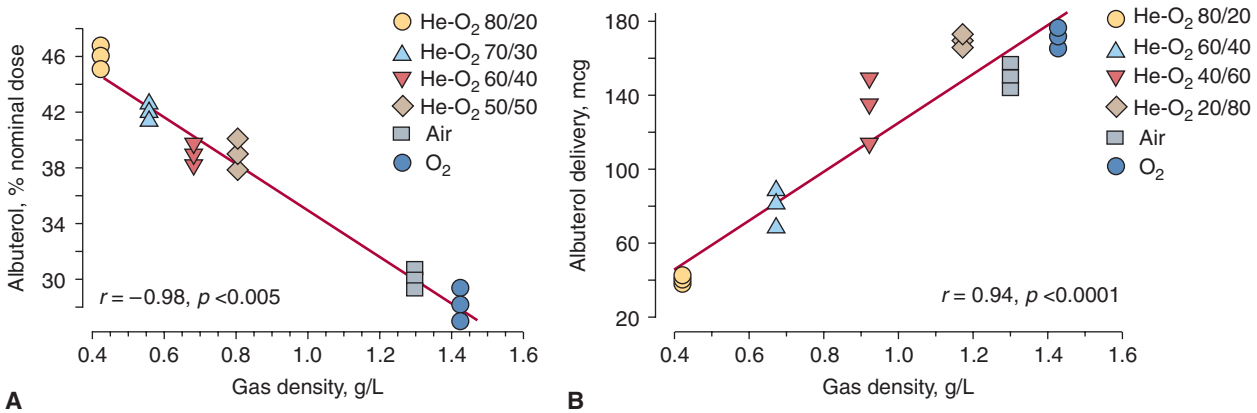

FIGURE 63-7 Effect of gas density on aerosol delivery from a pressurized metered-dose inhaler (pMDI) and jet nebulizer. **A**. Albuterol was administered via a pMDI and chamber spacer in an unheated dry ventilator circuit containing air, 100% oxygen, or several mixtures of helium-oxygen (80/20, 70/30, 60/40, and 50/50). Albuterol delivery from a pMDI (percentage of nominal dose) was inversely related ($r = -0.98$; $p < 0.005$) to gas density. **B**. Albuterol was administered with a jet nebulizer operated at a constant flow of 6 L/min of air, 100% oxygen, or helium-oxygen mixtures (as above) and albuterol output from the nebulizer was measured. Albuterol output from the nebulizer was positively correlated ($r = 0.94$; $p < 0.0001$) with the density of gas used to operate the nebulizer. (Reprinted with permission of the American Thoracic Society. Copyright © 2012 American Thoracic Society. Goode ML, Fink JB, Dhand R, et al. Improvement in aerosol delivery with helium-oxygen mixtures during mechanical ventilation. *Am J Respir Crit Care Med.* 2001;163:109–114. Official Journal of the American Thoracic Society.)

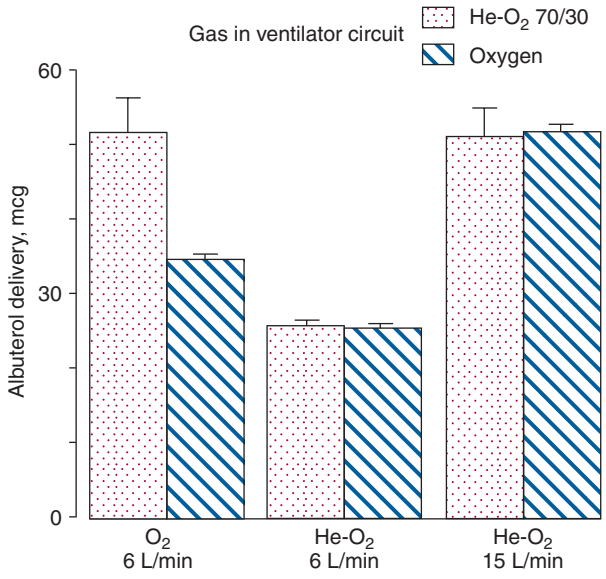

FIGURE 63-8 Effect of gas density and operating flow on aerosol delivery from a nebulizer. A jet nebulizer was operated with 100% oxygen at 6 L/min, helium-oxygen (70/30) at 6 L/min, or helium-oxygen (70/30) at 15 L/min. Drug delivery on filters was measured with the circuit containing helium-oxygen (*stippled bars*) or oxygen (*hatched bars*). Albuterol delivery was greatest when the nebulizer was operated with oxygen and the ventilator circuit contained helium-oxygen. Bars represent standard error (SE). (Reprinted with permission of the American Thoracic Society. Copyright © 2012 American Thoracic Society. Goode ML, Fink JB, Dhand R, et al. Improvement in aerosol delivery with helium-oxygen mixtures during mechanical ventilation. *Am J Respir Crit Care Med.* 2001;163:109–114. Official Journal of the American Thoracic Society.)

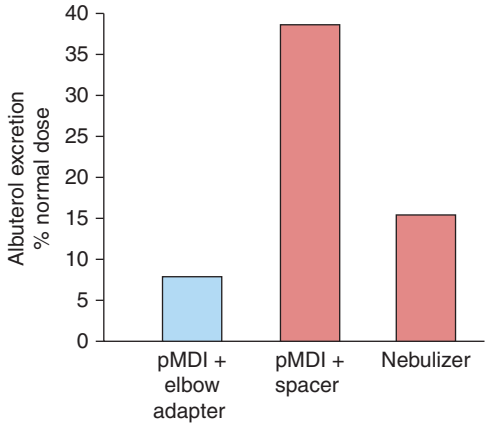

FIGURE 63-9 Comparison of systemic bioavailability of albuterol administered by pressurized metered-dose inhaler (*pMDI*) and right-angle elbow adapter, pMDI and chamber spacer, or jet nebulizer. Urine was collected for 6 hours after drug administration and the amounts of albuterol and its sulfate conjugate determined. The efficiency of the delivery device was determined by determining the percentage of drug excreted. The three delivery systems varied in the efficiency of drug delivery. The pMDI and elbow adapter had the lowest efficiency, the jet nebulizer was intermediate, and the pMDI with chamber spacer had the highest efficiency. (Data from Marik et al.[242])

IN VIVO STUDIES

Several investigators have used radionuclides and measured plasma or urinary drug levels to determine pulmonary deposition of aerosols in ventilated patients.

Radionuclide Studies. In ventilated patients, the pulmonary deposition of nebulized radiolabeled aerosol has been variously reported to be 1.22 ± 0.4%,[194] 2.22 ± 0.8%,[158] 2.9 ± 0.7%,[193] and 15.3 ± 9.5%.[199] Several factors, including type of radiolabel used, nebulizer brand, treatment time, circuit humidity, and methods used to calculate the amount of aerosol deposition,[199,200,208] contribute to the reported variation. With a pMDI and spacer chamber, approximately 6% of the dose was deposited in the lower respiratory tract;[194,214] this value was significantly lower than reported values (10% to 20%) with a pMDI and spacer in nonintubated ambulatory patients.[239,240]

Pharmacokinetic Studies. Unlike nonintubated patients, direct deposition of aerosol in the oropharynx and subsequent enteral absorption cannot occur in ventilated patients. Therefore, estimation of plasma levels of drugs administered by a pMDI should reflect lower respiratory tract deposition. After administration of albuterol with a pMDI and spacer, the area under the concentration-time curve was marginally lower in the patients than in healthy controls.[241] Moreover, measurement of urinary albuterol excretion in thirty ventilated patients with normal renal function showed that albuterol recovery was highest (38%) after administration with a pMDI and chamber spacer, intermediate with a nebulizer (16%), and lowest (9%) with a pMDI and right-angle port connected to the endotracheal tube (Fig. 63-9).[242] These results corroborated previous investigations that found very low efficiency of drug delivery with the adapter connected to the endotracheal tube.[208,209,214] Thus, pharmacokinetic studies show that with an optimal technique of administration, pulmonary drug deposition in ventilated patients is comparable to that achieved in healthy controls.

Pharmacokinetic studies have also been employed to compare the efficiency of drug delivery during mechanical ventilation. Moraine et al measured urinary ipratropium levels after ultrasonic nebulization in ventilated patients, and found no differences in urinary ipratropium levels with the nebulizer placed close to the patient Y or when it was placed before the heated humidifier.[243]

RECONCILING IN VITRO ESTIMATES OF DRUG DELIVERY WITH IN VIVO ESTIMATES OF DRUG DEPOSITION

The wide variation between in vitro[195,207–209] and in vivo estimates[194] of device efficiency can be reconciled by taking into account the effects of humidity in the ventilator circuit,[195] the quantity of exhaled aerosol that is not included in the in vitro measurement,[175] and by correcting for the quenching of radioactivity by the tissues of the chest wall.[214] When these factors are accounted for, in vitro data obtained with humidified ventilator circuits and in vivo gamma scintigraphic studies reveal that approximately

11% of the nominal dose from a pMDI and spacer chamber is deposited in the lower respiratory tract of ventilated patients. This value is remarkably close to values observed with the optimal use of a pMDI without a spacer (10% to 14%) in ambulatory patients.[239,240]

Drug delivery from nebulizers also shows discrepancies between values obtained with bench models versus those obtained by gamma scintigraphy.[158,193,194,219] Miller et al[200] found that accounting for circuit humidity and breath-actuated nebulization could reconcile most observed differences.

Thus, in vitro investigations that accurately simulate the clinical settings could play an important role in determining the performance of various inhalation devices under a variety of conditions encountered during mechanical ventilation.

CLINICAL USE OF BRONCHODILATORS

Bronchodilators Used

Bronchodilators are among the most commonly used drugs in the ICU.[13] In ventilator-supported patients with asthma or COPD, the goals of bronchodilator therapy are to reverse bronchoconstriction, decrease work of breathing, and/or relieve dyspnea. A response has been observed after administration of either aerosolized β-adrenergic[1,9,10,12,21,129,213,215,244–255] or anticholinergic bronchodilators.[129,252,256,257] Inhaled isoproterenol,[244,258] isoetharine,[259] metaproterenol,[2] fenoterol,[245,252] albuterol,[9,10,12,21,213,215,246–251,253–255] and salmeterol[29] produce significant bronchodilation in ventilated patients. The combination of fenoterol and ipratropium bromide was found more effective than ipratropium in ventilated patients with COPD.[260]

Selection of Patients

Ventilated patients with COPD demonstrate a significant decrease in airway resistance after administration of bronchodilators.[12,21,129,215,245,248,250,251,253,254,256,257] Bronchodilators have been successfully used to treat acute bronchospasm in the operating room,[244,258,259] and they are widely used in ventilated patients with severe asthma.[261] In addition, expiratory flow improved after bronchodilator administration in a heterogenous group of ventilated patients.[2] Nebulized metaproterenol reduced elevated levels of airway resistance in patients with acute respiratory distress syndrome.[4,5] Thus, a wide spectrum of patients receiving mechanical ventilation receive bronchodilators.[3]

Bronchodilator Efficacy

ASSESSMENT OF BRONCHODILATOR RESPONSE

The response to bronchodilators depends on several variables: patient airway geometry, degree of airway responsiveness, severity of disease, quantity of secretions, and counterregulatory effects of airway inflammation and other drugs. Most investigators assess response by measuring inspiratory airway resistance. Airway resistance in ventilated patients is commonly measured by performing rapid airway occlusions at constant flow inflation.[262,263] This technique involves performing a breathhold at end-inspiration by occluding the expiratory port. Total or maximal inspiratory resistance (Rrs max) can be partitioned into minimal inspiratory resistance (Rrs min), which reflects "ohmic" resistance of the airways, and additional effective resistance (ΔRrs). The latter resistance represents time-constant inhomogeneities within the lung ("pendelluft") and viscoelastic behavior of the pulmonary tissues.[262,263] Similarly, airway occlusion at end-expiration produces an increase in airway pressure to a plateau value, signifying intrinsic positive end-expiratory pressure.[12] Comparisons of airway resistance and intrinsic positive end-expiratory pressure before and after drug administration are useful for assessing response.

Most ventilated patients with COPD demonstrate a decrease in airway resistance and intrinsic positive end-expiratory pressure following bronchodilator administration.[4,9,12,21,213,215,245,248,250,251–255] That ΔRrs does not decrease significantly after albuterol delivery with a pMDI[12,212,215] suggests that the bronchodilator effect occurs predominantly in the central airways with little effect on viscoelastic behavior or time-constant inhomogeneities in the lung. Moreover, albuterol does not significantly influence the elastic properties of the lung.[12] In contrast, a greater decline in ΔRrs was noted after nebulizer delivery of albuterol and ipratropium bromide.[252] This difference in response between pMDIs and nebulizers could be due to higher drug deposition in peripheral airways with the use of a nebulizer.

In bench models, drug delivery was increased during simulated spontaneous breaths compared to controlled mechanical breaths.[195] In ventilated patients with acute exacerbations of COPD, however, the bronchodilator response did not differ between controlled mechanical ventilation and pressure support.[255] The use of propofol for sedation was a significant confounder of that study because of its known bronchodilator effect.[264]

DOSE RESPONSE TO BRONCHODILATOR ADMINISTRATION IN VENTILATED PATIENTS

Few investigators have examined the dose response to bronchodilators in ventilated patients.[213,215,224,245,254] Most investigators found that the response with the higher doses was no greater than that observed after the initial dose (Figs. 63-10 and 63-11).[215,245] Dose–response curves in stable, ventilated patients with COPD are shallow; when the technique of administration is carefully executed, most patients achieved near maximal bronchodilation with 4 puffs of albuterol.[215] Mouloudi et al[21,250,251,253] showed that, with an optimal technique of administration, alterations in mechanical ventilator settings do not influence

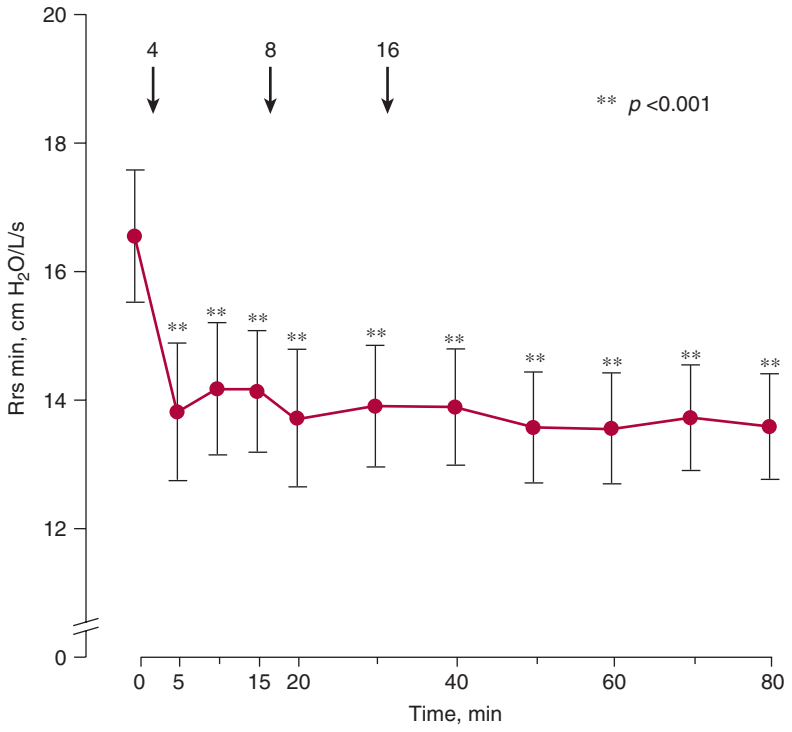

FIGURE 63-10 Effect of albuterol on minimal inspiratory resistance (*Rrs min*) in twelve stable mechanically ventilated patients with COPD. Significant decreases in Rrs min occurred within 5 minutes of administration of 4 puffs of albuterol. The addition of 8 and 16 puffs (cumulative doses of 12 and 28 puffs, respectively) did not achieve a significantly greater effect than that with 4 puffs ($p > 0.05$). Bars represent standard error (SE). **, $p < 0.001$. (Reprinted with permission of the American Thoracic Society. Copyright © 2012 American Thoracic Society. From Dhand R, Duarte AG, Jubran A, et al. Dose-response to bronchodilator delivered by metered-dose inhaler in ventilator-supported patients. *Am J Respir Crit Care Med.* 1996;154:388–393. Official Journal of the American Thoracic Society.)

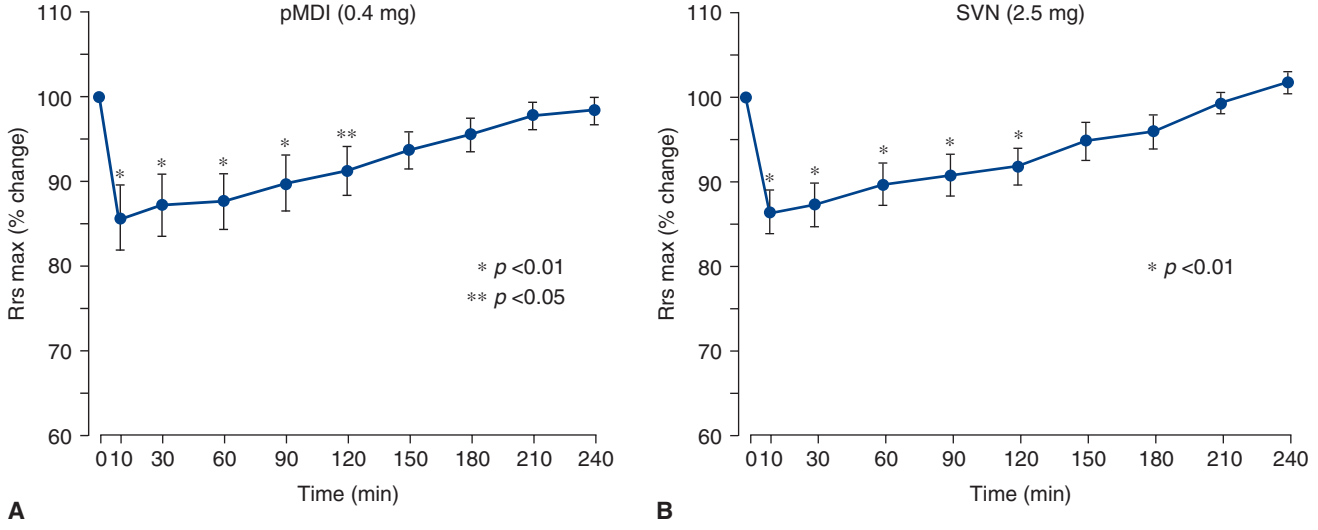

FIGURE 63-11 Effect of albuterol on maximum inspiratory airway resistance (*Rrs max*) in stable, mechanically ventilated patients with COPD. There was a decrease in Rrs max from baseline values within 10 minutes of albuterol administration. **A**. Change in Rrs max from baseline (time 0) after 4 doses of albuterol from a pMDI. **B**. Change in Rrs max from baseline (time 0) after 2.5 mg of albuterol given by nebulizer. Significant reductions in Rrs max were sustained for 2 hours and returned to baseline by 4 hours. The response to albuterol administered by pMDI (0.4 mg) was comparable to that achieved with 2.5 mg administered by nebulizer. Bars represent standard error of mean (SEM). (Used, with permission, from Duarte et al.[254])

the response to albuterol in stable patients with COPD. Patients with acute exacerbations of asthma or COPD may require higher doses.

DURATION OF BRONCHODILATOR RESPONSE

In stable, ventilated patients with COPD, the bronchodilator effect of albuterol is sustained for 2 to 3 hours.[21,254] Thus, in contrast to the four-times-a-day and as-needed albuterol dosing in ambulatory patients, ventilated patients may require dosing every 3 to 4 hours. Two or three times daily dosing may be feasible with salmeterol because its bronchodilator effect is sustained for approximately 8 hours in ventilated patients.[255]

AEROSOL THERAPY IN MECHANICALLY VENTILATED NEONATES AND INFANTS

Infants breathe with a high frequency and low tidal volume. This rapid shallow breathing pattern reduces drug deposition in the lung by limiting the time available for particle deposition. In nonintubated, spontaneously breathing infants, pulmonary deposition of radiolabeled aerosols administered via pMDI and face mask, or nebulizer and face mask, is as low as 0.3% to 2.6% of the nominal dose.[265–269] Several investigators report similar decreases in aerosol delivery in ventilated neonates and infants because of small-diameter endotracheal tubes and ventilator tubing, and the low tidal volumes employed.[235,270,271] Moreover, ventilator modes differ; pressure-limited and time-cycled modes of ventilation are more common, with continuous flow through the circuit and very-short-duty cycles.

In Vitro Studies of Aerosol Drug Delivery in Infants

METERED-DOSE INHALERS

When the pMDI was actuated into a prototype spacer chamber, there was a 10-fold variation (from 0.2% to 2.0% of the nominal dose) in drug delivery to a filter placed beyond the endotracheal tube.[272] Higher values of drug delivery were achieved when the pMDI was actuated before inspiration than after inspiration, and when higher tidal volumes and longer inspiratory times (inspiratory-to-expiratory timing [I:E] ratio 1:1) were employed. The type of spacer employed to actuate a pMDI has a dramatic influence on drug delivery (see Table 63-3).[273–276] In a dry infant ventilator circuit, drug delivery as high as 14.2% was achieved when an AeroChamber MV15 (Monaghan Medical Corp., Plattsburgh, NY) was placed between the ventilator Y and endotracheal tube and the pMDI was actuated at end-expiration.[273] With an ACE spacer in a humidified circuit during infant mechanical ventilation, an HFA-albuterol pMDI formulation gave marginally higher drug delivery than a CFC-albuterol pMDI formulation (5.7% vs. 4.8%, respectively).[276] When a HFA-pMDI was employed with a valved-holding chamber made of electrostatic charge dissipative polymer, aerosol delivery was lower during simulated mechanical ventilation compared to delivery with a manual resuscitation bag or during simulated spontaneous breathing.[277]

NEBULIZERS

Nebulizers have shown uniformly poor efficiency for drug delivery in infants. During simulated infant ventilation, nebulizers deliver less than 2% of the nominal drug

TABLE 63-3: EFFICIENCY OF DRUG DELIVERY WITH A pMDI AND SPACER IN INFANT VENTILATION

First author[a]	Spacer	ET(mm)	V_T(mL)	Mode	Efficiency (%)
Everard	Prototype	3.0	11 to 22	Pressure limited, 30 cm H_2O	1.5 to 2
Coleman	ACE	3.5	55	Pressure 60/5 cm H_2O	14.5
	AeroChamber MV				11.9
	AeroVent				6.8
	Inline adapter				6.4
Avent	AeroChamber	3.5	–	Pressure 20/2 cm H_2O	2.2
	Inline adapter			Humidified circuit	0.1
Lugo	CFC-pMDI with ACE	3.0	7	Pressure 25/4 cm H_2O	4.8
	HFA-pMDI with ACE			Humidified circuit	5.7
DiBlasi	HFA-pMDI with AeroChamber Mini/ Spontaneous breaths	2.5, 3.5, 4.0	6 to 60	Mechanical/manual Humidified circuit	3.7 to 13.4[a]

Abbreviations: ET, internal diameter of endotracheal tube; V_T, tidal volume

[a] Values are means of efficiency of drug delivery in various settings. Efficiency of drug delivery was lower during mechanical ventilation compared to manual resuscitation or spontaneous breathing probably because of the effects of high humidity in the circuit during mechanical ventilation.

Source: Data from Everard,[272] Coleman,[274] Avent,[275] Lugo,[276] and DiBlasi.[277]

dose.[273,274,278–280] Many factors influence drug delivery with a nebulizer: type of nebulizer[273,278] and its position in the circuit,[276] intermittent versus continuous nebulization,[280] nebulizer flow,[274] inspiratory time,[274] volume-limited versus pressure-limited ventilation,[276] humidity, and size of the endotracheal tube. Placement of a jet nebulizer in the inspiratory limb of a humidified pediatric ventilator circuit 15 cm from the Y-piece had a lower efficiency of drug delivery compared to placement between the humidifier and ventilator.[167] A vibrating mesh nebulizer achieved twofold to fourfold higher drug delivery than the jet nebulizer.[167] The highest efficiency of drug delivery occurred with the vibrating mesh nebulizer placed at the inlet of the humidifier and operated continuously with a bias flow of 2 L/min in the ventilator circuit. Higher bias flows (5 L/min) reduced the efficiency of drug delivery.[167] In contrast, Turpenin et al found that drug delivery was improved when the nebulizer was placed at the endotracheal tube compared to placement in the inspiratory limb.[281] Moreover, as expected, breath-synchronized nebulization resulted in higher drug delivery than continuous nebulization.[282] The very low efficiency of nebulizers during infant mechanical ventilation, however, means that pulmonary drug deposition would be marginally influenced by altering the ventilator conditions. In fact, underdosing is a concern when a jet nebulizer is employed with settings that have very poor efficiency (as low as approximately 0.1%) for drug delivery.

METERED-DOSE INHALERS VERSUS NEBULIZERS

Few investigators have compared the pMDI to nebulizer efficiency during infant ventilation.[273–276] With optimal technique, the efficiency of pMDIs (approximately 14%) is considerably higher than that of nebulizers (approximately 2%).

In Vitro Studies of Aerosol Drug Delivery in Older Children

In older children, the efficiency of pMDIs and nebulizers improve with increasing age,[270,271] and the factors influencing drug delivery are similar to those in adults.[177]

In Vivo Studies of Drug Delivery in Infants and Neonates

The lung deposition of radiolabeled aerosols in ventilated infants with bronchopulmonary dysplasia was as low as 0.98 ± 0.2% and 0.22 ± 0.1% with a pMDI and spacer or a jet nebulizer, respectively.[283] Minocchieri et al employed a premature nose–throat model to demonstrate that lung deposition was reduced from 61.8 ± 5% to 26.0 ± 1.5% and 9.0 ± 0.8% of the nominal dose at continuous flows of 1, 5, and 10 L/min, respectively.[284] Moreover, placement of the nebulizer closer to the endotracheal tube did not improve the low efficiency of aerosol delivery.[285] In macaque monkeys, pulmonary deposition of ^{99m}technetium diethylenetriamine pentaacetate with a vibrating mesh nebulizer (Aeroneb Pro prototype) was more than 20-fold higher than that with a jet nebulizer (MistyNeb, Airlife Inc., Mountain View, CA).[286]

Clinical Studies

The low efficiency of drug delivery is offset by the smaller size of the lung in infants and children. Compared to a standard 1.3 mcg of albuterol/kg body weight delivered by each actuation from a Ventolin-HFA pMDI in a 70-kg, spontaneously breathing, adult male, the range for spontaneously breathing infants and small children varies from 0.8 to 2.6 mcg of albuterol delivery/kg body weight/actuation with a HFA-pMDI and AeroChamber Plus valved holding chamber.[287] Similar considerations apply for infants and children receiving mechanical ventilation.

Inhaled bronchodilators (β-adrenergic and anticholinergic drugs)[6–10,288–292] are effective in ventilated neonates and infants with acute, subacute, and chronic lung disease. Response to inhaled albuterol was similar to that seen after intravenous administration.[289] Albuterol administered with a pMDI and AeroChamber was found to be more effective than administration with a nebulizer (Fig. 63-12).[10,291] Ultrasonic nebulizers may be as (or more) effective than pMDIs for bronchodilator administration in infants (Fig. 63-12). In addition to monitoring airway resistance and pulmonary compliance, changes in heart rate should be assessed to prevent overdosing. ICSs have been advocated in infants for prevention[293,294] and treatment of bronchopulmonary dysplasia,[295–297] but their efficacy has not been established. In summary, during infant mechanical ventilation, pMDIs appear to be more efficient than jet nebulizers; with a careful technique of administration, one or two doses from an albuterol pMDI

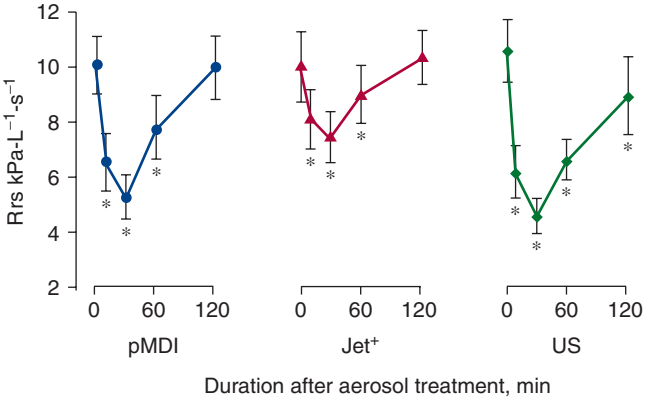

FIGURE 63-12 Total resistance of the respiratory system (*Rrs*) before and at 15, 30, 60, and 120 minutes after albuterol via pressurized metered-dose inhaler (*pMDI*), jet nebulizer (*Jet*), and ultrasonic nebulizer (*US*) during infant ventilation. *, posttreatment Rrs was significantly lower than pretreatment Rrs ($p < 0.0001$). The response to albuterol after administration with a pMDI was greater than that obtained with a jet nebulizer but was comparable to that obtained with an ultrasonic nebulizer. (Used, with permission, from Fok et al.[291])

and spacer chamber should suffice for routine therapy. The aerosol delivery efficiency of vibrating mesh nebulizers is comparable to pMDIs, but the clinical effectiveness of these devices in infants and children needs further study.

TECHNIQUES OF AEROSOL ADMINISTRATION

The optimal techniques for administration of inhaled drugs to ventilated patients are based on the various factors discussed above. The technique employed may have to compromise between the optimum operating characteristics of the device and the patient's condition. For example, although a higher duty cycle increases aerosol delivery,[195,199] it may worsen dynamic hyperinflation in patients with airflow limitation.[225] With this caveat in mind, the technique of administration for pMDIs in ventilated patients is shown in Table 63-4 and that for nebulizers in Table 63-5. The key aspects of the technique with pMDIs are to place an appropriate adapter at a short distance (approximately 15 cm) from the endotracheal tube and to synchronize actuation with inspiratory flow. For nebulizers, it is critical to use the device as recommended by the manufacturer and to place it at a distance from the patient. When these techniques are employed, adequate drug deposition is achieved in the lung[175,195,200] and a significant bronchodilator response is obs erved.[12,21,213,215,224,248,250–255] Most ventilated patients, however, do not show incremental effects with higher drug doses.[215]

Use of Metered-Dose Inhalers or Nebulizers

Nebulizers and pMDIs delivered an equivalent mass of aerosol beyond the endotracheal tube in a ventilator model;[202] in ventilated patients, both devices produced similar therapeutic effects.[246,252,254] When used optimally, pMDIs and nebulizers are equally effective in the treatment of patients with obstructive lung disease.[62]

pMDIs are preferred in ventilated patients because of several problems associated with the use of nebulizers.[155–157,226,232,233] Before using a nebulizer in a ventilated patient, it is imperative to characterize its efficiency in a ventilator circuit, under the typical clinical conditions in which it will be employed.

Unless scrupulously cleaned and disinfected, nebulizers can be a source for aerosolization of bacteria,[298] and thus predispose patients to nosocomial pneumonia.[299] The gas flow driving the nebulizer produces additional airflow in the ventilator circuit, but this is compensated for in most modern ventilators. In contrast, pMDIs are easy to administer, require less personnel time, provide a reliable dose, and do not pose a risk of bacterial contamination. Use of pMDIs rather than nebulizers saves cost and time.[300–302] Costs of bronchodilators have a significant impact on overall costs of care.[302]

In summary, pMDIs offer several advantages over nebulizers for routine bronchodilator therapy. One survey found that most reporting centers (57%) were using pMDIs in neonates and their use had steadily increased since 1988;[303] similar trends are observed in adults.

TABLE 63-4: OPTIMAL TECHNIQUE FOR DRUG DELIVERY BY pMDI IN VENTILATED PATIENTS

1. Review order, identify patient, and assess need for bronchodilator.
2. Suction endotracheal tube and airway secretions.
3. Shake pMDI and warm to hand temperature.
4. Place pMDI in spacer chamber adapter in ventilator circuit.
5. Remove HME. Do not disconnect humidifier.
6. Coordinate pMDI actuation with beginning of inspiration.
7. Wait at least 15 seconds between actuations; administer total dose.
8. Monitor for adverse response.
9. Reconnect HME.
10. Document clinical outcome.

Abbreviations: HME, heat and moisture exchanger; *pMDI*, pressurized metered-dose inhaler.

TABLE 63-5: OPTIMAL TECHNIQUE FOR DRUG DELIVERY BY JET NEBULIZER IN VENTILATED PATIENTS

1. Review order, identify patient, and assess need for bronchodilator.
2. Suction endotracheal and airway secretions.
3. Place drug in nebulizer to fill volume of 4 to 6 mL.
4. Place nebulizer in the inspiratory line 18 in (46 cm) from the patient Y connector.
5. Turn off flow-by or continuous flow during nebulizer operation.
6. Remove HME from circuit (do not disconnect humidifier).
7. Set gas flow to nebulizer at 6 to 8 L/min.
   a. Use a ventilator if it meets the nebulizer flow requirements and cycles on inspiration, *or*
   b. Use a continuous flow from external source.
8. Adjust ventilator volume or pressure limit to compensate for added flow.
9. Tap nebulizer periodically until nebulizer begins to sputter.
10. Remove nebulizer from circuit, rinse with sterile water and run dry, store in safe place.
11. Reconnect humidifier or HME, return ventilator settings and alarms to previous values.
12. Monitor patient for adverse response.
13. Assess outcome and document findings.

Abbreviation: HME, heat and moisture exchanger.

DRUG TOXICITY

Higher doses of β-agonists delivered by a pMDI can cause atrial and ventricular arrhythmias.[304–306] Manthous et al[213] observed sinus tachycardia or supraventricular ectopy after

a cumulative dose of 7.5 mg of albuterol administered by a nebulizer in four of ten patients, and most of the remaining patients developed premature atrial and ventricular contractions with a cumulative dose of 15 mg.[213] Although most investigators have reported no adverse effects following administration of albuterol with a pMDI,[12,129,194,213,214] a dose-dependent increase in heart rate occurs with higher doses.[215] No significant arrhythmias or other serious cardiovascular side effects were observed in ambulatory patients in an emergency department who were treated for acute asthma with up to 16 puffs each of albuterol or fenoterol administered with a pMDI attached to a holding chamber and face mask.[65] Continuous nebulization of β-agonists is effective and safe in nonintubated children[307] and adults[74] with acute severe asthma, but the efficacy and safety of continuous nebulization has not been established in ventilated patients. A few anecdotal reports have described cardiotoxicity secondary to CFCs.[308] Adverse cardiac effects are unlikely to occur with the doses recommended in clinical practice, particularly if there is a short interval between successive doses, because CFCs have a short half-life (<40 seconds) in blood after administration via pMDI in healthy volunteers.[309] With a catheter connected to a pMDI nozzle, however, a substantial portion of the total mass output of the pMDI is delivered directly onto the tracheobronchial mucosa and there is potential for local and systemic toxicity.[238]

Arterial oxygen tension (Pa_{O_2}) may decrease transiently after β-agonist inhalation, probably secondary to pulmonary vasodilation mediated by β_2-receptors.[310,311] In contrast, reduction in Pa_{O_2} was either not seen after inhalation of antimuscarinic agents[312] or was less than the decrement produced by albuterol and salmeterol.[43] The decrease in Pa_{O_2} with albuterol inhalation is transient and small; hence, its clinical significance is doubtful.[43] Significant drops in Pa_{O_2}, however, can occur occasionally,[311,313] and close monitoring may be required in patients with marginal oxygenation.

Blood glucose and insulin levels increase after β-agonist administration, whereas serum potassium levels decrease.[310,314] The clinical importance of these effects is inconclusive; however, in patients with severe airway obstruction fall in serum potassium in the presence of hypoxia has the potential to cause cardiac arrhythmias. A variety of central nervous system effects including anxiety, nervousness, tremor, irritability, insomnia and headaches are associated with use of β-adrenergic agents.

GUIDELINES FOR INHALED THERAPY

Subtle differences in the method of administration can markedly decrease aerosol deposition in the lower respiratory tract.[175,195,202,208,213,226] Routine bronchodilator therapy can be given successfully with assisted modes if aerosol delivery is synchronized with inspiratory flow from the ventilator. Based on the recommendation for use of pMDIs in ambulatory patients, some investigators use a postinspiratory breathhold after aerosol administration.[129,246] With an optimal technique, this maneuver does not influence bronchodilator response in ventilated patients.[250] Mouloudi et al[251,253] have also shown that increasing the tidal volume or using pressure-control (decelerating flow pattern) versus volume-control (constant flow pattern) ventilation did not affect the response to albuterol inhalation with a pMDI. These findings are consistent with other studies showing shallow dose–response curves in ventilated patients.[9,129,215,245,254] Thus, there may be little justification for manipulating ventilator settings to enhance drug deposition in the lung provided an optimal pMDI technique is employed.

Although humidification of the circuit reduces aerosol deposition by approximately 40%,[195,197] bypassing the humidifier is not routinely recommended because it would require disconnection of the ventilator circuit and several minutes would be added to each bronchodilator treatment while waiting for the circuit to become dry. Moreover, when heated wire circuits are employed, there was no reduction in delivery efficiency of albuterol with a pMDI and spacer for up to 60 minutes after turning on the heated humidifier,[315] and after 3 hours of humidifier operation, it took 10 minutes after shutting off the humidifier for aerosol delivery to improve. Even with a humidified circuit, a significant effect is observed with as few as 4 puffs.[215] Bypassing the humidifier may be one method to improve pulmonary drug delivery with more expensive, nonbronchodilator agents. Before such a practice can be routinely recommended, however, studies are needed to document the safety of repeatedly administering nonhumidified gases, albeit for limited periods, to ventilated patients.

BRONCHODILATOR THERAPY DURING NONINVASIVE VENTILATION

Noninvasive positive-pressure ventilation (NIPPV) is being increasingly employed for treatment of patients with acute and chronic respiratory failure.[316] Successful application of NIPPV with a nasal or face mask in patients with acute exacerbations of COPD can often obviate the need for endotracheal intubation and improve mortality.[317–320] Patients with acute or acute-on-chronic respiratory failure who are receiving NIPPV often require inhaled bronchodilators for relief of airway obstruction. One option is to remove the patient from NIPPV and administer bronchodilators by pMDI or nebulizer with a face mask as patients can tolerate brief periods of discontinuation needed for bronchodilator therapy.[321] It is preferable, however, to continue NIPPV without interruption, especially in acutely hypoxic or dyspneic patients.

The delivery of aerosols during NIPPV is complicated by high inspiratory flows that increase turbulence and the associated high inertial forces cause greater particle impaction in central airways.[223,322] On the other hand, application of positive pressure increases tidal volume and

reduces respiratory rate, both of which tend to enhance aerosol delivery.[323] Moreover, increase in expiratory time because of a slower respiratory rate could enhance particle sedimentation and alter the pattern of drug deposition during exhalation.[323] Initial enthusiasm for administration of bronchodilators with intermittent positive-pressure breathing[324] was generated when it was shown that higher plasma levels of albuterol were achieved by this technique compared to administration by pMDI alone. Later studies, however, found that drug delivery to patients with severe COPD and relatively fixed airway obstruction was reduced by administration with intermittent positive-pressure breathing.[325]

The use of continuous positive airway pressure (CPAP) may be more helpful than intermittent positive-pressure breathing in reducing work of breathing in patients with acute bronchoconstriction.[326,327] However, in a bench model, 10-cm H_2O CPAP reduced drug delivery from a jet nebulizer.[328] Mask CPAP is optimally employed with a continuous fresh gas flow that approaches or exceeds the patient's inspiratory flow rate so as to minimize the additional work imposed by a demand valve system.[329] Entrainment of aerosols into the high rates of gas flow used during CPAP dilutes the drug and favors evaporation leading to reduced droplet size, cooling, and hypertonicity,[152] with the potential to produce paradoxical bronchoconstriction. Likewise Chatmongolkolchart et al found that application of CPAP alone, especially higher levels of CPAP, reduced aerosol delivery.[330]

Noninvasive pressure support provides a more sustained boost to inspiratory effort than intermittent positive-pressure breathing by maintaining a constant preset airway pressure.[331] Application of pressure support reduces inspiratory muscle effort and respiratory rate, increases tidal volume and improves arterial blood-gas values.[332,333] Pressure support could also produce more uniform aerosol deposition in the lungs by reversing small airway closure and microatelectasis.[334]

During bilevel ventilation, Faroux et al [335] found that in children with cystic fibrosis, pulmonary deposition of radiolabeled aerosol was increased by the application of 10 cm H_2O pressure support. This study, however, employed a homecare ventilator that does not incorporate a leak port in the circuit and the nebulizer was active only during inspiration. Chatmongkolchart et al[330] found a fivefold variation (between 5% and 25% of the nominal dose) in the amount of albuterol delivered by a jet nebulizer in vitro; delivery was highest (25%) when the nebulizer was close to the patient (between the leak port and patient connection), inspiratory pressure was high (20 cm H_2O), and expiratory pressure was low (5 cm H_2O).[330] Although nebulizer operation during bilevel positive-pressure ventilation does not influence ventilator function,[330] nebulizer operation with bilevel positive-pressure ventilation enhances drug delivery and produces a finer aerosol with a higher proportion of respirable particles compared to nebulizer operation alone.[336] NIPPV, however, did not improve radioaerosol deposition compared to spontaneous breathing in healthy volunteers.[337]

Intrapulmonary percussive ventilation was found to produce a finer aerosol than standard jet nebulization, but pulmonary deposition of radiolabel was much more variable and unpredictable with this technique in healthy volunteers compared to standard nebulizer therapy, and it was not recommended as a mode of aerosol delivery.[338] The use of high-frequency oscillation for radioaerosol delivery was found to reduce total pulmonary drug deposition in normal subjects, and in patients with chronic airflow obstruction, despite a reduction in the size of the aerosol.[339] In normal subjects, the regional distribution of aerosol deposition was unchanged, but in the patients with airflow obstruction a larger proportion of total aerosol deposition occurred in the peripheral lung during high-flow oscillation.[339]

The optimum settings required for maximum drug delivery with a pMDI during NIPPV have not been established. Significant bronchodilator responses occur after albuterol administration with a jet nebulizer or a pMDI in stable patients receiving NIPPV with face mask.[340,341] Nava et al used a homecare ventilator and volume-assured pressure support with dry, unwarmed gas to obtain a guaranteed tidal volume of 10 mL/kg in clinically stable patients with severe COPD.[340] With the pMDI and spacer placed in the inspiratory limb of the ventilator circuit immediately after the patient Y, they found a higher change in FEV_1 after albuterol administration compared to placebo but the effect was comparable to that obtained with a pMDI and spacer during spontaneous breathing.[340] Similarly, Parkes and Bersten employed CPAP at 10 cm H_2O and used nonhumidified compressed gas at a flow rate of 50 L/min with a tight face mask fit in nine stable patients with asthma.[328] Despite reduction in total aerosol delivery, application of CPAP did not affect the bronchodilator response to nebulized albuterol.[328] Patients with acute asthma exacerbations who received albuterol administered during bilevel positive airway pressure ventilation[341] had more rapid and greater improvement in peak expiratory flow than did patients receiving a similar dose by nebulizer alone. It is unclear, however, if this was caused by relief provided by pressure support, or enhanced drug delivery or drug effect produced by NIPPV, or a combination of the two. Both pMDIs and nebulizers could be successfully employed during NIPPV by using the techniques recommended by Hess.[342]

The position of the leak port in the single-arm circuit used for bilevel positive-pressure ventilation influences nebulizer efficiency, but it does not influence pMDI efficiency of drug delivery.[343] Nebulizer efficiency is higher with the leak port in the circuit as compared to a leak port in the face mask.[343] Calvert et al reported that a nebulizer placed between the leak port and ventilator performs with a higher efficiency than placement of the nebulizer between the leak port and face mask.[336] In contrast, Abdelrahim et al found a higher drug delivery with the nebulizer placed between the leak port and face mask than with the nebulizer placed between the ventilator and leak port.[344] The difference in the results of the two studies[336,344] may be explained by the fact that the former investigators placed the nebulizer at a farther distance from the leak port than did the latter investigators.

Moreover, drug delivery with a vibrating mesh nebulizer at either position of the nebulizer was more than twice that delivered by a conventional jet nebulizer.[344]

In summary, delivery of aerosols to patients receiving NIPPV is extraordinarily complex. Several factors related to the type of ventilator employed, the type of aerosol generator and its position in the ventilator circuit, the mode of ventilation, tidal volume, inspiratory flow rate, inspiratory and expiratory pressure settings, circuit humidity, the density of the gas in the circuit, type of mask interface, mask size, and patient characteristics all influence the efficiency of aerosol delivery in this setting. Moreover, the single-circuit design, continuous air flow, and the presence of a leak port further complicate aerosol delivery.

IMPORTANT UNKNOWNS

Despite frequent use of bronchodilators in ventilated patients, their effects on clinically relevant outcomes, such as duration of mechanical ventilation, length of ICU stay, development of ventilator-associated pneumonia, and mortality have not been studied. In fact, few randomized controlled studies have been performed in this patient population.[62] Variations in the methods of administration and assessment of response make it difficult to compare results between various studies.

Further work is also needed to determine whether newer generation of vibrating mesh nebulizers, soft mist inhalers, and dry powder inhalers can be successfully adapted for use during mechanical ventilation.

THE FUTURE

Ventilated patients present a unique opportunity to exploit the advantages of the inhaled route for drug delivery. The past two decades have seen impressive gains in knowledge and understanding of methods to deliver inhaled therapies to ventilated patients. Within the past few years, newer aerosol-generating devices designed for use during mechanical ventilation have become available. These devices are far more efficient than previous jet nebulizers. In the future, further improvements in device design will result in higher efficiency devices that also ensure precision, reliability, and consistency of dosing.

Some modern ventilators have integrated aerosol-generating devices, and this integration should further improve the characterization of aerosols and consistency of drug dosing.

NIPPV is being increasingly employed, especially in patients with acute exacerbations of COPD. Further work is needed to improve our understanding of the factors influencing inhaled drug delivery in this setting. Delivery devices that are designed specifically for mask ventilation would be helpful. Moreover, recent gains in improving aerosol delivery to infants and children will lead to greater clinical application of inhaled therapies in this population.

SUMMARY AND CONCLUSION

Bronchodilator therapy is commonly employed in ventilated patients. Inhaled β-agonist and anticholinergic bronchodilators are widely used, whereas use of theophylline in the ICU has declined significantly. Although ICSs are being employed in ventilated patients, especially in combination with long-acting β-agonists, further investigations are needed to determine the optimal methods of administration, drug dosage, and efficacy; and to assess their risk-to-benefit ratio in this setting. Optimal techniques for employing pMDIs and nebulizers in ventilator circuits have been developed as a result of better understanding of the factors influencing aerosol delivery to the lower respiratory tract of ventilated patients. Important variables that influence aerosol delivery include the type of nebulizer used and its position in the circuit, actuation of a pMDI into an inline chamber spacer, timing of actuation, ventilator mode, tidal volume, circuit humidification, and duty cycle. With proper technique, drug deposition in the lower respiratory tract of ventilator-dependent patients is comparable to that in ambulatory patients. A somewhat higher dose than that used in ambulatory patients is recommended in ventilated patients, mostly to compensate for the effects of humidity in the ventilator circuit. Typically, dose–response curves to bronchodilators in ventilator-supported patients are shallow and the duration of the drug effect is variable. Although both nebulizers and pMDIs are employed for administering bronchodilators in mechanically ventilated patients, pMDIs offer several advantages over nebulizers for routine bronchodilator therapy.

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INHALED ANTIBIOTIC THERAPY

64

Jean-Jacques Rouby
Ivan Goldstein
Qin Lu

The incidence of ventilator-associated pneumonia ranges between 8% and 28% in patients receiving mechanical ventilation for more than 48 hours, and between 34% and 70% in patients with acute lung injury or acute respiratory distress syndrome.[1] It prolongs the duration of stay in the intensive care unit and hospital, and increases costs.[2] Associated mortality ranges from 24% to 76%, and appears far greater than the mortality resulting from other nosocomial infections. It may even exceed 85% when high-risk gram-negative bacteria, such as *Pseudomonas aeruginosa* or *Acinetobacter baumannii*, are the causative pathogens.[3] Many studies demonstrate that early intravenous administration of appropriate antibiotics improves the prognosis. Lung deposition of antibiotics, however, administered by the intravenous route is either limited or poorly documented and treatment failure is common, leading to increased dosage and risk of systemic toxicity. Despite antimicrobial therapy and adequate supporting treatment, the mortality rate from ventilator-associated pneumonia remains high, indicating a need for a more effective route of administration. Inhaled antibiotic therapy may represent such an alternative.

RATIONALE

At least three major theoretical arguments support the administration of inhaled antibiotics in critically ill patients with ventilator-associated pneumonia: the very pathogenesis of lung infection that originates in the tracheobronchial tree, the possibility of obtaining high lung-tissue concentrations by bypassing the alveolar–capillary barrier, and the potential for decreasing systemic toxicity.

Deep Lung Infection Originates in the Upper Airways

The normal human respiratory tract possesses efficient defenses against bacteria colonizing the pharynx. The glottis and larynx serve as natural anatomic barriers. The cough reflex, mucociliary clearance, and regional immunity contribute to elimination of invading pathogens and prevention of infection deep in the lungs. Endotracheal and tracheostomy tubes bypass the natural barrier between the

oropharynx and tracheobronchial tree. Bacteria penetrate into the trachea by leakage of infected secretions and/or contaminated gastric contents around the low-pressure cuff of an endotracheal tube.[4] In ventilated patients, deep sedation depresses the cough reflex whereas endotracheal intubation inhibits the ciliary escalator.[5,6] In addition, the internal wall of the endotracheal tube rapidly becomes coated with an antibiotic-resistant bacterial biofilm, which then can become fragmented and disseminated into the deep lung during tracheal suctioning or fiber-optic procedures.[7,8] Consequently, it appears reasonable to hypothesize that antibiotics administered by the inhalational route may reduce bacterial inoculum by stopping the continuous bacterial seeding from the upper airways.

Bypassing the Alveolar–Capillary Barrier May Provide High Antibiotic Tissue Concentrations

Killing bacteria infecting the lung parenchyma requires that an antibiotic achieve a pulmonary concentration at least five times greater than minimal inhibitory concentrations for the infecting pathogen. Reaching concentrations lower than mutant prevention concentrations in the infected parenchyma may trigger the emergence of resistant bacterial strains.[9] When antibiotics are intravenously administered, the alveolar–capillary barrier imposes a difficult-to-cross obstacle, which impairs lung deposition even if lung inflammation increases capillary permeability. Pulmonary vasoconstriction and regional thrombosis, two pathophysiologic abnormalities characterizing severe bronchopneumonia, reduce lung perfusion and tend to impair pulmonary penetration of circulating antibiotics. Major surgery and septic shock are associated with a significant decrease in the ratio between systemic and interstitial antibiotic concentrations (Fig. 64-1). All these factors contribute to markedly reduce the antibiotic concentrations at the site of infection, and may explain failure of intravenous antibacterial treatment.[10,11] During the initial phase of pulmonary infection, some degree of aeration persists within the bronchiolar lumen and alveolar space. Therefore, the early inhalation of antibiotics may represent a unique opportunity to reach bactericidal concentrations at the site of infection. In the presence of severe bronchopneumonia, the existence of the alveolar–capillary barrier and reduced lung perfusion are far from deleterious; instead, they may be beneficial by limiting systemic absorption and reducing systemic toxicity of nebulized antibiotics.

FACTORS INFLUENCING LUNG DEPOSITION

A number of factors influence lung deposition of nebulized antibiotics during mechanical ventilation: aerosol particle size, type of nebulizer, ventilator settings, grade of bronchopneumonia, and lung aeration. A better understanding of the conditions regulating lung deposition and the tremendous growth of technological innovations[12] potentially make the nebulization of antibiotics an attractive alternative to the classic intravenous administration.

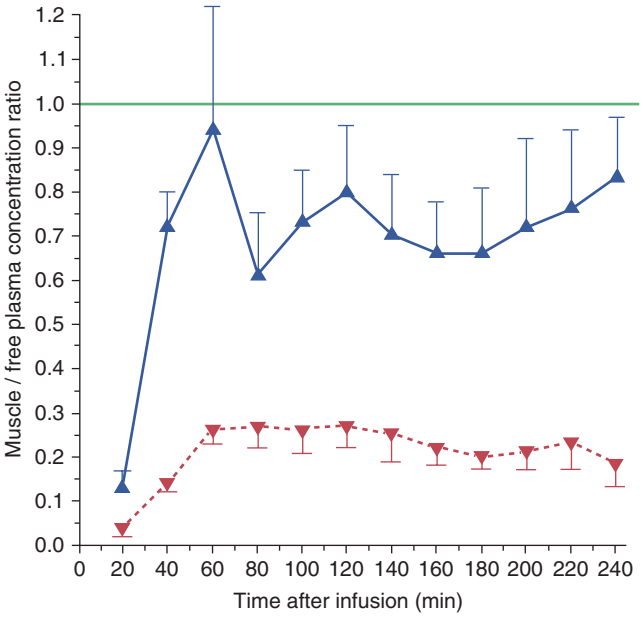

FIGURE 64-1 Time course of the ratio between unbound piperacillin concentrations measured in the interstitial space fluid of skeletal muscle and the concentrations measured in the plasma (mean ± standard error of mean) after administration of a single intravenous dose of 4 g to six septic patients (*inverted triangle dotted line*) and six control healthy volunteers (*triangle solid line*). Piperacillin levels were measured using high-pressure liquid chromatography via microdialysis probes inserted into skeletal muscles. (Used, with permission, from Joukhadar et al.[11])

Aerosol Particle Size

An essential condition for an aerosol particle to reach the deep lung is to ensure that the mass median aerodynamic diameter ranges between 1 and 5 μm.[13] Larger particles tend to impact and attach to ventilator circuits and endotracheal tubes, thereby limiting lung deposition.[14,15] Aerosol-generating devices, such as dry powder inhalers, metered-dose inhalers, jet nebulizers, ultrasonic nebulizers, or vibrating plate nebulizers, all produce particles whose mass median aerodynamic diameter is less than 5 μm. It has to be emphasized that nebulizers that produce the smallest particles require considerably more time to deliver a standard antibiotic dose.[16]

Type and Position of Nebulizers

A nebulizer equipped with a large reservoir is needed for delivering sufficient amounts of antibiotics to the respiratory

system. As a consequence, metered-dose inhalers are not the most appropriate devices for nebulizing antibiotics and should be reserved for inhaled bronchodilators and corticosteroids.[12]

Jet nebulizers produce aerosol particles by superimposing an additional flow on the inspiratory flow that comes from the ventilator. The high-speed turbulent flow that generates the aerosol, however, also promotes particle impaction on ventilator circuits and proximal airways, thereby limiting deposition deep in the lung.

Ultrasonic nebulizers are appropriate for antibiotic nebulization for several reasons: They are generally equipped with a large reservoir; they generate particles whose mass median aerodynamic diameter is less than 5 μm through quartz vibrations; and the aerosol is entrained into the tracheobronchial tree by a low flow, independent of the inspiratory flow coming from the ventilator. The quartz vibration increases the temperature of the antibiotic solution and may alter the chemical structure of the antibiotic molecule.

Recently, vibrating plate nebulizers have been developed and seem appropriate for inhaled antibiotic therapy.[17] The aerosol is generated by a ceramic vibrational element and a domed aperture plate, which has approximately 1000 tapered holes that are electroformed in a sheet. The antibiotic is placed in a reservoir above the domed aperture plate. Powered by an alternating current, the vibrational element expands and contracts causing the domed aperture plate to move upward and downward; this action causes a micropump effect that produces the aerosol.[17] Particle size depends on the aperture diameter that can be changed by the manufacturer to optimize lung deposition. Vibrating plate nebulizers have several potential advantages over ultrasonic nebulizers: At the end of nebulization, the residual volume in the reservoir is negligible; the temperature of the antibiotic solution in the reservoir does not increase, thereby limiting the risk of altering the chemical structure of the antibiotic; the aerosol generation can be synchronized with inspiration, minimizing aerosol waste during exhalation;[18] and the aerosol can be delivered through an intratracheal catheter that can be inserted into a flexible bronchoscope.[19] Both ultrasonic and vibrating plate nebulizers should be placed in parallel with the inspiratory limb before the Y-piece. The ventilator tubing between the nebulizer and the Y-piece serves as a reservoir containing the aerosol generated during the expiratory phase, which is entrained into the tracheobronchial tree during the next inspiration (bolus effect). Ultrasonic nebulizers should be placed 40 cm before the Y-piece to provide enough flexibility; vibrating plate nebulizers, which are less bulky, can be placed 10 cm before the Y-piece. When aerosol delivery is synchronized with inspiration, the vibrating plate nebulizer can be placed between the Y-piece and the proximal tip of the endotracheal tube, thus limiting extrapulmonary deposition.[18] Limiting the nebulization period to a portion of the inspiratory phase, however, significantly increases the time of nebulization, which, in turn, reduces the maximal dose that can be nebulized.

If the nebulizer is placed distally to the endotracheal tube, instead of being directly connected to it, the inner diameter of the endotracheal tube does not markedly influence the efficiency of aerosol delivery.[20]

Ventilator Modes and Settings

During mechanical ventilation, a laminar inspiratory flow provides better distal lung deposition of aerosol particles than a turbulent flow.[21] Turbulence causes wall impaction of particles in the trachea and proximal bronchioles, thereby limiting antibiotic deposition in the lung parenchyma. As a consequence, specific ventilator settings aimed at limiting inspiratory flow turbulence should be implemented during the nebulization phase. In a patient fully adapted to the ventilator, a volume-controlled mode is preferred with the following settings: constant and low inspiratory flow, a minute ventilation limited to 6 L/min, a respiratory frequency of 12 breaths/min, an inspiratory-to-expiratory ratio of 50%, and an end-inspiratory pause that constitutes 20% of the duty cycle to facilitate settling of aerosol particles in the alveolar spaces.[22] Decelerating flows should be avoided[23] as should patient triggering.[24] Inspiratory-to-expiratory ratios less than 50% should not be used because they do not provide enough time for settling of particles in the bronchoalveolar space.[25] These ventilator settings may not provide adequate CO_2 elimination in partially awake patients with acute bronchopneumonia. Consequently, dyssynchrony with the ventilator may result, generating turbulences and impaction of aerosolized particles in the ventilator circuits and the tracheobronchial tree. To provide adequate lung deposition, complete adaptation to the ventilator is required and can be achieved through a continuous infusion of propofol limited to the nebulization period.

Heat, Humidity, and Density of the Carrying Gas

If the gas coming from the ventilator is heated and humidified, distal lung deposition of aerosol particles is markedly reduced.[12,16] Two factors contribute to this undesirable effect: increase in the mass median aerodynamic diameter of aerosol particles[26] and increased deposition in ventilator circuits.[27] If the period of nebulization does not exceed 30 minutes, it is recommended to simply remove the heat and moisture exchanger; the aerosol will provide partial humidification of the inspired gas coming from the ventilator. If the period of nebulization exceeds 30 minutes, then a conventional humidifier should be inserted in the inspiratory limb to avoid damage to the tracheal and bronchial mucosa caused by prolonged administration of cold, dry inspiratory gas. As a result, the aerosol deposition might be reduced by 40%.[12]

Several in vitro studies have shown that reducing the density of the inspired gas, by replacing nitrogen with helium,

increases lung deposition of aerosol particles.[12,28,29] This beneficial effect likely results from helium-induced reduction in flow turbulence, limiting extrapulmonary deposition and tracheobronchial wall impaction of aerosol particles. On the other hand, operating the nebulizer with heliox (helium–oxygen gas mixture) reduces drug output and disposable mass.[30] Thus, it is recommended to operate the nebulizer with a nitrogen–oxygen mixture and to entrain aerosol particles with heliox to maximize lung deposition.[12] These in vitro studies have been confirmed in a recent experimental study performed in mechanically ventilated piglets with healthy lungs: Ceftazidime lung-tissue concentrations following aerosol administration were fivefold to 30-fold higher than after intravenous administration, and increased by 33% when heliox (65%/35%) was used as the operating gas of the ventilator.[31] Unfortunately, this beneficial effect was not confirmed in animals with experimental *P. aeruginosa* bronchopneumonia; presumably, the loss of alveolar aeration resulting from bronchiolitis predominated over the helium-induced reduction in flow turbulence.[31] At present, the routine use of heliox cannot be recommended for nebulizing antibiotics in ventilated patients with infected lungs.

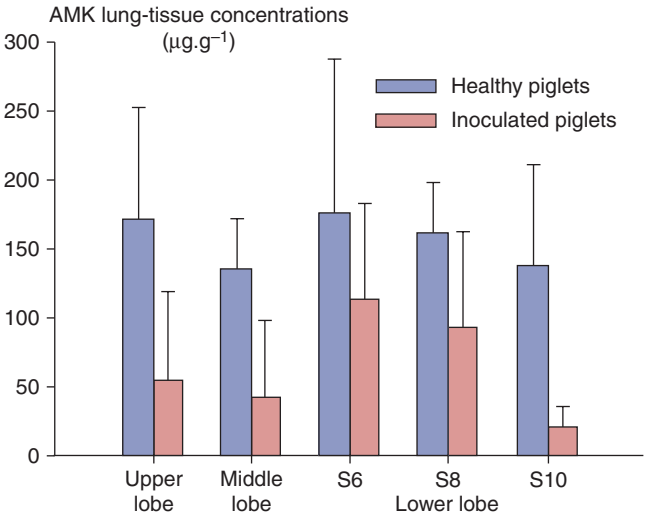

FIGURE 64-2 Amikacin (*AMK*) lung-tissue concentrations (mean ± standard deviation) measured in different pulmonary lobes and segments 1 hour after a second daily nebulization of amikacin 45 mg/kg in mechanically ventilated piglets with healthy lungs (*blue bars*, $n = 5$) and in piglets with infected lungs (*red bars*, $n = 8$), inoculated 24 hours before the first administration with a solution of *Escherichia coli*. In the lower lobe, postmortem specimens were sampled from dependent (segments 6 and 10) and nondependent (segment 8) lung regions. (Used, with permission, from Goldstein et al.[33])

Patient-Related Factors

Experimental studies performed in anesthetized piglets receiving prolonged mechanical ventilation have demonstrated that lung deposition of nebulized antibiotics is significantly greater in animals with healthy lungs than in animals with severe inoculation pneumonia.[32–35] In addition, lung-tissue concentrations of antibiotics were homogeneously distributed in healthy animals, whereas they were heterogeneously distributed in infected animals. As shown in Figure 64-2, dependent lung segments that were heavily infected by *Escherichia coli* had the lowest amikacin lung-tissue concentrations. The loss of lung aeration, the severity and extension of parenchymal infection, and the injury to the alveolar–capillary barrier are the factors that determine lung deposition of nebulized antibiotics.

LUNG AERATION

In patients with ventilator-associated bronchopneumonia, the obstruction of distal bronchioles by purulent plugs[36] may impair lung deposition of inhaled antibiotics, and result in lower pulmonary concentrations than those obtained in patients with healthy lungs. In anesthetized piglets receiving prolonged mechanical ventilation for a severe experimental *E. coli* bronchopneumonia, amikacin pulmonary tissue concentrations were three to thirty times higher after nebulization than after the intravenous administration of an equivalent dose.[33] As shown in Figure 64-3, the degree of lung aeration had the opposite effect in animals receiving intravenous amikacin and in animals receiving nebulized amikacin. The loss of lung aeration tended to increase amikacin tissue concentrations in the intravenous group, whereas the opposite effect was observed in the nebulization group. Very likely, the increased permeability of the alveolar–capillary barrier resulting from severe lung infection tends to promote intravenous amikacin penetration into the lung, whereas the multiple purulent plugs obstructing distal bronchioles tend to impair lung deposition of nebulized amikacin. It should be pointed out that despite the increased permeability of the alveolar–capillary barrier, amikacin lung-tissue concentrations remained hopelessly low after intravenous injection. From these experimental data, it is reasonable to hypothesize that ventilator settings aimed at recruiting nonaerated lung areas, such as positive end-expiratory pressure or recruitment maneuvers, may increase lung deposition of nebulized antibiotics.

SEVERITY AND EXTENSION OF BRONCHOPNEUMONIA

The extension and severity of human lung infection can be evaluated according to an histologic classification proposed in the early 1990s.[36,37] Bronchiolitis is the immediate stage preceding lung infection. It is characterized by the proliferation of polymorphonuclear leukocytes within the bronchial lumen, forming purulent plugs, necrosis, and disruption of the bronchial mucosa. Neutrophilic infiltrates present in alveolar septa and distal bronchioles are characteristic of interstitial bronchopneumonia. The intense proliferation of polymorphonuclear leukocytes into surrounding alveoli characterizes foci of bronchopneumonia and decreases lung aeration. These foci of lung infection

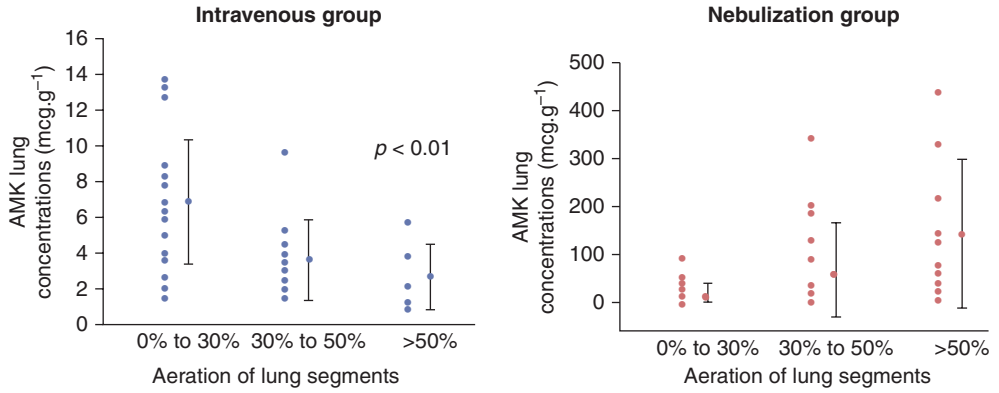

FIGURE 64-3 Amikacin (*AMK*) pulmonary concentrations according to aeration of lung segments (each *dot* represents a single segment) measured in anesthetized piglets mechanically ventilated for a severe *Escherichia coli* bronchopneumonia. In the intravenous group, animals received an intravenous dose of amikacin (15 mg/kg). In the nebulization group, animals received an equivalent dose by the inhalation route (via ultrasonic nebulizer). Lung aeration was quantified on postmortem histologic samples using an image analyzer computerized system coupled to a high-resolution color camera and an optical microscope. (Used, with permission, from Elman et al.[38])

may extend to one or more pulmonary lobules resulting in confluent bronchopneumonia characterized by a severe aeration loss. Pulmonary abscess and purulent bronchopneumonia, the most severe forms of lung infection, are characterized by tissue necrosis, disruption of the normal lung architecture, vascular destruction, consolidation, and complete loss of aeration. In anesthetized piglets receiving prolonged mechanical ventilation for severe inoculation pneumonia, lung-tissue concentrations of nebulized amikacin, ceftazidime, or colistin were markedly higher in pulmonary segments with early stages of bronchopneumonia than in segments with confluent bronchopneumonia and lung abscess.[34,35,38] As shown in Figure 64-4, such differences were not observed when the antibiotic was intravenously administered. These experimental data clearly support the administration of nebulized antibiotics in the early stages of ventilator-associated pneumonia.

INJURY TO THE ALVEOLAR–CAPILLARY BARRIER

A critical factor influencing antibiotic lung deposition is the diffusion through physiologic barriers, such as the bronchial epithelium or vascular endothelium. The normal alveolar–capillary barrier offers high resistance to lung penetration of intravenous antibiotics and systemic diffusion of nebulized antibiotics.[32] Lung infection, as with any type of lung injury, results in increased permeability of the alveolar–capillary barrier, which, in turn, facilitates the diffusion of nebulized antibiotics into the bloodstream.[33,34] Experimentally, amikacin and ceftazidime plasma concentrations are no different after nebulization or intravenous administration in the presence of severe lung infection.[33,34] In addition, systemic bioavailability is markedly increased. In other words, damage to the alveolar–capillary barrier, resulting from the infectious process, facilitates leakage of nebulized aminoglycosides

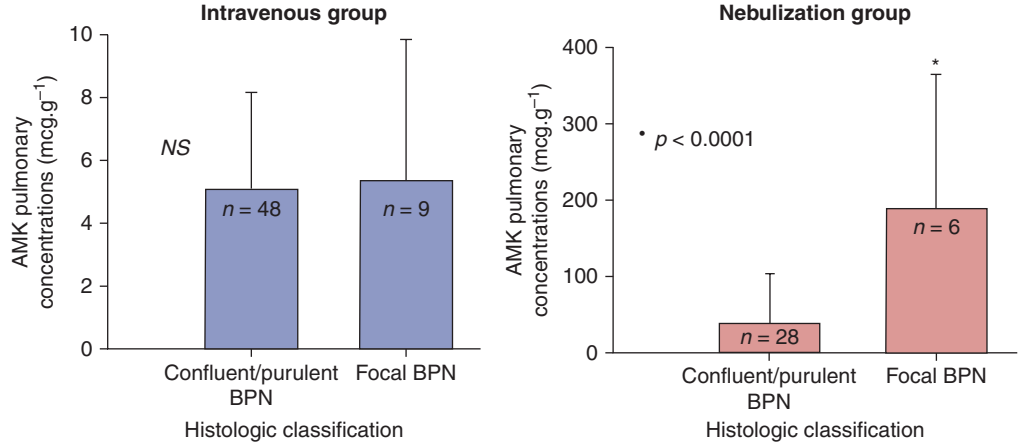

FIGURE 64-4 Amikacin (*AMK*) lung-tissue concentrations according to histologic stages of bronchopneumonia (*BPN*) characterizing lung segments (mean ± standard deviation), measured in anesthetized piglets mechanically ventilated for a severe *Escherichia coli* bronchopneumonia. In the intravenous group, animals received an intravenous dose of amikacin (15 mg/kg). In the nebulization group, animals received an equivalent dose by the inhalational route (via ultrasonic nebulizer). (Used, with permission, from Elman et al.[38])

and cephalosporins toward the systemic compartment, thereby decreasing the tissue concentration and increasing the risk of systemic toxicity. Interestingly, systemic diffusion of nebulized colistin was limited in piglets with inoculation *P. aeruginosa* pneumonia, suggesting a means of decreasing the systemic toxicity of polymyxins.[35]

Efficiency of Aerosol Delivery

In the 1980s, lung deposition of aerosolized antibiotics was assessed using radiolabeled aerosols and gamma-scintigraphy.[39] In the early studies, mechanical ventilation was considered to limit the aerosol lung deposition to less than 5% of the dose placed in the nebulizer.[40] Over the following 15 years, improvements in aerosol technology, as well as an understanding of factors influencing lung deposition during mechanical ventilation, increased aerosol delivery efficiency to 30% to 80%.[15,16,20,32–35] Pneumatic jet nebulizers deliver less than 20% of the initial dose, because of high residual volume, massive deposition of aerosol particles in ventilator circuits and the endotracheal tube, and loss to atmosphere by the expiratory limb.[20] Ultrasonic nebulizers have increased the efficiency of aerosol delivery to 30% to 40%.[32,33] The recent development of aerosol devices using vibrating plate technology, together with synchronizing aerosol delivery to the inspiratory phase, may even increase aerosol efficiency above 70%.[20,34,35] Figure 64-5 illustrates the multiple factors influencing aerosol efficiency and lung deposition of nebulized antibiotics.

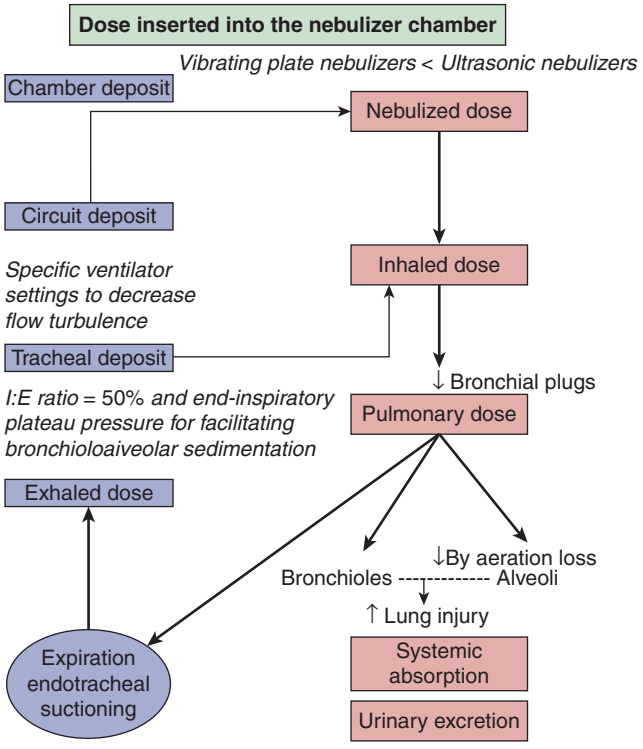

FIGURE 64-5 The mechanisms by which the dose of antibiotic inserted into the nebulizer may differ markedly from the dose delivered to the distal lung. Patient-related factors and medical interventions can interfere with different steps in the nebulization process. (Thin arrows indicate limitation of lung deposition [arrow oriented down] or facilitation of systemic diffusion [arrow oriented up]).

ASSESSMENT OF THE MICROBIOLOGIC RESPONSE

Methods for Assessing Microbiologic Response

In experimental animals, antibacterial efficiency of nebulized antibiotics can be directly assessed by measuring antibiotic lung-tissue concentrations and assessing quantitative bacteriology of postmortem lung-tissue samples.[32–35] Concentrations measured from homogenized lung-tissue samples are representative of antibiotic present in interstitial and cell compartments. Most bacteria do not penetrate into cells and remain in the interstitial space, where antibiotics exert their bactericidal activity by binding to bacterial cell membrane. Therefore, antibiotic concentrations measured from homogenized lung biopsies underestimate "effective" interstitial concentrations, secondary to a dilution factor caused by intracellular components.[41]

In patients with ventilator-associated pneumonia, it can only be assessed indirectly as the regression of clinical, biologic, and radiologic signs of lung infection, and the disappearance of pathogens initially found in cultures of distal pulmonary samples. In ventilated critically ill patients, a number of confounding factors may hamper the clinical evaluation. The bronchial deposition of nebulized antibiotics may render cultures of distal samples falsely negative although the lung parenchyma is still positive. Critically ill patients frequently have several sites of infection, and persisting fever and biologic signs of infection may be related to a persisting extrapulmonary infection.

Antibiotic concentrations representative of the alveolar space can be assessed from a bronchoalveolar lavage. To obtain the antibiotic concentration representative of the epithelial lining fluid, the concentration measured in the aspirated fluid is corrected by a dilution factor, which is derived from the ratio between urea concentrations simultaneously measured in plasma and the bronchoalveolar lavage.[42] Such measurements may fail to provide true representations of antibiotic concentrations at the site of lung infection because of confounding factors such as dilution errors or cell lysis.[42] Of particular interest is a bronchoscopic microsampling method for measuring the antibiotic concentration in bronchial epithelial lining fluid.[43] It consists of introducing, through a bronchoscope positioned in the airways, an inner 1.9-mm polyester fiber rod probe, which immediately adsorbs fluid when placed on a bronchial wall for 10 seconds. Antibiotic concentrations are then measured from the probe without any dilution. To date, this attractive but expensive technique remains limited to research studies.

Microbiologic Response to Concentration-Dependent Antibiotics in Experimental Studies

Most experimental studies of nebulized antibiotics included aminoglycosides[32,33,38,44–46] and polymyxins,[35] families of antibiotics exerting a concentration-dependent antibacterial effect.[32,33,35,38,44–46] With concentration-dependent antibiotics, a single daily nebulization, ensuring high lung-tissue concentrations, is enough to achieve a bactericidal effect at the site of infection for a period of 12 to 24 hours. The postantibiotic effect prevents the regrowth of bacterial strains despite the antibiotic lung-tissue concentrations falling below the minimal inhibitory concentration. After several consecutive daily nebulizations of aminoglycosides, there is no time-dependent tissue accumulation.[47]

In the late 1970s, experimental studies performed in nonventilated mice with *Klebsiella pneumoniae* bronchopneumonia had reported enhanced bacterial killing and higher survival rates when kanamycin was nebulized in comparison to intramuscular administration.[44,45] In spontaneously breathing squirrel monkeys, these investigators demonstrated that nebulized kanamycin efficiently protected against *K. pneumoniae* bronchopneumonia induced by intratracheal bacterial instillation, whereas the intramuscular administration was not protective.[45] Antibiotic clearance curves indicated that nebulized kanamycin remained longer in the lungs and at higher concentrations than intramuscular kanamycin. In the early 1990s, a study performed in spontaneously breathing guinea pigs demonstrated that a combination of aerosolized and intramuscular tobramycin achieved slightly higher survival and total eradication of *P. aeruginosa* compared to nebulized or intramuscular tobramycin alone.[46] Ten years later, an experimental study looked at the antibacterial efficiency of nebulized amikacin in anesthetized piglets ventilated for a severe *E. coli* bronchopneumonia.[33] Twenty-four hours after a massive bronchial inoculation, ventilated animals received equivalent doses of amikacin, either by ultrasonic nebulization or intravenously. Because of a 60% extrapulmonary deposition, 45 mg/kg were nebulized in a single dose and 15 mg/kg administered intravenously. The animals received a second dose after 24 additional hours of mechanical ventilation and were killed 1 hour later, and five subpleural specimens were excised from the upper, middle, and lower lobes. Amikacin lung-tissue peak concentrations were threefold to 30-fold higher after nebulization than after intravenous administration. As shown in Figure 64-6, after two nebulizations and 25 hours of treatment, 71% of lung segments were sterile, whereas cultures of lung segments were comparable in nontreated and intravenously treated animals. In 2010, the antibacterial efficiency of nebulized colistin was assessed in anesthetized piglets ventilated for severe *P. aeruginosa* bronchopneumonia.[35] Twenty-four hours after a massive bronchial inoculation, ventilated animals received equivalent doses of colistin, either by nebulization or intravenously. Because of a 60% extrapulmonary deposition, 16 mg/kg were nebulized in two daily doses and 10 mg/kg administered intravenously in three doses. The animals were killed 1 hour after the third aerosol and the fourth intravenous administration, and five subpleural specimens were excised from the upper, middle, and lower lobes. Colistin lung-tissue concentrations were not detectable following intravenous administration and onefold to 12-fold higher than minimal inhibitory concentrations after nebulization. After three nebulizations and 25 hours of treatment, 67% of lung segments were sterile, whereas 88% of lung segments were positive in nontreated animals and 72% in intravenously treated animals.

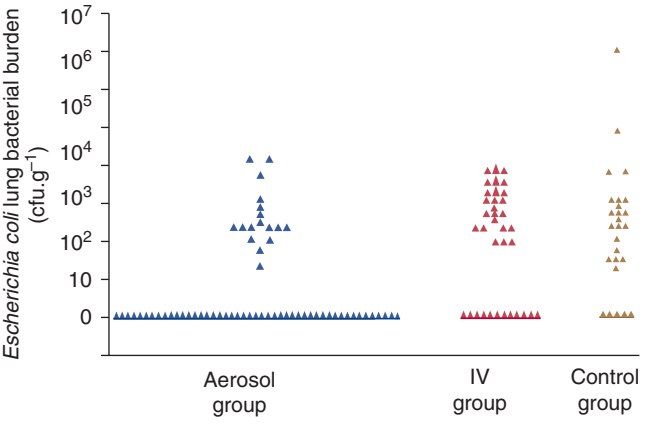

FIGURE 64-6 Lung bacterial burden of *Escherichia coli* (expressed in colony-forming units per gram [cfu/g] of lung tissue) in lung segments of anesthetized piglets mechanically ventilated for severe *E. coli* bronchopneumonia. Postmortem tissue samples were collected 1 hour after the second aerosol or intravenous (*IV*) dose of amikacin, or 48 hours after the bacterial inoculation in the untreated control group. Each triangle refers to a single lung segment. The lung bacterial burden is significantly lower in the aerosol group as compared with the intravenous or control groups. (Used, with permission, from Goldstein et al.[33])

Microbiologic Response to Time-Dependent Antibiotics in Experimental Studies

With time-dependent antibiotics, such as cephalosporins, tissue concentrations have to be maintained permanently above minimal inhibitory concentrations to provide a bactericidal effect. Therefore, aerosols have to be repeated several times a day.

An experimental study looked at the lung-tissue concentrations of ceftazidime administered to anesthetized piglets ventilated for a severe *P. aeruginosa* bronchopneumonia.[31] Twenty-four hours after a massive bacterial inoculation, animals received equivalent doses of ceftazidime either by ultrasonic nebulization or intravenously. Because of a 30% extrapulmonary deposition, 50 mg/kg were nebulized in a single dose and 33 mg/kg administered intravenously. The animals were sacrificed 1 hour later, and five subpleural specimens were excised from the upper, middle, and lower lobes. Ceftazidime lung-tissue concentrations following

nebulization were fivefold to 30-fold higher than after intravenous administration.[31] In a second study performed in the same experimental model, animals received either nebulized or intravenous ceftazidime for 24 hours.[34] Twenty-four hours after a massive *P. aeruginosa* bronchial inoculation, ventilated animals received equivalent doses of ceftazidime, either by nebulization or intravenously. Because of a 60% extrapulmonary deposition, 200 mg/kg were nebulized in eight daily aerosols of 25 mg/kg each, and 90 mg/kg was administered by continuous intravenous infusion. The animals were killed 3 hours after the eighth aerosol and 24 hours after initiation of intravenous administration, and five subpleural specimens were excised from the upper, middle, and lower lobes. Ceftazidime trough lung-tissue concentrations were fourfold higher after nebulization compared to continuous intravenous administration. After nine nebulizations and 25 hours of treatment, 80% of lung segments were sterile, whereas 90% of lung segments were positive in nontreated animals and 70% in intravenously treated animals.

Clinical Response in Human Studies

The experimental studies reported above clearly suggest that aminoglycosides, polymyxins, and cephalosporins have a higher bactericidal efficiency when administered by nebulization as compared to the parenteral route. Beneficial effects of nebulization and endotracheal administration of antibiotics have been repeatedly reported in spontaneously breathing patients with cystic fibrosis.[48] Several human studies have also demonstrated that the endotracheal administration or nebulization of aminoglycosides and polymyxins may prevent bronchial infection and ventilator-associated pneumonia in ventilated critically ill patients.[49–52] The risk of encouraging resistive strains, however, has limited this prophylactic approach.[53] Two studies performed in ventilated patients treated by intravenous antibiotics demonstrated that the addition of endotracheal tobramycin is useful for eradicating the pathogens that cause gram-negative pneumonia.[54,55] In 1992, a comparative pharmacokinetic study, performed in ventilated patients with nosocomial pneumonia, reported high antibiotic bronchial concentrations following the nebulization or the endotracheal administration of 1 g of ceftazidime.[56] In addition, the minimal inhibitory concentrations for 90% of the most important pathogens responsible for nosocomial infections were exceeded by concentrations in bronchial secretions for up to 12 hours after intravenous infusion and for up to 24 hours after endotracheal and aerosol administration.[56]

More than 40 years ago, aerosols of colistin were successfully administered to spontaneously breathing patients with pulmonary suppuration.[57] In the early 1970s, two spontaneously breathing patients with *P. aeruginosa* pneumonia were treated with inhaled polymyxin B, but aerosols had to be stopped because of airway obstruction.[58] Over the last decade, several investigator groups have reported microbiologic response following nebulization of antibiotics to critically ill patients with ventilator-associated pneumonia.[59–70] Most of these studies were retrospective and concerned patients treated by nebulized colistin for ventilator-associated pneumonia caused by multidrug-resistant pathogens.[59,60,62,63,66–69] Three studies were prospective[64,65,70] and two were randomized.[65,70] Most investigators reported "beneficial" effects, either resulting from a combination of nebulized and intravenous antibiotics[59,60,65,65] or from nebulized antibiotics alone.[61–63,67–70] Except for a prospective randomized study published in 2011,[70] ventilator settings were not optimized in these studies and the rationale for choosing the aerosol dose was not given. Clinical response was considered beneficial when aerosol antibiotics were efficient in treating patients whose lungs were infected with multidrug-resistant microorganisms.[60,62,64,65,67,69,70]

In a matched case-control study, aerosolized plus intravenous colistin was not more efficient than intravenous colistin alone for treating ventilator-associated pneumonia caused by multidrug-resistant pathogens.[68] In a double-blind, randomized, placebo-controlled study performed in forty-five critically ill patients with ventilator-associated tracheobronchitis, aerosolized gentamicin or vancomycin administered over the course of 14 days and combined with systemic antibiotics were associated with several benefits[65]: better resolution of ventilator-associated pneumonia, less bacterial resistance, reduced used of systemic antibiotics, and facilitation of weaning from mechanical ventilation. Several limitations, however, preclude drawing firm conclusions from the study: The small number of patients included in the aerosol group ($n = 19$), the small doses used in the aerosol group (gentamicin = 180 mg/day and vancomycin = 180 mg/day), the lack of optimization of ventilator settings during nebulization, and the heterogeneity of clinical and bacterial criteria for determining efficiency of antimicrobial therapy. In a randomized, controlled, phase II trial performed in forty critically ill patients with ventilator-associated pneumonia caused by *P. aeruginosa*, aerosolized ceftazidime and amikacin were compared to intravenous ceftazidime and amikacin.[70] In both arms, antimicrobial therapy was administered over the course of 7 days. Resolution of ventilator-associated pneumonia was assessed by objective criteria based on eradication of *P. aeruginosa* from bronchoalveolar lavage, resolution of clinical signs of sepsis, and lung reaeration on computed tomography. During aerosol administration, ventilator settings were optimized to minimize extrapulmonary deposition and intravenous and nebulized doses were determined so as to deliver comparable amounts of ceftazidime and amikacin in the trachea and pulmonary artery. Aerosol and intravenous antibiotics had a similar efficiency for treating ventilator-associated pneumonia caused by *P. aeruginosa* sensitive to ceftazidime and amikacin. Unlike systemic antibiotics, aerosolized antibiotics were efficient against intermediate strains and they reduced the emergence of resistive *P. aeruginosa*. Because of the small number of patients included, no conclusion could be drawn about the potential benefit of aerosol antibiotics on emergence of resistive strains, duration of mechanical ventilation, length of stay in the intensive care unit, and mortality.

Multicenter randomized trials are required to determine the clinical impact and the indications of nebulized antibiotics, and more specifically their efficiency in ventilator-associated pneumonia caused by multidrug-resistant microorganisms. Apart from potential benefit in patients with ventilator-associated pneumonia, nebulized antibiotics may also prevent microbial biofilm formation on the endotracheal tube internal surface,[74] thereby suppressing a reservoir of infecting microorganisms for the deep lung.[7]

IMPORTANT UNKNOWNS AND ISSUES TO BE RESOLVED

Two major issues must be taken into consideration before nebulized antibiotics can be recommended as an alternative to intravenous anti-infectious therapy in critically ill patients.

Side Effects of Nebulized Antibiotics

Very few complications have been described in patients receiving inhaled antibiotics. Bronchoconstriction, chest tightness, and apnea are the main adverse effects of colistin aerosols.[72,74,75] Hypoxemia may result from aerosol nebulization of any drug, particularly in patients with acute lung injury or acute respiratory distress syndrome. With aminoglycosides, the most common adverse effects are tinnitus, hoarseness, voice alteration, wheezing, cough, dyspnea, and bronchospasm.[73] Nebulized cephalosporins or other antibiotics are usually well tolerated. Cough, nasal congestion, wheezing, taste disturbances, and chest tightness have been reported.[73] Obstruction of the expiratory filter caused by repetitive aerosols of cephalosporin have been reported in ventilated patients with a risk of increased airway pressure and cardiac arrest.[70]

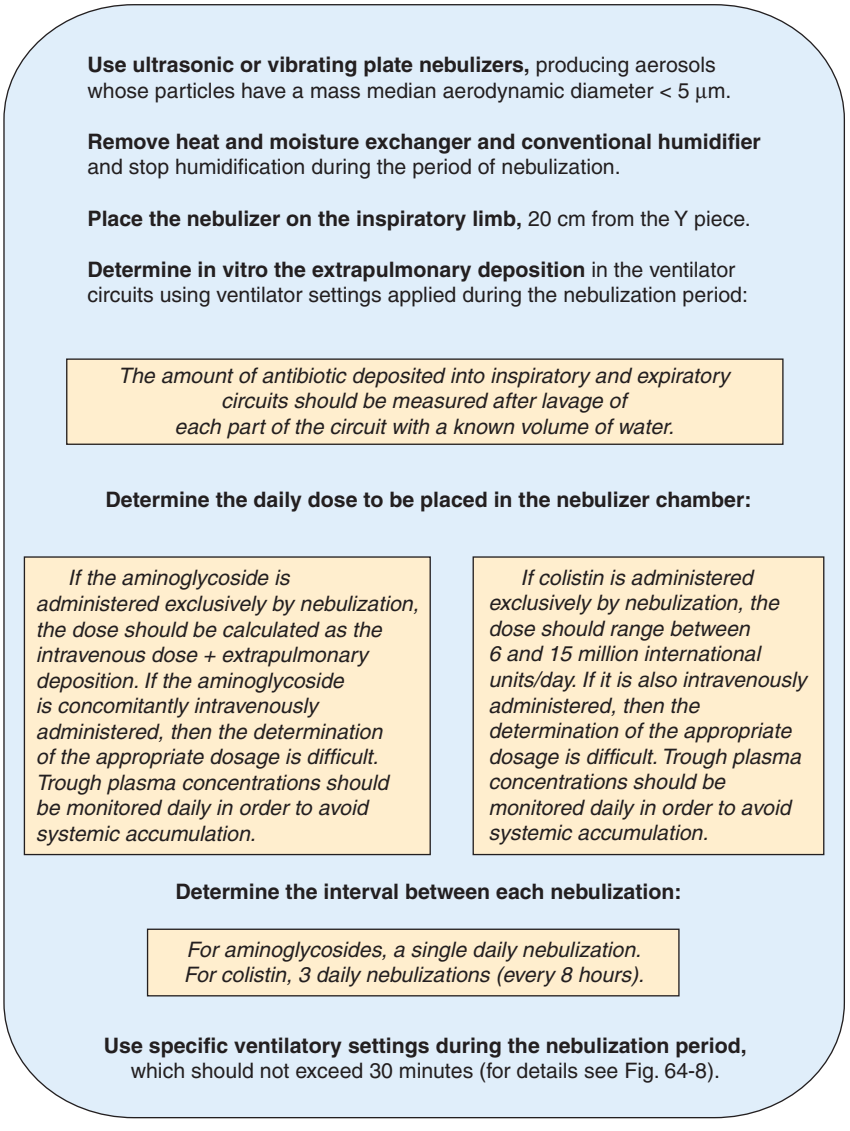

FIGURE 64-7 Guidelines for inhaled antibiotic therapy in ventilated patients.

Another serious potential risk of nebulized antibiotics is the emergence of multiresistant pathogens. Some old studies reported the emergence of resistant strains complicating the intratracheal administration of gentamycin, sisomicin, or colistin for preventing and treating ventilator-associated pneumonia.[49,52,53,76] Other experimental[51] and clinical[77] studies did not find an increase in the incidence of resistant pathogens when polymyxin B or colistin were endotracheally administered to prevent ventilator-associated pneumonia. Interestingly, nebulized antibiotics for treating ventilator-associated pneumonia seem to reduce the emergence of multidrug-resistant strains.[65,70]

Determination of the Aerosol Dose

Different rationales can be adopted for optimizing the aerosol dose. To deliver comparable amounts of antibiotics in the trachea and pulmonary artery, aerosol dose can be determined as intravenous dose plus extrapulmonary deposition. Extrapulmonary deposition can be assessed by rinsing nebulization chamber and the inspiratory and expiratory circuits with saline and measuring antibiotic concentration in the recovered fluid.[31–35,38,70,78] Another rationale is to define the "best" aerosol dose as the dose providing systemic concentrations in the range of those obtained after intravenous administration.[79] Such a rationale requires repetitive systemic dosages and appears difficult to implement in clinical practice. Studies are required to assess the impact of these different strategies on clinical efficiency of inhaled antibiotics.

GUIDELINES FOR INHALED ANTIBIOTIC THERAPY

It is important to recognize that inhaled antibiotics for treating ventilator-associated pneumonia differ in several ways from inhaled bronchodilator therapy for treating bronchospasm in ventilated patients. Nebulized antibiotics must penetrate into the distal lung, whereas bronchodilators only need to reach the bronchial tree. Because antibiotic tissue concentrations in the infected lung parenchyma should largely exceed minimal inhibitory concentrations of causative pathogens, optimizing dosage, an unresolved issue, is more critical for inhaled antibiotic therapy than for inhaled bronchodilator therapy. Great attention must be paid to the period of nebulization: Specific ventilator settings should be used to limit flow turbulence, and a short-acting sedative may be required to avoid flow triggering and dyssynchrony with the ventilator. Figures 64-7 and 64-8 summarize guidelines for delivering nebulized antibiotics during mechanical ventilation.

CONCLUSIONS AND THE FUTURE

Although inhaled antibiotic therapy has been episodically used in ventilated patients for more than 40 years, convincing clinical data are still unavailable to support its routine use. The recent understanding of physical and physiologic factors influencing lung deposition of aerosolized antibiotics together with an impressive growth of new technologies fuel a renewed interest for treating ventilator-associated pneumonia with nebulized antibiotics. In 2012, administration of inhaled antibiotics to ventilated patients should be judged a potentially efficient therapy for treating ventilator-associated pneumonia caused by resistant microorganisms. In critically ill patients with ventilator-associated pneumonia caused by sensitive bacteria, well-conducted phase II trials suggest that inhaled antibiotic therapy is at least equivalent to intravenous antibiotics and may decrease the emergence of resistant strains.[65,70] Multicenter randomized studies should be set up to assess the impact of inhaled antibiotic therapy on mortality, morbidity, antibiotic consumption, and costs in critically ill patients with ventilator-associated pneumonia.

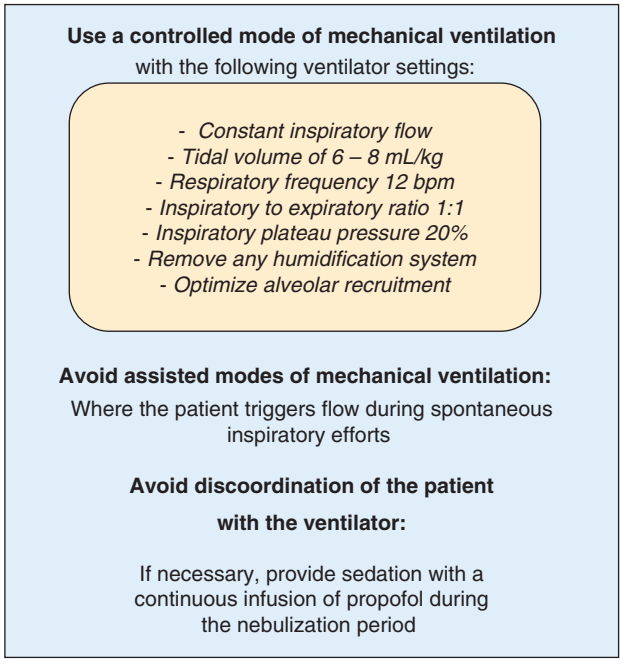

FIGURE 64-8 Specific ventilator settings for inhaled antibiotic therapy in ventilated patients.

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65

FLUID MANAGEMENT IN THE VENTILATED PATIENT

Andrew D. Bersten

Fluid management during mechanical ventilation is complicated by both the influence of positive-airway pressure on normal homeostatic control of bodily fluids, and the interaction of mechanical ventilation with fluid status. Hypovolemia may lead to hemodynamic intolerance of positive-airway pressure, and fluid overload may result in both impaired gas exchange and respiratory mechanics and deleterious systemic effects. In patients with acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS), positive fluid balance has been associated with both fewer ventilator-free days, and longer intensive care unit (ICU) stay, and with mortality in prospective randomized[1] and observational[2] studies, respectively.

PHYSIOLOGIC CONSIDERATIONS

Fluid Compartments[3]

In the normal adult male, total body water accounts for approximately 60% of body weight. In turn, approximately 40% of body weight is intracellular water and approximately 20% is distributed into the extracellular fluid volume, made up of interstitial fluid (approximately 16%), plasma volume (approximately 4%), and usually negligible volumes of lymph and transcellular fluid (cerebrospinal fluid and pericardial, intrapleural, and peritoneal fluid). Tissues such as brain, kidney, liver, and muscle have high water contents (70% to 80%) but adipose tissue has low water content (approximately 10%). Consequently, women, who tend to have more adipose tissue, have a lower total body water (approximately 50% of body weight). Total body water decreases in the elderly because of a loss of muscle mass.

The extracellular volume is distributed in interstitial fluid and plasma volume, and consists of two compartments. Seventy percent of the volume is rapidly equilibrating (approximately 20 minutes), and the remainder slowly equilibrates (approximately 24 hours) in dense connective tissue and bone. Sodium balance regulates the extracellular volume, whereas water balance regulates the intracellular volume.

WATER BALANCE

Water balance is primarily determined by thirst and the renal action of arginine vasopressin, also termed *antidiuretic hormone,* which is secreted from the posterior pituitary following synthesis in the hypothalamus, in response to a wide variety of stimuli, particularly plasma osmolality. Vasopressin activates V_2 receptors on the basolateral surface of the distal renal tubule and collecting duct, leading to an increase in water permeability, and reabsorption of filtrate, through fusion of aquaporin-2 with the luminal membrane. Vasopressin also reduces water clearance by decreasing renal medullary blood flow, and independently increases the renal medullary concentration gradient by stimulating a urea transporter.[4]

Under normal circumstances, a plasma osmolality of 280 mOsm/kg suppresses vasopressin secretion allowing maximal urinary dilution. As osmolality progressively rises to 295 mOsm/kg, so does the secretion of vasopressin, with an associated reduction in free water clearance. The kidney

TABLE 65-1: FACTORS THAT INFLUENCE VASOPRESSIN SECRETION

Increase Vasopressin Secretion	Decrease Vasopressin Secretion
Plasma osmolality >280 mOsm/kg	Ethanol
Hypovolemia	Drugs
Hypotension	Narcotic antagonists
High-pressure baroreceptors	Phenytoin
Low-pressure baroreceptors	Clonidine
Angiotensin II	Atrial natriuretic peptide
Pain	
Nausea	
Drugs	
Nicotine	
Narcotics	
Barbiturates	
Carbamazepine	
Amitriptyline	
Cyclophosphamide	
Vincristine	
Clofibrate	
Hypercapnia	
Hypoxemia	

can normally concentrate filtrate up to 1200 mOsm/kg under the influence of vasopressin, although this tends to deteriorate with age and renal dysfunction. Table 65-1 lists other stimuli that influence vasopressin secretion. High-pressure stretch receptors in the aortic arch and carotid sinus sense a significant (>10%) fall in blood pressure (BP), leading to an increase in vasopressin release. As vasopressin also causes vasoconstriction through stimulation of V_1 receptors, this is an important homeostatic response in shock,[4] but appears to be reset within 32 hours of sustained hypovolemia.[5] Stimulation of low pressure stretch receptors in the atria primarily results in an increase in both sympathetic tone and renin, and a decrease in atrial natriuretic peptide (ANP), with vasopressin release unaffected until the systemic BP falls.

SODIUM BALANCE

The extracellular volume is primarily regulated through control of sodium balance, which is, in turn, regulated through control of effective plasma volume and its composition. The total body sodium content is approximately 4000 mmol; most of which is found extracellularly, and about half is rapidly exchangeable. Although the standard Western diet contains approximately 150 mmol of sodium per 24 hours, this varies widely and urinary sodium excretion varies between 0.2 and 242 mmol per 24 hours,[6] reflecting a balance between sodium input and output. Although a moderate range of total body sodium content is well tolerated, once effective plasma volume is significantly affected, short-term and longer-term homeostatic responses are initiated.

A fall in effective plasma volume leads to activation of baroreceptors with augmentation of myocardial performance and peripheral vascular tone, and defense of plasma volume through shift of fluid from the interstitium. Longer-term responses include reduced sodium loss by the kidney and sweat glands, through a direct effect of aldosterone. When the baroreceptors are stimulated the increase in sympathetic tone reduces sodium loss through reduced glomerular filtration rate, and through increased tubular sodium reabsorption, both through a direct effect and through the actions of increased renin, angiotensin II, and aldosterone. In addition, ANP is released from the cardiac atria in response to stretch, and directly increases glomerular filtration rate through afferent arteriolar vasodilation, increases renal medullary blood flow, antagonizes vasoconstriction secondary to angiotensin II, and decreases sodium reabsorption by the collecting duct. Dopamine is produced in the kidney following conversion from L-dopa under the action of the cytosolic enzyme L-amino acid decarboxylase present in the proximal tubules.[7] This is upregulated following a high-salt diet, leading to increased urinary sodium loss as dopamine acts to inhibit sodium reabsorption in the proximal tubule,[8] and contributes to the increase in urine output sometimes seen following administration of low-dose dopamine. The renal synthesis of prostaglandins, such as prostaglandin E_2 and prostacyclin (PGI_2), tends to maintain renal blood flow and glomerular filtration rate through vasodilation, and directly increase water and sodium excretion. Consequently, in stressed patients cyclooxygenase inhibitors can precipitate renal dysfunction. Dopaminergic renal vasodilation in part acts through release of PGI_2, because administration of dopaminergic antagonists leads to reduced urinary prostaglandins and loss of dopaminergic vasodilation,[9] perhaps explaining why low-dose dopamine appears to be ineffective in septic ICU patients[10] who already have a prostaglandin-driven kidney.

Influence of Positive-Pressure Ventilation on Fluid Balance

Positive-pressure ventilation and positive end-expiratory pressure (PEEP) raise intrathoracic pressure, resulting in reduced venous return and transmural pressure (see Chapter 36), with consequent complex neurohumoral responses leading to sodium and water retention. Because assisted, supported, and spontaneous modes of ventilation progressively ameliorate the elevation of intrathoracic pressure and its consequences, different ventilator modes variably reduce venous return. Reductions in stroke volume, cardiac output, and BP then lead to stimulation of high-pressure baroreceptors, and altered regional blood flow. Both low- and high-pressure baroreceptor stimulation lead to increased sympathetic outflow, and release of renin, aldosterone, and ANP. Renal denervation does not prevent sodium and water retention.[11] Angiotensin-converting enzyme inhibitors[12] and deliberate hypervolemia,[11] however, reduce sodium and water retention during positive-pressure ventilation.

Right atrial transmural pressure and stretch are also reduced by PEEP and positive-pressure ventilation, and this leads to reduced secretion of ANP,[13,14] with consequent reduction in water and sodium excretion reversed by restoration of venous return with lower body positive pressure. PEEP levels above 10 cm H_2O may lead to an increase in central venous pressure (CVP), and regional venous pressures, which in the kidney contribute to reduced sodium and water excretion, independent of neurohumoral effects.[15]

In summary, various neurohumoral responses to positive-pressure ventilation lead to retention of sodium and water, as a homeostatic response to raised intrathoracic pressure. A major consequence of this response is expanded plasma volume, and a tendency toward systemic and pulmonary edema.

The Starling Equation

The major difference between plasma volume and interstitial fluid is the lower concentration of plasma proteins in the interstitial fluid, typically 40% of their plasma concentration. Although this concentration difference has little effect on the osmotic pressure between these two compartments, it leads to an important difference in oncotic pressure, and 80% of this is attributed to differences in albumin concentration. The normal plasma osmotic pressure is approximately 5500 to 6000 mm Hg, with approximately 28 mm Hg contributed by plasma proteins, despite having an osmolality of approximately 1.2 mOsm/kg.

The Starling equation quantitates the transvascular flux of fluids across the microcirculation (J_v). It is usually written as:

$$J_V = K_{f,c}\left(\left[P_{cap} - P_{int}\right] - \sigma\left[\pi_{cap} - \pi_{int}\right]\right)$$

where $K_{f,c}$ is the capillary filtration coefficient, P_{cap} is the hydrostatic microvascular pressure, P_{int} is the interstitial pressure, π_{cap} is the plasma oncotic pressure, π_{int} is the interstitial oncotic pressure, and σ is the osmotic reflection coefficient. $K_{f,c}$ is determined by both endothelial hydraulic conductance and endothelial surface area, and σ is a measure of protein selectivity. The osmotic reflection coefficient is thought to be 1 in the cerebral microcirculation where the blood–brain barrier effectively prevents protein flux, and approximately 0.7 to 0.8 in the normal pulmonary microcirculation, although this is markedly reduced during lung injury.[14] In a typical systemic microcirculatory bed, the arterial end of P_{cap} is 30 mm Hg and the venous end is 10 mm Hg. Assuming σ equals 1, P_{int} is −3 mm Hg, π_{cap} is 28 mm Hg, and π_{int} is 8 mm Hg, the net driving pressure out of the capillary at the arterial end of the microcirculation will be ([30−3] − [28−8]) or 13 mm Hg, although the effective π_{int} may be a little lower.[16] At the venous end of the microcirculation the net driving pressure into the capillary will be 7 mm Hg, and most of the filtered fluid is reabsorbed, with the lymphatics draining the remainder.

In the healthy lung, P_{cap} is usually assumed to be 7 mm Hg, P_{int} as −8 mm Hg, and π_{int} as 14 mm Hg. Consequently, the driving pressure across the pulmonary circulation is thought to be positive (Fig. 65-1), leading to net filtration of fluid, with lymphatic absorption usually estimated to be approximately 20 mL/hour. The final filtration rate is determined by the capillary surface area, convective forces, and diffusive forces. When P_{cap} is suddenly raised, the filtration rate may increase more than threefold.[16]

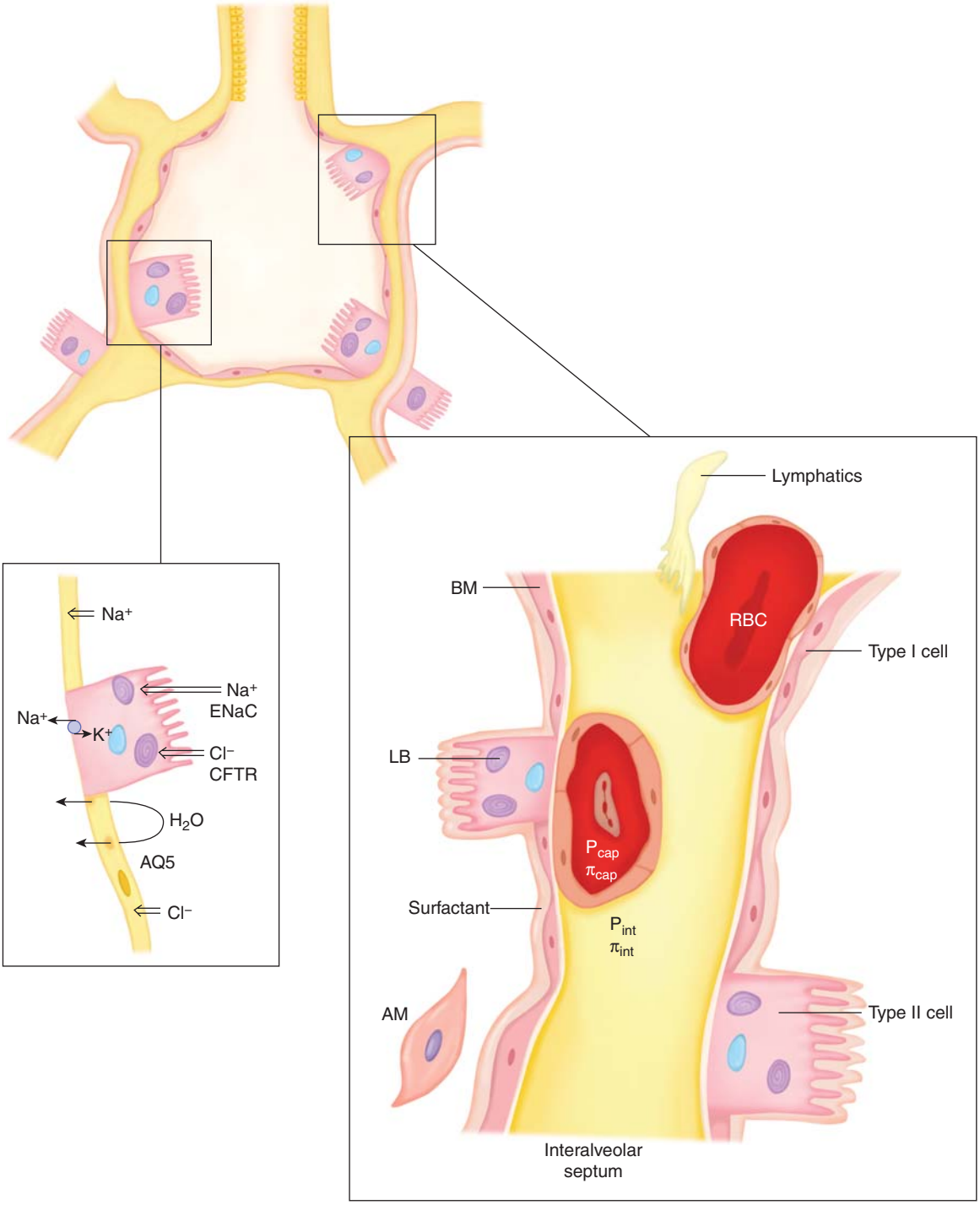
There are a number of safety factors that are thought to help prevent alveolar edema. These include low epithelial permeability (pore size approximately 10% that of the endothelium), low alveolar surface tension reflecting normal surfactant function, active vectorial transport of ions across the epithelium (see Fig. 65-1), and favorable interstitial function and lymphatic drainage (edema fluid moves along a negative-pressure gradient centrally away from the alveolus, while an associated reduction in the negative pressure and dilution of interstitial oncotic pressure reduce filtration).[17] Changes in either Starling forces or these safety factors can lead to pulmonary edema. For example, an increase in P_{cap} is the basis for hydrostatic pulmonary edema; a decrease in P_{int}, as might be seen with an obstructed airway and vigorous respiratory efforts, is thought to cause postobstructive pulmonary edema; although a decrease in σ is the basis for permeability pulmonary edema, concurrent surfactant dysfunction leads to an increase in surface tension and a decrease in P_{int}, also favoring the development of edema.[18–20] Remodeling of the lung parenchyma in chronic heart failure and conditions of persistently elevated P_{cap} such as mitral stenosis allow patients to tolerate a relatively high P_{cap} without developing marked pulmonary edema. Models of chronic heart failure suggest important homeostatic responses including a reduction in $K_{f,c}$, which together with further reduction in surface tension associated with increased surfactant content, can prevent pulmonary edema despite elevated P_{cap}.[21,22]

FLUID TARGETS

In formulating an approach to fluid management in the ventilated patient, a balance between parsimonious and generous fluid therapy needs to be considered. Although this is commonly termed the "dry or wet" approach, and this may be an appropriate general description for particular groups of patients, most clinicians classify fluid therapy as (a) maintenance, (b) replacement, and (c) resuscitation fluids. In general, the tendency of ventilated patients to retain fluids, and the benefits of fluid restriction, argue for the dry approach provided there is due attention to adequate resuscitation. A consensus statement classified fluid restriction as grade IIa evidence in ALI and ARDS.[23]

Maintenance Fluids

The volume of appropriate maintenance fluids in a ventilated patient is usually the most contentious of these parameters. As noted in Table 65-2, approximately 1150 mL of fluid per day should be adequate maintenance in ventilated patients;



P_{cap} +7 mm Hg P_{int} –8 mm Hg

π_{cap} +28 mm Hg π_{int} +14 mm Hg

$\Delta P = [7- -8] - [28-14] = +1$ mm Hg

FIGURE 65-1 Schematic of an alveolus, associated interstitium, and capillary network in the normal lung. Typical pressures involved in fluid flux result in net positive filtration of fluid. The epithelium is both a tight barrier with pore size approximately one-tenth the endothelium, and participates in vectorial ion and water and movement out of the alveolus. Sodium is absorbed at the epithelial surface through a sodium channel (*ENaC*) and actively moved across the basolateral membrane into the interstitium by Na^+,K^+-adenosine triphosphatase (ATPase). *AM,* alveolar macrophage; *AQ5,* aquaporin 5; *BM,* basement membrane; *CFTR,* cystic fibrosis transmembrane conductance regulator; *LB,* lamellar body; P_{cap}, pulmonary capillary pressure; π_{int}, interstitial oncotic pressure; π_{cap}, pulmonary capillary oncotic pressure; P_{int}, interstitial pressure; *RBC,* red blood cell.

TABLE 65-2: TYPICAL FLUID BALANCE IN HEALTHY (NONVENTILATED) SUBJECTS AND VENTILATED PATIENTS

	Healthy Subjects (mL)	Ventilated Patients (mL)
Typical obligatory fluid (water) losses		
Gastrointestinal fluid	200	200
Insensible skin loss	500	500
Humidification of inhaled air	500	0
Urine output	1000	800
Total	2200	1500
Typical fluid (water) intake		
Metabolically generated water	350	350
Water content of food	750	0
Remaining fluid intake	1100	1150
Total	2200	1500

In practice, many clinicians ignore the metabolic production of water, and prescribe 1500 mL of fluid in a ventilated patient.

this amount is less than in nonventilated subjects because all gases are humidified. In practice, metabolic production of water is usually ignored, allowing a total intake of 1500 mL/day; this represents a baseline volume that needs to be reviewed following clinical and biochemical assessment of plasma volume and total body water. Nevertheless, in balance, this volume should be sufficient to generate a urine output of approximately 800 mL/day or 0.5 mL/kg/hour; because the normal daily solute load excreted by the kidney is approximately 600 mOsm, this is easily achieved by the normal kidney with this urine volume by concentrating urine to 700 to 800 mOsm/L. The planned sum of enteral and parenteral maintenance fluids, however, may be less than this because of obligatory fluids given with drug infusions and hydrostatic pressure transducer flush (approximately 3 mL/hour per transducer). Other factors influencing maintenance fluids include the size of the patient, covert losses, such as a diaphoresis, fever that increases fluid loss by approximately 10 mL/kg/day for each degree of temperature elevation, and the ease of supplying adequate nutrition. Although 1500 mL is given as an adequate maintenance fluid volume, many centers use greater volumes, and many patients tolerate greater maintenance fluid volumes.

THE DRY APPROACH

The neurohumoral response to positive-pressure ventilation tends to retain sodium and water, which may lead to both peripheral and pulmonary edema. Daily weights are inconvenient and infrequently performed in ventilated patients. Peripheral edema needs to be carefully sought, and is often evident in the limbs of bedridden patients, and as a wedge-shaped swelling in the flanks. Pulmonary edema is typically detected as dependent crackles on auscultation, but this is a late sign and requires an appropriately placed stethoscope. Other techniques include chest radiographs and measurement of extravascular lung water. In addition to lack of sensitivity, these methods may be troublesome to interpret in disease states such as ALI.

Moderate hypohydration (mean 4.5% loss in body weight) leads to a reversible improvement in lung volume and airflow resistance in normal subjects.[24] Excess fluids may lead to pulmonary edema, which is associated with impaired oxygenation, prolonged ventilation and ICU stay, and difficulty weaning. In both ALI and ARDS,[25] however, and in acute cardiogenic pulmonary edema,[26] extravascular lung water does not correlate with CVP or pulmonary artery occlusion pressure (PAOP). Although the PAOP is an important determinant of the pulmonary capillary filtration pressure, the extravascular lung water is also influenced by permeability and temporal effects. In acute pulmonary edema, empiric treatment with diuretics, nitrates, and ventilator support will often lead to marked reduction of CVP and PAOP before resolution of the pulmonary edema.[26] Indeed, there may be transient hypovolemia secondary to extravasation of fluid in the lung, requiring volume loading.

In ALI and ARDS, extravascular lung water is usually elevated despite normal filtration pressure. Excess lung water portends a worse outcome.[27] Patients with ARDS who achieve a significant reduction in PAOP[28] or total body water, as estimated from weight loss or cumulative fluid balance,[29] are more likely to survive. Prospective, randomized studies report improved oxygenation in hypoproteinemic patients with ALI when a negative fluid balance was produced using furosemide and concentrated albumin;[30] and management of pulmonary edema according to lung water, as compared to PAOP, can lead to a lower cumulative fluid balance, fewer ventilator days, and shorter ICU stay.[31] Prevention of acute left-ventricular failure by diuresis allows weaning in some ventilator-dependent patients with chronic obstructive pulmonary disease.[32] Positive fluid balance is associated with increased mortality in both ALI,[2] and in critically ill patients with acute kidney injury.[33] Liberal fluid management in ALI reduces ventilator-free days and increases ICU stay,[1] with a trend to increased dialysis (14% vs. 10%, $p = 0.06$) consistent with reduced recovery of renal function with fluid overload in acute kidney injury.[33] An important aspect of these data is that the patients were enrolled following the diagnosis of ALI in ventilated patients, and may not apply to the initial resuscitation phase. Taken together, these data suggest that accumulation of excess fluid is common, often difficult to detect, and may be associated with serious adverse events, and mortality.

Replacement Fluids

There is little argument regarding replacement of excess fluid loss. Once the volume becomes significant or contributes to difficulties with fluid balance, it should be replaced. Table 65-3 lists typical electrolyte compositions of gastrointestinal fluids. In the setting of a postobstructive diuresis, it is

TABLE 65-3: COMPOSITION OF GASTROINTESTINAL LOSSES

	Volume (mL)	Na^+ (mmol/L)	K^+ (mmol/L)	Cl^- (mmol/L)	HCO_3^- (mmol/L)
Salivary	500 to 1000	50	20	40	30
Gastric	1500	60 to 100	10	150	30(H^+)
Pancreatic	400 to 1000	140	5	75	115
Bile	400 to 1000	140	5	100	35 to 60
Ileal	1000 to 3000	140	5	70 to 115	30 to 50
Colon		60	70	15	30

As noted above, gastric fluid is usually acidic with an H^+ concentration of approximately approximately 30 mmol/L; this will be markedly reduced by the use of proton pump inhibitors or H_2-antagonists.

common to use 0.45% normal saline with 10 mmol KCl per 500-mL flask; however, greater certainty regarding composition of excess fluid losses can be gained by measuring the electrolyte composition.

Resuscitation Fluids

Critically ill ventilated patients commonly require administration of resuscitation fluids to correct hypovolemia. Underpinning the use of resuscitation fluids is the relationship between increased ventricular preload and increased stroke volume. The trigger for a bolus of fluids often appears fairly obvious: for example, hypotension in a patient with overt bleeding. On other occasions, it may be unclear as to whether a patient will be fluid responsive or whether hemodynamic support is indicated. Yet, early recognition of the need for fluid resuscitation with rapid and titrated administration cannot be underestimated.

CHOICE OF RESUSCITATION FLUIDS

A variety of isotonic and hypertonic fluids have been examined for resuscitation, with varied results. This is often simplified as the "crystalloid versus colloid" controversy. Colloids are fluids with oncotically active contents, such as albumin (molecular weight 66 kDa), which theoretically should ensure that the fluid primarily expands the plasma volume, with little contribution to interstitial volume and edema. If permeability is increased, however, these oncotic substances may also leak across into the interstitium possibly contributing to edema formation. Table 65-4 lists typical electrolyte compositions of commonly used crystalloids and colloids.

Blood and Blood Products. These fluids preferentially expand the plasma volume, and may be indicated for appropriate correction of coagulopathy or maintenance of oxygen carriage and delivery. An important distinction needs to be made between stable and unstable patients when considering transfusion. Data from a large randomized study of stable critically ill patients supports use of a restrictive transfusion policy using a hemoglobin threshold of 7 g/dL, to aim for a target hemoglobin of 7 to 9 g/dL.[34] Although even mild degrees of anemia can result in angina in patients with severe coronary artery disease, observational data of transfusion practice in acute myocardial infarction do not strongly argue for a higher transfusion threshold.[35] In unstable patients a different approach should be considered, and recent recommendations for management of severe

TABLE 65-4: COMPOSITION OF TYPICAL CRYSTALLOIDS AND COLLOIDS

	Osmolality	Na^+	K^+	Cl^-	Organic Anion
0.9% saline[a]	300	150		150	
Hartmann's solution[a]	274	129	5	109	29 (lactate)
Ringer's lactate	272	130	4	109	28 (lactate)
Plasma-Lyte 148	296	140	5	98	50 (acetate, gluconate)
Albumex 4[b]	260	140		128	6.4 (octanoate)
Gelofusine[c]	283	144		120	
Dextran 40 in 0.9% saline	325	150		150	
Dextran 70 in 0.9% saline	306	150		150	
Hetastarch 6% in 0.9% saline	310	154		154	
7.5% saline in 6% dextran 70	2567	1283		1283	

[a]Baxter Healthcare, Toongabbie, Australia.

[b]CSL Limited, Parkville, Australia.

[c]Braun, Bella Vista, Australia.

sepsis and septic shock suggest a transfusion threshold of 100 g/L during the initial 6-hour resuscitation period.[36]

Crystalloid or Colloid Resuscitation. Comparing colloids and crystalloids for fluid resuscitation in critically ill patients, a recent Cochrane review[37] and a megatrial (total: 6997 patients) of saline versus albumin (SAFE)[38] found no difference in outcome. In the SAFE study more than 60% of the patients were ventilated, and the trigger for fluid loading was based on common clinical grounds and clinician judgment. Although specific groups, such as post–cardiac surgery, post–liver or post–kidney transplantation, and burns were excluded, the data from the SAFE study are widely applicable to critically ill patients.[39] In current practice,[40] there is wide variation in the use of crystalloids and colloids between countries, but colloids are used more often. Crystalloids offer equivalent efficacy, cost, and fewer adverse effects, while colloids offer more rapid volume correction, longer duration of action, reduced risk of pulmonary and interstitial edema, and they may be more appropriate for the clinical setting. Although clinical practice will be influenced by the SAFE study, it seems likely that issues such as patient subgroups, cost and availability, and clinician preference will still influence choice of fluid for volume expansion.

Albumin. Albumin is usually administered as either an isoosmotic solution (e.g., 4% albumin, which has 40 g/L albumin and sodium 140 mmol/L) or as a more concentrated form (e.g., 20% albumin). It appears to be the safest of the commonly used colloids[41] with a reported serious adverse event rate of approximately 1 per 10^6 infusions.[42] Compared to albumin, the anaphylactoid reaction rates of comparable colloids are higher with risk ratios approximately 2 for dextran, approximately 4.5 for hydroxyethyl starch, and approximately 12 for gelatin, with a pooled rate of approximately 9 per 10^5 infusions.[41] In normal subjects, albumin has a metabolic half-life of 16 to 20 days, with a turnover of 12 to 15 g/day.[43] The normal escape of albumin from plasma occurs at about 10% per hour, which is markedly increased during sepsis with 32% of the initial rise following albumin administration lost by 4 hours.[43] Increased catabolism and reduced production of albumin by the liver also contribute to reduced serum albumin levels in critically ill patients. Albumin binds numerous substances such as fatty acids, calcium, thyroxine, amino acids, and hydrogen ions; in addition, many commonly used drugs such as warfarin, phenytoin, midazolam, and antibiotics are highly protein bound.[23] Consequently, hypoalbuminemia may have important physiologic and pharmacologic effects.

Post hoc analysis of the SAFE study suggested that patients with severe traumatic brain injury may have a higher mortality rate with albumin resuscitation (relative risk [RR]: 1.88; 95% confidence interval [CI]: 1.31 to 2.70; $p < 0.001$),[44] and that patients with severe sepsis[45] may have a reduced mortality rate following multivariate logistic regression with adjustment for baseline factors, adjusted odds ratio for death for albumin versus saline was 0.71 (95% CI: 0.52 to 0.97; $p = 0.03$). In patients with severe liver disease and spontaneous bacterial peritonitis, albumin reduces renal dysfunction and mortality.[46] Circulatory dysfunction following paracentesis in cirrhotic patients, defined as an increase in plasma renin activity, is reduced with albumin as compared to gelatin, dextran,[47] or saline,[48] and albumin appears preferable to gelatin for reversal of diuretic-induced hepatic encephalopathy, possibly caused by a reduction in oxidant stress.[49] Finally, albumin and furosemide may have some benefit in hypoproteinemic patients with ALI.[30]

Hydroxyethyl Starch. Hydroxyethyl starch is available in a variety of molecular weights (high, medium, and low: 450 to 480, 130 to 200, and 40 to 70 kDa), C2:C6 ratios (high and low: >8, <8), and molar substitutions (high or low: 0.6 to 0.7, 0.4 to 0.5), which alter their breakdown, intravascular half-life, and in vivo molecular weight.[50] There are, however, significant concerns regarding their safety. The bleeding risk after cardiac surgery may be increased, and starches have been associated with hepatic dysfunction, pruritus, and renal dysfunction;[51] the high in vivo molecular weight[50] is thought to contribute to hyperoncotic renal injury.[52] The newer, smaller, lower half-life starches and volumes less than 1500 mL tend to be associated with few adverse effects,[50] and the starches are commonly used as colloids for resuscitation. There are concerns, however, that even the newer starches increase the risk of renal dysfunction,[53] and their routine use has not been recommended.[54]

Other Colloids. Dextrans are rarely used as volume expanders in ventilated patients because of increases in both bleeding risk and allergic reaction,[41] and possible increased risk of renal dysfunction.[54] They are glucose polymers of either average molecular weight 40 or 70 kDa, with dextran 70 sometimes used to reduce red cell and platelet sludging. Gelatins are a group of volume expanders with a low molecular weight (35 kDa), leading to a half-life of approximately 2 hours. Again allergic reactions are more common, and the main use of gelatins is outside the ICU or for short-lived periods of volume expansion, such as post–cardiac surgery.

Crystalloids. Crystalloids are usually isotonic solutions (e.g., 0.9% saline), but hypertonic solutions (e.g., 7.5% saline) have been increasingly used, particularly in the prehospital management of trauma where this may correct hypotension and reduce cerebral edema. A double-blind, prospective, randomized study, however, comparing 7.5% saline with Ringer lactate solution in 229 prehospital trauma patients, with a systolic BP less than 100 mm Hg and a Glasgow Coma Scale score less than 9, found similar rates for hospital mortality and 6-month neurologic outcome.[55] Large volumes of 0.9% saline, or colloids that contain this electrolyte composition, may lead to a non–anion gap acidosis. An alternative approach is to use balanced crystalloids, such as Ringer lactate (or Hartmann solution), which contain a modest amount of organic anion (e.g., lactate or acetate)

that is metabolized to bicarbonate, and tend to maintain a more normal acid–base state. Various adverse effects, such as increased production of nitric oxide, ALI, hypotension, renal dysfunction, impaired gastric perfusion, nausea, abdominal pain, and bleeding have been attributed to this acidosis.[56,57] Apart from the change in acid–base state, however, there is little evidence of improved clinical outcome with a balanced solution.[58]

Isotonic fluids freely distribute into the extracellular space leading to edema and greater volume requirement than colloids. Although the ratio of crystalloid to colloid needed to achieve the same effect is expected to be at least 3:1, in the SAFE study it was 1.4:1.[38] This was associated with a small but significantly greater heart rate, however, and both lower CVP and transfused volume in the crystalloid arm. In normal subjects, rapid infusion of 0.9% saline at 30 mL/kg over 20 to 30 minutes may reduce forced vital capacity, reduce forced expiratory volume in 1 second,[59] and produce premature airway closure and hypoxemia.[60] Maximum oxygen consumption may also be reduced, possibly because of edema of skeletal muscle and impaired O_2 diffusion.[61] A smaller volume of rapidly infused saline (10 mL/kg), however, only leads to adverse effects in patients with left-ventricular dysfunction.[61] Although there are no direct comparisons of crystalloid with colloid loading, these adverse effects, and the benefits of reducing lung water, argue for care with crystalloids. If a choice is available, it also seems sensible to use a balanced electrolyte fluid, provided there is adequate hepatic function and perfusion to metabolize the associated organic anion.

MONITORING FLUID THERAPY

An excess of body water in relation to sodium is manifest as hyponatremia, and deficiency of water in relation to sodium as hypernatremia, which is often associated with a disproportionate increase of urea relative to plasma creatinine. Factitious results (e.g., hyponatremia in the setting of hyperglycemia) and coexistent disease processes, such as Addison disease, may result in hyponatremia, while sepsis and gastrointestinal blood are other common causes of a disproportionate rise in urea.

Monitoring of both the trigger and response to volume loading can be very useful because excessive fluid therapy can result in adverse events, and only 40% to 72% of critically ill patients increase stroke volume or cardiac output with volume loading.[61] The SAFE study[38] used simple triggers for volume loading, while recent guidelines for management of severe sepsis and septic shock[36] used a lower mean BP threshold (65 mm Hg) and aimed for central or mixed venous oxygen saturation equal to or greater than 70% based on improved survival and reduced organ dysfunction in a randomized study of early goal-directed therapy.[63] Although perioperative mortality may be reduced in high-risk patients with a strategy that targeted increased oxygen delivery,[64] studies in critically ill patients show no benefit[65] or a worse outcome,[66] perhaps reflecting later intervention when organ dysfunction has already been initiated.

Minimally Invasive Methods

CHEST RADIOGRAPHS

In addition to heart size, and the presence of pulmonary infiltrates and pleural effusions, the vascular pedicle width, measured as the horizontal distance between a line dropped from the point where the left subclavian artery leaves the aortic arch to the point where the right main bronchus crosses the superior vena cava, may provide an additional useful measure of volume status. A vascular pedicle width greater than 63 to 70 mm can help distinguish hydrostatic from permeability pulmonary edema,[67] and it falls with negative fluid balance in ALI.[68] A decrease in vascular pedicle width of 5 mm, however, corresponded to a 3.2-L negative balance,[68] suggesting that this technique may not be sensitive enough for acute fluid management decisions, and most patients with permeability pulmonary edema have some signs usually ascribed to volume overload.[67]

DYNAMIC MEASURES

Blood Pressure Variation. Positive-pressure ventilation alters left-ventricular loading conditions leading to both systolic pressure and pulse pressure, and stroke-volume variation during the respiratory cycle, which is predictive of an increase in cardiac output, following a fluid bolus.[69] Validation, however, has mostly been in stable patients without impaired left-ventricular function, and there are important preconditions and caveats. There should be absence of inspiratory or expiratory effort and a stable cardiac rhythm. Because these dynamic measures have also not been shown to be predictive of fluid responsiveness when used with smaller tidal volumes or in the presence of pulmonary hypertension,[69] and respiratory effort is present in many critically ill patients, they have limited applicability. Similar reservations apply to the recently described use of respiratory variations in the preejection period (the time between the Q wave on the electrocardiogram and the upstroke of the arterial pressure waveform)[70] and stroke volume[71] as a measure of fluid responsiveness.

Passive leg raising to 45 degrees results in variable autotransfusion and a temporary increase in venous return, which has been used to test fluid responsiveness. Although the subsequent change in pulse pressure is predictive of fluid responsiveness, the change in cardiac output has a significantly higher predictive value.[72] If patients who increased their CVP by at least 2 mm Hg with passive leg raising are analyzed,[73] then both measures have a higher predictive performance, but again the change in pulse pressure is inferior. An increase in CVP was present in about half of the subjects studied, of whom one-third were fluid responsive, suggesting limited clinical utility.

Ultrasound. Although left-ventricular end-diastolic area is not predictive, echocardiography has been used to assess respiratory variation in the diameter of the vena cava as a measure of fluid responsiveness. In septic patients, a threshold of 36% for superior vena cava collapse during inspiration is both sensitive and specific,[74] and is not correlated with the CVP, but is similar to dynamic pulse pressure changes as a measure of fluid responsiveness. Echocardiography, however, offers the advantage of detection of severe right-ventricular failure, which may lead to false-positive results with pulse pressure variation. Respiratory changes in inferior vena cava diameter also appear promising, but may be invalidated by raised intraabdominal pressure.[75] Because both techniques require similar conditions to those needed for BP variation measures, they may not be widely applicable in the ICU. Lung ultrasound has been promulgated as a measure of subpleural interstitial pulmonary edema,[76] which may reflect PAOP when permeability is normal and in the absence of rapid changes in filtration pressure.

Parameters derived from the esophageal Doppler, such as the heart-rate corrected time to peak flow (a preload measure) and the descending aortic flow, may be used to predict volume responsiveness. A number of studies have used the esophageal Doppler to guide perioperative fluid management; fewer complications and shorter hospital stays were associated with greater fluid administration.[77] The use of this technique, however, appears limited in most ventilated ICU patients; they will not tolerate an esophageal probe without additional sedation. A fixed 70% of the aortic blood flow is assumed to pass to the descending aorta, and patients with irregular cardiac rhythms, an intraaortic balloon pump, or esophageal disease are usually excluded. Although good agreement of esophageal Doppler with thermodilution cardiac output has been reported,[78] others have found substantial variability.[79,80]

Invasive Measures

CENTRAL VENOUS CATHETER

The CVP is determined by the venous return and right-heart function. It is increased by many factors, including high levels of PEEP and decreased venous capacitance; it does not correlate particularly well with right or left end-diastolic volume in critically ill patients. Although a number of studies have not found the CVP predictive of volume responsiveness,[62] it may still be a useful measure.[81] Above a CVP of 12 mm Hg, few patients are volume responsive, and changes in the CVP may be helpful. An unchanged CVP after volume loading is suggestive of volume responsiveness, whereas a large increase is not. Similarly, the absence of a fall in CVP with spontaneous respiratory effort suggests lack of volume response.[81] Rivers et al[63] used a target CVP of 8 to 12 mm Hg, and continuously measured the central venous oxygen saturation in their goal-directed group with a target of equal to or greater than 70%. Under normal conditions, a mixed venous oxygen saturation of 75% corresponds to an intracellular partial pressure of oxygen (P_{O_2}) of 11 mm Hg, but this falls to 0.8 mm Hg at a saturation of 50%. Consequently, central venous access may be useful in determining fluid responsiveness or the need for other means of augmenting cardiac output.

Transpulmonary thermodilution is a technique that allows intermittent and continuous measurement of cardiac output, and closely agrees with pulmonary artery thermodilution measurement.[82] Additional measures include extravascular lung water and global end-diastolic volume, which is a measure of the total volume of the four heart chambers, and may be a useful preload measure.[83] However, concern has been expressed about the accuracy, including thermally silent areas as a result of hypoxic pulmonary vasoconstriction, of the extravascular lung water measure.[84,85] In addition to central venous access, this technique requires insertion of a thermodilution arterial catheter, which is usually inserted via the femoral artery although it can be inserted via the brachial artery. Although it is a promising technique, it does increase the risk of complications, and requires further investigation.

PULMONARY ARTERY CATHETER

Although the PAOP should be a measure of left-ventricular preload, it correlates poorly with left-ventricular end-diastolic volume in critically ill patients, and is a poor marker of volume responsiveness. Measurement of the PAOP requires insertion of a pulmonary artery catheter, which may allow measurement of a number of variables, including cardiac output, pulmonary artery pressure, mixed venous oxygen saturation, and right-ventricular volumes; numerous derived variables can be subsequently calculated. The accuracy and interpretation, however, of some of these data have been questioned, and serious complications from the catheter and its insertion are well described. Retrospective analysis found that use of the pulmonary artery catheter in critically ill patients was associated with increased mortality, hospital stay, and costs despite careful adjustment for severity.[86] A more recent prospective observational study found that there was a marked increase in postoperative events.[87] Nevertheless, data measured by the pulmonary artery catheter can be extremely useful in particular patients, and central venous oxygen saturation,[63] a surrogate for mixed venous oxygen saturation, may be an important end point for resuscitation.

Mortality, morbidity, and complications are not influenced by the presence of a pulmonary artery catheter in patients with shock and/or ARDS.[88,89] Although high-risk surgical patients may have a higher rate of pulmonary embolism,[90] this was not confirmed by the ARDS Network trial comparing pulmonary artery with central venous catheter guided management in ALI.[89] Apart from more insertion-related arrhythmias with the pulmonary artery catheter, this large trial did not confirm the suggestion of more complications. In the subgroup of surgical patients, randomization to the pulmonary artery catheter group was associated with

increased fluid administration and fewer ventilator-free days,[91] suggesting that interpretation and consequent management decisions have a greater influence on outcome than does the catheter itself.

CONCLUSION

As both physiologic measures and outcome are influenced by fluid management, an integrated approach is essential to the management of ventilated patients. The tendency to retain sodium and water, the adverse effects of pulmonary and peripheral edema, and improved outcomes from both observational and randomized clinical trials argue for a parsimonious approach to maintenance fluids, provided there is adequate resuscitation. Although colloids appear as safe as crystalloids, there may be particular circumstances in which one is preferable, even though it remains unclear whether balanced salt solutions improve clinical outcomes. Dynamic measures of fluid responsiveness, such as respiratory variations in BP, are superior to static measures, such as an isolated CVP or PAOP reading, but common clinical conditions often render these data invalid. Perhaps, more important than the choice of fluid, or assessment of fluid responsiveness, is the definition of integrated pathways that can be simply applied to patient care.

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XV

ETHICS AND ECONOMICS

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66

THE ETHICS OF WITHHOLDING AND WITHDRAWING MECHANICAL VENTILATION

Michael E. Wilson
Elie Azoulay

To save the lives of critically ill patients, intensivists utilize sophisticated technologies to support vital organs until treatments reverse underlying medical conditions. Most patients recover from the acute event, a few die rapidly, and the remainder fail to improve and remain dependent on life-sustaining treatments. In this last group, the chance of recovery changes from one day to the next, and questions often arise about the appropriateness of continuing life support, especially mechanical ventilation.[1]

Over the last half century, health care professionals in intensive care units (ICUs) have been forced to make decisions for patients who remain dependent on mechanical ventilation with death in the short term as the only possible outcome.[2] In these patients, continued treatment in the hope of cure is rarely the best option.[3] Mechanical ventilation may be prolonged beyond the point of beneficence, robbing patients of their dignity and families of their right to honest prognostic information and an opportunity to prepare for bereavement. The best option here is a decision to forego life-sustaining treatment.

Because respiratory failure, shock, and coma are common reasons for ICU admission, mechanical ventilation is the most widely used life-sustaining treatment in the ICU.[4] Thus, mechanical ventilation is also the most common target of a decision to forego life-sustaining treatment.[5–10] Although most patients are successfully weaned off the ventilator, a few die while on the ventilator or immediately after weaning.[11] Ideally, a decision to forego life-sustaining treatment, which consists of moving from curative care to comfort care, should be based on the patient's wishes.[12,13] When the issue of comfort care arises, however, fewer than 5% of patients are able to participate in decisions, and knowledge of their preferences is usually unavailable.[14,15] Therefore, concern that curative care may be harmful is often voiced first by the ICU team, which then broaches the issue with the family or surrogate decision maker. Thus, barely a few years after the creation of ICUs, intensivists realized that, in addition to fighting death, their duties included the daunting task of accepting and managing death. This task requires (a) identifying situations in which all hope of recovery is lost and life-prolonging treatments become death-prolonging treatments, which should be withdrawn or withheld; (b) promptly initiating a continuous process of family care based on sensitive and straightforward information and communication; and (c) improving the ability to manage death, via epidemiologic studies of practices, interventional studies of end-of-life

strategies, and continuing education aimed at honing the information and communication skills of all ICU professionals. Warding off death and restoring self-sufficiency have been the main goals of intensivists for decades; now, ICU professionals are becoming acutely aware that they must develop a professional approach to dying patients, learn what makes a "good death," and provide dying patients and their families with support, reassurance, comfort, dignity, and freedom from guilt.

The literature on end of life in the ICU comprises epidemiologic studies (descriptive, deductive, or quantitative) and qualitative studies of theoretical concepts that allow subtle interpretations of structures, experiences, roles, interactions, and perspectives. This review provides an interpretation of published data on limiting mechanical ventilation and other life-supporting treatments in patients dying in the ICU. Its goal is to help readers understand and organize the decision-making process within an ICU team and to ensure that decisions are implemented so as to give the patient a "good death" and families bereavement support.

FUNDAMENTAL ISSUES OF ETHICS

The field of bioethics, born in the late 1960s, rests on four fundamental ethical principles (beneficence, nonmaleficence, autonomy, and distributive justice) and describes a spectrum of patient–physician relationship styles ranging from paternalism to autonomy (Fig. 66-1).[16] The four fundamental ethical principles guide decisions in the ICU management of dying patients and their families. Regarding beneficence and nonmaleficence, we discuss studies that address the specific needs and expectations of dying patients. We then briefly contrast paternalism and autonomy, and argue that the long-standing controversy opposing these two models should give way to emphasis on the shared decision-making model. We also discuss the double-effect principle accepted by the U.S. Supreme Court, Society of Critical Care Medicine recommendations, and international consensus in the support of the use of sedation and analgesia to relieve symptoms, provided death is not intended, although it may be foreseen.[17–20] The unresolved debate regarding the relative merits of terminal extubation and terminal weaning for taking dying patients off the ventilator is mentioned. Regarding justice, we do our utmost to convince the reader that cost considerations are irrelevant to a decision to forego life-sustaining treatment.

In a study by Singer et al,[21] patients identified five domains of quality end-of-life care: adequate relief from pain and anxiety;[22] avoiding inappropriate prolongation of dying; achieving a sense of control; relieving burden; and strengthening relationships with loved ones. When a patient is dying, intensivists must make it clear that they are dedicated to providing optimal care throughout the dying process;[23] to treating the patient with respect and dignity; and to relieving pain caused by physical, emotional, social, and spiritual factors.[24,25] Patients fear to be abandoned. They should be assured that the doctor is and will remain on their side, stopping useless interventions, and providing treatments that ensure comfort.[26] Encouraging family and friends to be present at all times is another component of this effort to ensure beneficence; however, some family members may be unbearably distressed by having to spend long hours with

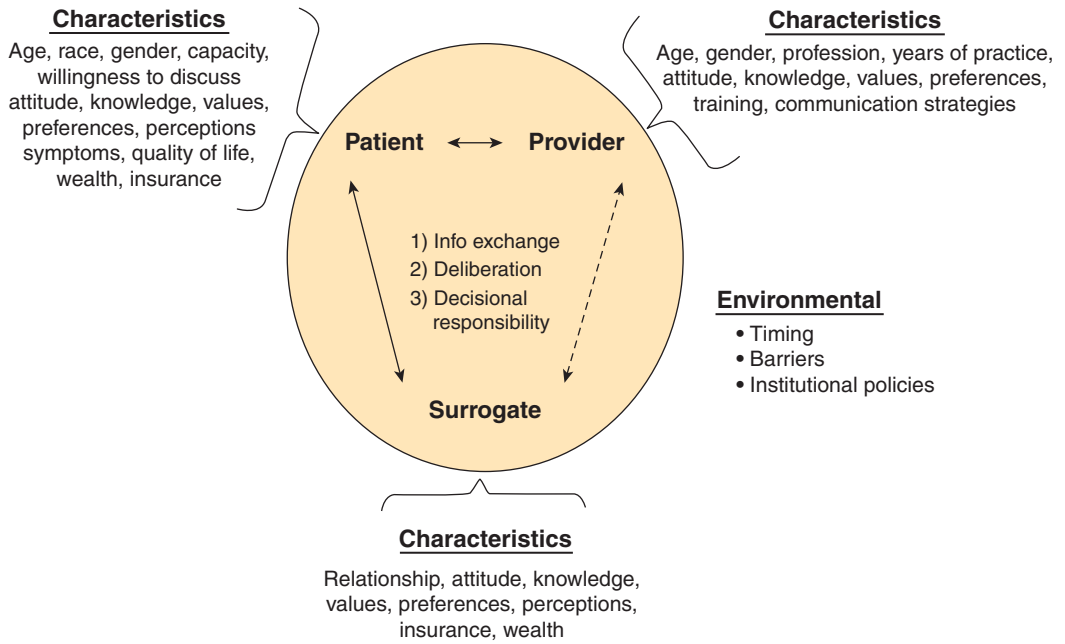

FIGURE 66-1 Conceptual framework of a patient–physician interaction. (Adapted, with permission, from Heyland DK, Rocker GM, Dodek PM, et al. Family satisfaction with care in the intensive care unit: results of a multiple center study. *Crit Care Med*. 2002;30:1413–1418.)

their dying relative. The presence of a chaplain, chosen by the patient and family, and access to religious rites should be encouraged.[27]

After years of heated debate opposing autonomy and paternalism, a model in which decision making is shared with family members is gaining precedence (Fig. 66-2). This model upholds patient autonomy[28] without forcing family members to be involved in decisions they do not want to make[29] or are not ready to make.[30] The shared decision-making model stands in sharp contrast to paternalism, in which the physician shields the patient, making decisions alone so as to protect the patient and family from the potentially harmful effects of making painful decisions.[13] Because most ICU patients are unable to make decisions,[31,32] sharing in a decision to forego life-sustaining treatment shifts to the family members.[12] Attempting to wake ICU patients so that they can participate in decisions in the name of autonomy clashes violently with the principles of beneficence and nonmaleficence.[33] Beneficence requires that family members be empowered to understand the patient's situation,[34] to identify and meet their expectations,[35,36] and to gain awareness of possible anxiety or depression that might impair their decision-making capabilities.[37] Under no circumstance should anxiety or depression in family members be used to justify benevolent paternalism; on the contrary, communication with families must receive close attention as a means of empowering families to share in decisions.[12] Reports from Canada, Sweden, and the United States describe sharing discussions and decisions as rational[38] and as crucial to family satisfaction.[39–42] In addition, studies of family outcomes several weeks or months after the death of a patient in the ICU have highlighted major difficulties and profound inadequacies in information.[27,43–45] Finally, nonmaleficence in this setting requires intensive communication with families if needed; a multidisciplinary approach can be used, or external ethical advice obtained, with the objective of empowering families to achieve their own goal (whether this is sharing in decisions or leaving decisions to the intensivists) and of convincing families that comfort care is preferable over aggressive interventions.[46–48] When family members have not received optimal information, involving them in the decision-making process probably carries a risk of subsequent posttraumatic stress and abnormal grief reactions.[30]

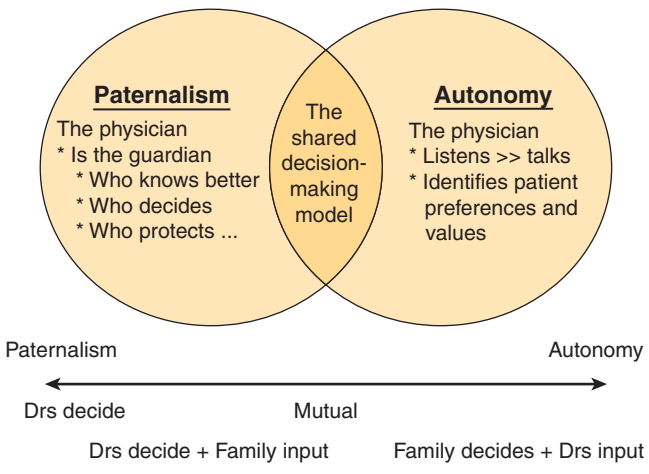

FIGURE 66-2 The shared decision-making model.

The SUPPORT (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments) studies showed a high rate of unacceptable pain in dying patients.[49,50] When withholding or withdrawing mechanical ventilation is in order, clinicians have the duty to emphasize comfort and to relieve pain and anxiety in their patients. Opioids and anxiolytics remain the reference treatment for these symptoms.[17–20] Opioids may hasten death by inducing respiratory depression,[51] but this risk is legally and ethically acceptable.[19,52–54] In contrast, use of high-dose opioids to cause death by a person making the decision alone is not consonant with optimal end-of-life care. This is voluntary euthanasia and is illegal, even in The Netherlands, Belgium, and the states of Oregon and Washington, where patients can request and obtain the assistance of a physician to commit suicide.[19,52] Because it is the physician's intention that separates opioid use to relieve pain and anxiety from opioid use to hasten death, the line between the ethical and the unethical, the legal and the illegal, is subjective.[18,55] Although some physicians may tend to use higher doses to ensure patient comfort, this practice cannot be likened to euthanasia.[56] Nevertheless, eliminating ambiguity from end-of-life decisions can be extremely difficult.[57]

The optimal method for taking dying patients off the ventilator remains actively debated. The controversy consists of advocates of terminal weaning, in which volumes, respiratory rate, and fractional inspired oxygen concentration (FI_{O_2}) are reduced gradually, versus proponents of terminal extubation with sedation,[58] which restores the normal appearance of the patient but carries a risk of respiratory secretion accumulation with asphyxia and gasping.[59,60] Terminal weaning is perceived as less active and therefore less distressing for health care professionals; furthermore, the family members are spared the ordeal of witnessing gasps, which they interpret as suffering.[61] In addition, extubation may wrongly suggest to the family that the patient is better and no longer needs the ventilator.[61] Opponents of extubation for ventilation withdrawal have pointed out that even patients who survive extubation remember the weaning period as a time of stress, discomfort, loss of hope, and extreme fear.[62]

Cost considerations[63] have entered into the treatment-limitation debate on the grounds that using ineffective treatments in one patient may deprive another patient of lifesaving treatment or ICU admission, thereby violating the principle of distributive justice.[64] Guidelines[65] suggest that elderly patients and patients with chronic conditions (cancer, hematologic malignancies, or chronic obstructive pulmonary disease) should be denied ICU admission or should receive a decision to forego life-sustaining treatment earlier than other patients. Whether the principle of distributive justice applies to a decision to forego

life-sustaining treatment is controversial, and the relevance of the cost/efficacy concept to ICU management has been challenged.[66] Denying ICU admission to a seriously ill patient for cost-containment reasons makes little sense, because other resources will then be used for the patient elsewhere, sometimes for a longer period and to the detriment of patient comfort.[67] Furthermore, patient-centered care allows the patient to die with dignity, free of pain and anxiety, while placing the family in optimal conditions for preparing the bereavement process.[64,68,69] Interventional studies of intensive communication with families of patients dying in the ICU found cost savings related to conflict prevention[70,71] that diminished the use of ineffective treatments.[46–48,72]

TERMINOLOGY

Five mutually exclusive categories of a decision to forego life-sustaining treatment have been defined. The first category is the do-not-resuscitate order for cardiac arrest. The second category comprises a decision to forego life-sustaining treatment in patients who are in a chronic vegetative state. Third is the decision to withhold a potentially beneficial treatment (e.g., mechanical ventilation, catecholamine administration, or dialysis). Fourth is withdrawal of life-sustaining treatment. The fifth category involves active induction of death (administration of a treatment that results in death). Do-not-resuscitate orders are not relevant to the present chapter. We do not discuss patients in a chronic vegetative state, because they raise specific issues whose resolution relies on concepts that do not apply to other ICU patients. Neither do we deal with euthanasia (injection of a lethal substance), which has been used in the past but is no longer an acceptable component of end-of-life care in ICU patients. Euthanasia does not constitute care, virtually never involves a rational collegial decision-making process, leaves anxiety and pain unrelieved, and fails to respect the dignity of the patient and family. We believe that euthanasia should be banned from ICUs and all other places where medical care is delivered.

EPIDEMIOLOGY OF THE DECISION TO FOREGO LIFE-SUSTAINING TREATMENT IN THE INTENSIVE CARE UNIT: GEOGRAPHIC, CULTURAL, AND RELIGIOUS VARIATIONS

In most countries, most deaths in the ICU are preceded by a decision to forego life-sustaining treatment.[6,7,9,40,56,73–81] In addition, the incidence of decisions to forego life-sustaining treatment may be increasing over time.[82,83] In patients discharged alive from the ICU, a decision to forego life-sustaining treatment taken in the ICU influences hospital survival.[84] In practice, withholding mechanical ventilation precedes or occurs concomitantly with withdrawal of all other life-sustaining treatments.[10,73] Withholding and withdrawal occur within 3 days after ICU admission, and the patient usually dies within the next 24 hours.[85] There is widespread agreement that there is no ethical difference between withholding and withdrawal,[86] although withdrawal has been described as more difficult for intensivists[74] and is not used in some countries.[73]

TABLE 66-1: VARIATIONS ACROSS COUNTRIES IN THE INCIDENCE OF DECISIONS TO FOREGO LIFE-SUSTAINING TREATMENTS AND IN FAMILY INVOLVEMENT IN THESE DECISIONS

	References	WH/WD in Dying Patients (%)	Involvement of Families in Discussions and Decisions (%)
United States	6, 11, 75, 78, 82, 102	>90	90
Canada	94	80	90
Europe	73	76	—
Israel	79	91 (no WD)	28
England	102	85	>90
France	7, 9, 30	50	50
Hong Kong	126	23 to 61	95
Spain	76	34	41
Italy	98	8	58
Australia	101, 105	70 to 81	—
India	103	49	100

Abbreviations: WD, withdrawal; *WH*, withholding.

Wide variation exists regarding the incidence of decisions to forego life-sustaining treatment (Table 66-1).[87] These variations across countries and cultures have been identified in studies comparing practices,[88,89] studies of responses to ethical scenarios,[74,90] and descriptive studies.[7,9,10,73,75,78,82,91–105] The Ethicus study described the variable practices to forego life-sustaining treatments in thirty-seven ICUs in seventeen European countries (Table 66-2). In southern Europe, the proportion of deaths after unsuccessful resuscitation was greater than in the rest of Europe. In northern Europe, the time from a decision to forego life-sustaining treatment to death was shorter.[73] These data confirm the considerable variability in approaches to bioethical issues in Europe.[88,106]

Additionally, the role given to the patient's and family's opinion in the decision to forego life-sustaining treatment also varies widely, although compassion and respect for the patient are universally recognized as crucial.[12,13] Some differences may be explained by the fact that in the late 1980s the United States adopted a model based on patient autonomy and self-determination,[96,107] whereas other countries kept a paternalistic model in which the physician

TABLE 66-2: DISTRIBUTION OF CATEGORIES OF DYING PATIENTS IN EUROPE

	Unsuccessful CPR	Brain Death	WH	WD	Active Shortening of the Dying Process
Northern Europe	154 (10.2%)	48 (3.2%)	575 (38.2%)	714 (47.4)	14 (0.9%)
Central Europe	217 (17.9%)	92 (7.6%)	412 (34.1%)	409 (33.8%)	79 (6.5%)
Southern Europe	461 (30.1%)	190 (12.4%)	607 (39.6%)	275 (17.9%)	1 (0.1%)
Whole of Europe	832 (19.6%)	330 (7.8%)	1594 (37.5%) 1	1398 (32.9%)	94 (2.2%)
Hospital mortality	100%	100%	89%	89%	100%
Total	832 (19.6%)	330 (7.8%)	1594 (37.5%)	1398 (32.9%)	94 (2.2%)

Abbreviations: CPR, cardiopulmonary resuscitation; *WD*, withdrawal; *WH*, withholding.

Source: Adapted, with permission, from Sprung et al.[73]

alone determines the appropriate level of treatment intensity.[7,9,74,90,91,108,109] Evidence, however, suggests that variability exists within a given country, with some physicians in traditionally paternalistic countries involving patients and families in the life support decision making process, and vice versa.[75,78,82,94]

Religious beliefs of both patients and providers are reported to influence the attitudes of intensivists towards life support decisions.[88,110,111] The Ethicus study identified variations across religions with Jewish, Greek Orthodox, and Moslem physicians more likely to withhold therapy, and Catholic and Protestant physicians more likely to withdraw therapy. Time to first therapy limitation also varied from 1.6 days for Protestant physicians to 7.6 days for Greek Orthodox physicians.[73,112]

Variable ICU admission rates and policies may influence the variable incidence of decisions to forego life-sustaining treatment. The SUPPORT study group found that half the patients with chronic diseases were in the ICU within the 3 days preceding death and that one-third of patients spent at least 10 days in the ICU during the hospitalization that preceded death.[50] In 1995, 20% of deaths in the United States or Canada occurred in the ICU.[113,114] In other countries, ICU admission policies are more restrictive,[102,115–117] so that comparisons are inherently biased. Predictors of increased end-of-life ICU utilization include age, number of comorbidities, hospital type, number of available hospital beds, and lack of outpatient to inpatient continuity of care.[118–120] The high incidence of in-hospital and in-ICU deaths, which has emerged over recent decades in industrialized countries, must be considered under the harsh light of data showing poorer quality end-of-life care in hospitals and ICUs as compared to home hospice care,[121,122] in addition to minimal gains in survival.[123] Important differences also exist among race. In the United States, black and Hispanic patients are more likely to die in an ICU[124] and incur 30% to 50% more health care expenditures in the 6 months preceding death than white patients,[125] even after control for variables such as geography and socioeconomic status. Additionally, there is limited evidence that white patients who prefer intensive end-of-life care are more likely to receive it than are black patients with the same preference.[111]

LEGAL DECISIONS TO DATE

The courts recognize that withholding or withdrawing life-sustaining treatment and giving palliative care are legal. In the United States, the ethical principle informing laws that allow decisions to forego life-sustaining treatment is autonomy, manifesting as informed consent from the patient or family, who can also refuse treatment withholding or withdrawal.[14,19,52,126] Among European countries, The Netherlands was the first to allow euthanasia and physician-assisted suicide.[106] Belgium followed suit in 2002.[127,128] Nevertheless, in neither country does the law deal specifically with patients receiving life support in the ICU.[129] In France, the Senate has passed a law authorizing physicians to let patients die if they are kept alive only through artificial means, treatment is futile, and death is imminent.[130]

After the advances in mechanical ventilation achieved in the 1970s and 1980s, the notion that mechanical ventilation should at times be withheld or withdrawn was deeply disturbing to many intensivists. By the 1980s, however, intensivists could no longer deny that life-sustaining treatment merely prolongs the dying process in some patients.[22,86,107]

The confusion that exists between ethical concepts and legal concepts is frequently disconcerting to intensivists. From both the ethical and legal points of view, a decision to forego life-sustaining treatment is acceptable only when it constitutes an expression of the patient's personal autonomy, that is, when it is made with the informed consent of a competent patient or, when the patient is incompetent, based on knowledge of the patient's wishes. All adults have the right to accept or refuse treatment and to define their preferences and values.[28,33,131,132] This right does not end when an ICU patient becomes mentally incompetent, and it can be exercised by the patient's surrogate decision maker.[14,52] In 1990, the U.S. Supreme Court upheld the withdrawal of life-sustaining treatment at a patient's request;[131] more recently, it stated that decisions to forego life-sustaining treatment in ICUs did not constitute physician-assisted suicide or euthanasia.[133] These rulings apply to all fifty states, in theory at least. Furthermore, the Supreme Court has ruled that physicians cannot use futility

as a basis for making a decision to forego life-sustaining treatment of their own accord. Nevertheless, the Supreme Court issued detailed recommendations on palliative care, acknowledging that sedatives and analgesics may be given, when needed, to alleviate the symptoms of a dying patient, even when this is expected—but not intended—to hasten death (the doctrine of double effect).[19]

The information above relates to the law. Physicians must comply with the laws of their country. A medical decision, however, may be legal yet unethical. We believe that the confusion between ethical principles and legal obligations that exists in the minds of many physicians can distort the decision-making process. When decisions to forego life-sustaining treatment are entirely based on standardized criteria, which comply with the law but ignore the specific factors characterizing each individual patient,[134] they may produce deleterious effects, ranging from loss of opportunity to treat to administration of useless treatments. Furthermore, the confusion between ethical and legal obligations may hinder openness in communicating decisions; for instance, physicians may be reluctant to record the nature and implementation of a decision to forego life-sustaining treatment in the patient's medical record.[135]

When decisions to forego life-sustaining treatment are made, fewer than 5% of patients are able to participate in the discussions or decisions.[136] In addition, patient preferences are usually not known.[20] Consequently, intensivists have turned to families as the primary partners for initiating a decision to forego life-sustaining treatment. The patient may be represented by a surrogate decision maker holding a durable power of attorney for health care; if the patient has not designated a surrogate, the intensivists discuss decisions with family members. The person representing the patient is asked for advice in some countries[130,137] and for decision-making input in others.[19,138] Whether the information on patient wishes used to make a decision to forego life-sustaining treatment in patients receiving mechanical ventilation should be obtained from family members has been challenged. Many families do not understand what is at stake;[139] have no knowledge of the patient's wishes;[140] want, but do not have, written instructions from the patient;[141] have opinions that disagree with patient wishes;[142] and, most importantly, suffer a burden of stress and anxiety that may impair their decision-making capacities.[37]

Advance directives have been suggested as a means of allowing patients to remain in control of their care, even when they have lost their decision-making capacity, as is the case for intubated patients in the ICU.[143] Unfortunately, a complex set of reasons[144] impairs the effectiveness of advance directives in ensuring that patient wishes are honored[145] and that treatments given in the ICU or wards are changed in accordance with patient instructions.[68,146] In addition, patients may change their minds over time, so that advance directives may no longer reflect their wishes at the time decisions to forego life-sustaining treatment are made.[68,144–147] Interestingly, a 1990 survey among members of the American Thoracic Society found that one-third of respondents provided care that contradicted the wishes of patients and surrogates, and that more than 80% unilaterally made and implemented a decision to forego life-sustaining treatment, at times over the objections of patients and surrogates.[92] Finally, the SUPPORT investigators found that 10% of older inpatients with serious illnesses received care they did not want[49] and that advance directives or families' wishes were often disregarded.[50] Having a specifically trained nurse talk to the patients, families, physicians, and other hospital staff members failed to improve compliance with patients' wishes.[50]

THE DECISION-MAKING PROCEDURE: HIGH COMPLEXITY, HIGH STAKES

Evaluating the prognosis is the key issue: When continuing mechanical ventilation and other aggressive interventions that may ensure recovery from the acute life-threatening event that prompted ICU admission, full care must be provided, without which the patient may suffer a loss of chance. Therefore, intensivists must be able to identify those patients whose chances of recovery are virtually nonexistent. For these patients, aggressive care, far from inducing benefits, prolongs the dying process, puts the patient's dignity in jeopardy, and hinders the bereavement process for family members. Clearly, the stakes are extraordinarily high for all concerned with the decision, who must achieve a consensus about what to do and how to do it.

Because decisions to forego life-sustaining treatment force patients, families, and health care professionals to stand very close to the line that separates killing from allowing patients to die, they carry a destructive power that must be acknowledged and kept under control. To this end, intensivists have worked on developing decision-making procedures that maximize objectivity, legitimacy, serenity, and agreement among all those involved. Two main factors govern a decision to forego life-sustaining treatment: the imminence of death and the patient's wishes regarding life support. The first factor was investigated by pursuing two avenues concomitantly: one consisted in defining futility, a concept based on clinical experience, and the other in developing mortality-prediction tools based on physiologic disturbances or organ failures. These efforts were intended to assist in objectively identifying situations that warrant a decision to forego life-sustaining treatment; however, they failed to reduce the complexity of the decision-making process. The second factor, patient wishes, faced a major obstacle: The inability of most patients to express their wishes at the time a decision to forego life-sustaining treatment is considered.[10,20,73] To ensure that patient wishes would nevertheless be honored, three approaches were suggested: advance directives, formal designation of a surrogate decision maker holding a durable power of attorney, and family participation in decisions.

Predicting mortality has relied chiefly on severity scores developed in the United States and Europe[148–151] to characterize patients (based on age, chronic morbidities, recruitment type, and severity of each organ involvement) and to constitute homogeneous patient groups (i.e., groups with a similar risk of hospital death). These scores have proved useful for measuring the performance of ICUs (via determination of the standardized mortality ratio [SMR]) and for establishing homogeneous patient groups for inclusion in therapeutic trials. Their poor calibration and discrimination, however, make them unhelpful for predicting the risk of death in the individual patient. Furthermore, because these scores are determined at a single point in time (ICU admission) and developed in a given population, they fail to reflect changes in organ failures over time[152,153] or advances made in the management of a specific condition.[154] Therefore, mortality-prediction scores are of no assistance in deciding when treatment withholding or withdrawal is appropriate.

Futility is a concept that was widely used to determine that a decision to forego life-sustaining treatment was appropriate. The patient-benefit-centered view defines futility as use of interventions that are unlikely to benefit the patient.[155] We prefer the definition suggested by Schneiderman et al in 1990: "When physicians conclude (either through personal experience, experiences shared with colleagues, or consideration of published empiric data) that in the last 100 cases a medical treatment has been useless, they should regard that treatment as futile," and "if the likelihood of functional recovery after a proposed course of therapy is less than 1%, then physicians may assert the prerogative to withdraw therapy without the consent of the patient or surrogate decision maker."[156]

The concept of futility has been fiercely criticized. Its opponents argue that the definition of futility is neither clear nor reproducible, the concept is clearly intended to increase the power of the physician while undermining patient autonomy, treatment data do not necessarily apply to an individual patient, the 1% cutoff is not supported by scientific evidence, and the use of futility allows physicians to make decisions unilaterally.[157,158] The futility debate ultimately condenses into a conflict in which patients or families and physicians disagree about the patient's right to receive a treatment that is highly unlikely to succeed. The futility concept fails to acknowledge the huge amount of excellent work done by ICU professionals to involve families in the decision-making process and to recognize the emotional and social problems raised by family participation in decision making.[29,30] Rather than speak of the physician's right to withhold or withdraw treatment, we should speak of the physician's duty to prepare the ICU team and the family for a clearly identifiable shift from curative care to care aimed at optimizing patient comfort and dignity while alleviating distress in the family members.[159] ICU teams must move beyond the futility debate toward a position firmly rooted in a care, an ethic that gives a meaningful role to all staff members (physicians, nurses, and other health care professionals) in organizing the decision-making process with the patients and families, while interfacing with health care institutions, third-party payers, and, the general public.[160]

FACTORS ASSOCIATED WITH DECISIONS TO FOREGO LIFE-SUSTAINING TREATMENT

As discussed in the previous section, the two main factors that should influence decisions to forgo life-sustaining treatments are patient preferences and the imminence of death (poor patient prognosis). An assessment of prognosis usually takes into account factors such as patient age, previous health status (cognitive function, self-sufficiency, and chronic morbidities), time spent in the ICU, severity at ICU admission, and worsening organ failure despite ICU management.[7,9,11,73] Nevertheless, these factors may be overshadowed by events or perceptions that develop during an ICU stay,[161] such as dependency on catecholamines and intensivists' perceptions that the prognosis is poor and the condition irreversible.[10] Thus, multiple factors exist and may compete with one another, clearly indicating a need for a rigorous and collegial decision-making process based on consensus-building centered on the patient's and family's preferences.[9,108,162,163] Several studies show that intensivists pay close attention to quality of life.[7,9,74,92,94] Nevertheless, there is evidence that intensivists underestimate the quality of life of their patients, and that quality of life does not influence patient preferences regarding the intensity of treatment received in the ICU.[163]

Studies have found that the frequency and nature of decisions to forego life-sustaining treatment vary with the personal characteristics of physicians and with their experience.[28,164] As pointed out above, religious beliefs and cultural background play a role. In addition, physician gender,[89] specialty,[165] time working in ICUs,[166] working in private versus public institutions,[167] and teaching status of the hospital[78] influence practices regarding end-of-life care. It should be noted that participating in decisions to forego life-sustaining treatment and caring for dying patients has been associated with higher rates of burnout syndrome and conflict in the ICU.[168,169] Conflict increases job strain,[168] and burnout syndrome has been associated with high employee turnover rates, absenteeism, and poor communication with families, all of which may impact the quality of a decision to forego life-sustaining treatment.[169]

Christakis et al identified four major sources of bias affecting the nature of treatments withdrawn from patients in whom a decision to forego life-sustaining treatment had been made.[170] These biases may have clinical, social, and ethical consequences. Intensivists were more likely to withdraw treatments supporting organs that failed for chronic or "natural" reasons than for iatrogenic reasons, treatments started recently, and treatments whose withdrawal would result in immediate death, although when the diagnosis was

uncertain, they preferred treatment withdrawals that resulted in delayed death. Similarly, Asch et al found that intensivists preferred to withdraw treatments that were expensive, scarce, and invasive.[171] The incidence of decisions to forego life-sustaining treatment increases with ICU stay duration, indicating that intensivists respond rationally to persistent or worsening organ failures by adapting their management strategy.[20] Thus, Cook et al identified several time-dependent factors associated with withdrawal of mechanical ventilation: dependency on catecholamines, the physician's prediction of a low likelihood of surviving the ICU stay or a high likelihood of poor cognitive function, and physician perception that the patient did not want life support.[10]

Recent data on prolonged mechanical ventilation in ICU patients showed a high rate of major dependency among survivors.[172–174] Asch et al reported that treatment withdrawal in the ICU usually occurs in the following order: blood products, dialysis, catecholamines, mechanical ventilation, parenteral nutrition, antibiotics, infusions, and enteral nutrition.[175] Whereas Cook et al found that mechanical ventilation was often stopped at the same time as dialysis or catecholamines,[10,176] others reported that mechanical ventilation was sometimes continued after the withdrawal of dialysis and catecholamines.[7,9] In France, nutrition and hydration are rarely withdrawn.[7,9] Thus, even when a decision to forego life-sustaining treatment is made, the sequence of withdrawals is influenced by multiple, complex, nonclinical factors that may seem irrelevant. These factors may be ethical, social, religious, or related to family preferences.[94] In one study, the same intensivists made contradictory decisions about the same clinical scenarios at different points in time.[177] Similarly, our group and others have shown that making a decision to forego life-sustaining treatment influences survival independently of all other factors known to affect survival, indicating that a decision to forego life-sustaining treatment depends in part on setting-specific characteristics that are difficult to identify.[178–180]

WHO DECIDES?

End-of-life management of ICU patients can be artificially distinguished into two phases. The first phase is making the decision to forego life-sustaining treatment by building a consensus that treatment must move from curative interventions to palliative (comfort) care.[26] Ideally, this consensus is achieved using the shared decision-making model recommended by Society of Critical Care Medicine in 2001 and an international consensus conference in 2003.[17,18] In this model, the decision to forego life-sustaining treatment is made by a well-organized team in which physicians and nurses communicate openly, provide relevant medical information, elicit patient values and preferences, explore the family's preferred role in the decision process, and achieve a consensus that is most consistent with the patient's values and preferences.[181] From the beginning of the decision-making process, the family members participate, either by bearing witness to the patient's wishes or by explaining their own wishes.[12]

Although the current goal standard of decision making is a consensus shared by health care providers and surrogate decision makers acting in the patient's best interest, diverging opinions often emerge, and conflict may be inevitable.[168] A previous conflict, inadequate information, or economic restrictions imposed by managed care may lead families to view a decision to forego life-sustaining treatment with distrust.[182] When such conflict occurs, physicians should refrain from unilaterally enforcing their own decision over the objections of the family.[183] On the contrary, physicians should intensify communication with families,[3] initiate a process of negotiation,[96,184–186] seek external advice, or show families that the decision is consistent with institutional policies and recommendations issued by learned societies.[136,187] Physicians should must be aware that their own value judgments may be different than those of the patient, surrogates, and other members of the health care team such as nurses.[188,189] Although surrogate decision makers fulfill a vital role in the decision-making process, as many as one-fourth of all deaths in the ICU occur in patients without decision-making capacity and without a surrogate decision maker. Few guidelines exist to guide a decision to forego life-sustaining treatment in such circumstances, and wide variability exists in how health care teams address a decision to forego life-sustaining treatment in this patient population, often without institutional oversight.[190]

The second phase in the end-of-life management of ICU patients consists in implementing the decision to forego life-sustaining treatment. This requires an organized strategy relying on both human and technological resources to meet the expectations of patients and families. ICU teams must learn this approach, if needed with the help of palliative care teams or consulting ethicists, where available.[17,18,20,46,71,162,184,187,191–195]

This phase may last a few hours to a few days. Support must be provided not only to families, but also to ICU staff members, who should be confident at all times that comfort care is preferable over the use of sophisticated technologies that prolong life artificially.[196] The ICU team may need to orchestrate the dying process by adjusting the treatment to the needs of the family (e.g., maintaining mechanical ventilation unchanged until the entire family is ready or a family member arrives from a far-away location).[196,197]

Making and implementing a decision to forego life-sustaining treatment that is in the patient's best interest, especially in the setting of complex negotiation, is a clinical procedure that must be learned, practiced, refined, and evaluated, just as are other ICU skills.[191] Physicians must take into account both ethical principles and the dignity of patients and families.[192,198,199] Because decisions to forego life-sustaining treatment are often irreversible and associated with imminent mortality, it is imperative that ICU physicians be trained and evaluated in assessing and implementing decisions to forego life-sustaining treatment, and in providing support to dying patients and their families.[40,193,198,200–204]

THE INTENSIVE CARE UNIT HEALTH CARE TEAM: A KEY ROLE IN COMMUNICATING WITH FAMILIES OF DYING PATIENTS

Several studies have sought to identify the needs and expectations of families of ICU patients.[35,36,39,41,205–207] The specific needs of families of dying patients have been investigated in studies of the overall long-term impact on families of the ICU experience and bereavement,[27,43–45,208,209] in studies of interventions (the presence of families during resuscitation or involvement of families in decisions),[30,210] and in studies of the impact of family conferences on the decision to forego life-sustaining treatment process.[200,211] Families have stated that a pain-free death was a key priority,[49] and that they often perceived information as quantitatively or qualitatively inadequate. For instance, some families complained that they did not know the cause of death. These data have been used to identify specific needs of families of patients dying in the ICU (Tables 66-3 and 66-4).[18,20] Keenan et al found that families had seven major needs directly related to the decision-making process: that the process be well explained; that it proceed as expected; that the patient be comfortable; that the discussion be initiated by a member of the ICU team; that the family and friends be prepared for the decision; that the family be allowed privacy during implementation of the decision to forego life-sustaining treatment;[212] and that the family be given opportunities to voice concerns and to make special requests.[208] Others have emphasized the importance of meeting the spiritual and religious needs of patients and family members.[27,213,206,214]

Meeting these needs empowers and motivates families to participate in the process of deciding to forego life-sustaining treatment. Burdens weighing on families should not be construed as reasons to exclude families from decision making.[12] Conversely, involving families at all costs without previously providing them with information and with psychological and social support may lead to severe residual disorders, including severe persistent guilt and abnormal bereavement.[30,210] Thus, sharing decisions with families is intricately linked with a procedure of intensive communication that supports and guides the family at the time of the decision to forego life-sustaining treatment.[46–48,187,195,215] The reasons justifying a decision to forego life-sustaining treatment and, subsequently, the specific implementation modalities are discussed, usually during family conferences attended by members of the family and members of the ICU team (physicians, nurses, and social workers).[162] Informal conversations, however, at the bedside or in the hallway or waiting room are also useful and may involve a smaller number of people (often the intensivist and the patient's spouse). Nevertheless, formal family conferences are invaluable for strengthening communication between the family and the ICU team. They should be offered as often as needed, and at least once for each family.

During the conferences, the ICU team members are familiar faces for the family members, and the physician leading the conference starts by introducing each person. Each conference is prepared by the ICU team to establish a consensus among staff members[201,216–219] as a prerequisite to the development of a consensus with the family.[20,185,186,217] Regular decision-making and debriefing meetings of physicians and nurses are essential to ensure that all team members understand one another's points of view.[12] Similarly, because resident physicians receive insufficient training in ethical principles,[220] informal discussions between residents and senior ICU physicians should be encouraged to improve residents' confidence in withdrawal decisions. Residents should also be encouraged to participate in family meetings.[221] During family conferences, the word "death" should be used and the manner in which the patient will die should be explained to the family members, with emphasis on patient comfort. The ICU staff must allow the family members to speak and to vent their emotions, but they must also anticipate questions the family members cannot bring themselves to ask.[200,211] Studies show not only that inadequate information is a source of dissatisfaction among families of patients dying in the ICU, but also that targeted interventions aimed

TABLE 66-3: TEN MOST IMPORTANT NEEDS OF FAMILIES OF CRITICALLY ILL DYING PATIENTS

1. To be with the person
2. To be helpful to the dying person
3. To be informed of the dying person's changing condition
4. To understand what is being done to the patient and why
5. To be assured of the patient's comfort
6. To be comforted
7. To express emotions
8. To be assured that their decisions were right
9. To find meaning in the dying of their loved one
10. To be fed, hydrated, and rested

Source: Used, with permission, from Truog et al.[18]

TABLE 66-4: A DOZEN NEEDS OF THE FAMILY IN THE SETTING OF CRITICAL ILLNESS

1. To have questions answered honestly
2. To know specific facts about what is wrong with the patient
3. To know the prognosis for recovery
4. To be called at home about changes in the patient's status
5. To receive information from the physician (at least) once daily
6. To receive information in understandable language
7. To believe that hospital personnel care about the patient
8. To be assured of the patient's comfort
9. To be comforted
10. To express emotions
11. To find meaning in the death of their loved one
12. To have the opportunity to eat, drink, and sleep

Source: Used, with permission, from Prendergast et al.[20]

at improving communication may be ineffective.[50,215,222–228] In addition, clinicians lack training in techniques that help families consider decision sharing, express their opinions, and cope with the attendant burden.[192,220,229,230]

A key objective of the family conference is to assure family members that the patient's wishes will be honored, although the patient is incompetent.[192] Neither families nor health care professionals know how to predict patients' wishes regarding a decision to forego life-sustaining treatment in the ICU.[139,141,147,219,231] In practice, the physicians must first ask the family whether the patient has expressed wishes about end-of-life care. If the patient has expressed wishes, then the family members describe them and use substituted judgment to participate in a decision to forego life-sustaining treatment. When nothing is known about the patient's wishes, the best interests of the patient guide the decision-making process. Placing the patient's wishes at the center of the discussions and negotiations ensures that decision making is of high moral and ethical quality despite the absence of patient participation.[186] Surrogate decision makers should receive active support from the ICU team.[46] Furthermore, by making it clear that families speak for their loved one and not for themselves, this approach should minimize feelings of guilt secondary to involvement in a decision to forego life-sustaining treatment.[232]

For most decisions to forego life-sustaining treatment, a consensus is achieved rapidly with the family.[82] In difficult cases, a process of negotiation should be initiated to convince the family that the patient cannot survive and that the patient's best interests govern decisions.[233] It may be possible to continue life support for an interval time so as to help the family understand that the patient's condition is irreversible. Compassion and understanding must sustain the relationship with families. Families are often dissatisfied with the level of communication, but are unable to express their dissatisfaction because they do not wish to provoke an open conflict. Intensive communication is the only road leading from a potential battle of diverging opinions to a consensus in which the family accepts, probably with pain and sadness, that the best care available for their loved one is discontinuation of aggressive artificial treatments and continuous painstaking attention to comfort. This awareness that treatments must be withheld or withdrawn is acquired via a multifaceted process whose components are cognitive (understanding the information and trusting the ICU team), emotional (believing that the patient is not being abandoned but has reached the end of his or her life),[20] and interpersonal (protecting the family and friends from long-term harm related to participation in decision making).[209,234] At this stage, lifting restrictions on visiting hours and encouraging participation in patient care (washing, massaging, pain relief treatment, and so on) provides families with a sense of comfort, intimacy, and utility. Family members have a strong desire for opportunities to communicate with the patient (by touching, speaking, looking at photos, and listening to music). The health care professionals must respect the silence, rituals, emotions, and religious practices of each family. Again, everything must be done to minimize feelings of guilt.

IMPORTANT UNKNOWNS

Despite considerable advancements made in the past 20 years, significant barriers to optimal decision making regarding life support and end-of-life care in the ICU still exist. In a recent survey, nursing and physician directors of ICUs in the United States reported major barriers in the following areas: clinician training in effective communication with patients and patients' families, as well as with the medical team; competing demands for clinician time; unrealistic patient and family expectations about prognosis; inability of patients to participate in treatment decisions; and disagreements within families about goals of care.[235] Despite a general consensus on basic principles that should guide the delivery of end-of-life care in the ICU, numerous studies show that the implementation of these principles is lagging. Many ICU physicians are unaware of patient wishes,[236] physicians do not document patient preferences,[237] many patients still die in moderate or severe pain,[50] and half the families experience inadequate communication with physicians.[34] Physicians do not discuss basic prognosis for survival in one-third of all family conferences[238] and lack basic communication skills, such as showing empathy[207]and responding to family members' emotional cues.[239] Additionally, many physicians are reluctant to give a recommendation regarding decisions to forego life sustaining treatment, even when directly asked to do so by surrogates.[240] Families with limited English proficiency may be at risk for further communication deficiencies.[241] Various solutions to the aforementioned barriers have been proposed,[235] and these solutions form the emphasis of current investigations.

THE FUTURE

In the future, intensive multidisciplinary programs and early incorporation of palliative care into ICU management should be encouraged so as to improve information and communication. Multidisciplinary teams could either handle communication with families of dying patients or assist the ICU staff members and teach them palliative care strategies. Data from the literature strongly support a heavy emphasis on palliative care.[242,243] By facilitating prognostic information and promoting communication with patients and families, huge efforts on the part of investigators have been successful in identifying patient preferences and wishes regarding treatment intensity. A program of intensive palliative care offered to dying ICU patients holds promise as a means of improving communication at a time when openness is crucial.[47,48,187,242,243] Nevertheless, the generalizability and feasibility of this strategy require evaluation in a range of countries and cultures.[50]

SUMMARY AND CONCLUSION

Mechanical ventilation is the life-sustaining treatment most often used in the ICU. Most patients are successfully weaned off the ventilator. A few, however, cannot recover from their disease, remain dependent on the ventilator, and have a very high likelihood of death in the short term. In this situation, intensivists must engage in the complex process of deciding to withdraw mechanical ventilation. These patients must be offered the best possible death. We must remain at their side and on their side, keeping them comfortable at all times, while encouraging family involvement in decisions and care, if they so wish, welcoming family members in the ICU as partners rather than as visitors, alleviating their guilt, and helping them to prepare for the bereavement process.

Over the last 20 years, several descriptive studies have provided detailed epidemiologic data on practices and changes to practices over time, as well as on targets for improvement. Qualitative studies have helped us to understand the complexity of the decision-making process, to recognize that upholding ethical principles requires more than compliance with the law, and to distinguish intentions from practices. The results of these studies indicate a need for major improvements in end-of-life care for ICU patients, most notably regarding our skill in communicating, imparting information, and organizing and implementing treatment withholding and withdrawal. Further knowledge of the decision-making process and of the individuals involved in it will help to improve our end-of-life practices, rest our decisions to forego life-sustaining treatment on ethical principles, and validate the shared decision-making model by studies of outcomes in family members long after the ICU experience. Serving the principle of autonomy requires not only that a patient's wishes be honored, but also that the family be able to proceed through the bereavement process with the least possible guilt, remorse, and regret. Thus, our end-of-life practice should be tailored to the specific characteristics of each region and culture, each clinical situation, each patient, each family, and each ICU professional.

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67

ECONOMICS OF VENTILATOR CARE

Shannon S. Carson

One of the most urgent targets for improved efficiencies in inpatient hospital care is critical care services. Between 2000 and 2005, critical care medicine beds increased in the United States by 6.5% (from 88,252 to 93,955), and occupancy rates increased by 4.5%.[1] In that period, critical care costs per day increased by 30.4% (from $2698 to $3518). In 2005, critical care medicine accounted for 13.4% of hospital costs in the United States and consumed 0.66% of gross domestic product. Patients requiring mechanical ventilation are among the largest consumers of critical care resources, and hospitals often experience financial losses in providing care for them. As many as 2.8% of hospitalized patients in the United States received mechanical ventilation in 2005, representing 2.7 episodes of mechanical ventilation per 1000 population.[2] Estimated national costs were $27 billion. This chapter reviews the economic implications of mechanical ventilation. Basic principles of health economics are reviewed to provide a framework for interpreting health economic analyses related to mechanical ventilation. Actual costs of mechanical ventilation are addressed, followed by a discussion of whether mechanical ventilation is cost-effective. Finally, strategies for cost containment are reviewed.

BASIC PRINCIPLES OF HEALTH ECONOMICS

The goal of *health economics* is to ascertain the highest level of efficiency in providing health care.[3,4] A key assumption in this field is that health resources are a finite commodity. In such a system, a series of questions should be answered regarding any new or current medical intervention:

- Is the intervention effective relative to other available therapies?
- How much does it cost relative to other available therapies?
- From whose perspective are the costs being considered?
- How widely will the intervention be utilized?

Measured approaches to answering these questions allow health care systems to select medical therapies based upon evidence rather than assumptions, commercial marketing, or bias. Economic analysis has become a standard component of decision making for health systems in countries such as the United Kingdom or Australia, where health care policymaking is centralized on a national level. In countries

such as the United States, delivery of health care is much less regulated, and many practitioners and most patients have unbounded access to any available therapies. Few physicians in the United States, however, are able to practice without significant awareness of the resource implications of their decision making. One goal of recent health care reform efforts in the United States is cost control, and it is highly likely that third-party payers will increase efforts to balance available services with more efficient delivery. The formation of Accountable Care Organizations, in which providers are incentivized to organize care delivery in a way that improves quality and outcomes and reduces costs, is mandated in the recent Affordable Care Act.[5] Other delivery reform initiatives include pay-for-performance measures,[6] expansion of medical homes, bundled payments, and value-based purchasing. Consequently, a basic understanding of how the efficiency of various health care practices is defined is becoming essential to the practicing clinician. The following section outlines some of the common definitions and methodologies employed in health economic analysis.

Costs

When considering the cost of therapies, the unit price of a drug or piece of equipment is often the basis of discussion in the clinical setting, especially if the analysis is being performed in the interest of the physician or hospital. Payers may have a broader view, especially if they are responsible for health care costs after hospital discharge. Patients and society view the cost of illness from an even larger perspective that includes a longer time horizon. Ideally, economic analyses determine the true costs that are accrued from the beginning of a patient's disease to the long-term outcome for the patient. These costs are categorized as direct medical costs, direct nonmedical costs, and indirect costs.[3,4,7]

DIRECT MEDICAL COSTS

Direct medical costs are expenses for the provider of a service. These can include *variable costs* such as physician labor, drug costs, or use of diagnostic or therapeutic equipment.[8] Variable costs are not generated unless the service is provided. An important subgroup is *direct variable costs,* which are defined as variable costs excluding staff salary and equipment costs.[9] Nursing labor and equipment are usually considered *fixed costs,* as nurse salaries must be paid regardless of bed occupancy, unless staff are laid off. Another form of fixed costs that is more removed from medical practice is *overhead costs,* which include general operations of the hospital or clinic such as utilities, leases, capital improvement, insurance, and administrative overhead or taxes.

DIRECT NONMEDICAL COSTS

Direct nonmedical costs include costs incurred by the patient that are not related to care provided by the physician or hospital. These costs may include emergency transportation to the hospital, transportation and lodging for the patients' family, and domestic help and rehabilitative services after discharge. Although these costs are difficult to measure, they can have an important impact on the patient and their perception of the benefits of care.

INDIRECT COSTS

Indirect costs include the overall financial burden of illness to the patient. This can include loss of wages and benefits as a consequence of missed work or loss of earnings and unpaid care provided by family members. This, too, is difficult to measure, but it has substantial impact on the well-being of the patient and family.[10–13] Indirect costs for the patient can ultimately affect direct costs for a health system. If economic burdens on the patient decrease access to resources, affect medical adherence, and result in incomplete recovery, then recurrence of hospitalization or even critical illness can result.

MEASURING COSTS

One of the greatest challenges in health economic analysis is accurate measurement of relevant costs. Many hospitals have adopted sophisticated cost-accounting systems that assign a specific cost to each service based on hospital expenses.[8] Expenses can be determined from either the hospital's acquisition costs or the service-specific relative-value units based upon the Center for Medicare and Medicaid Services Resource-Based Relative Value Scale. Overhead costs are assessed internally and assigned to each department.

Most hospitals increase the patient charge for many services above acquisition costs and expenses to help pay for services that are otherwise inadequately reimbursed. Because this practice can vary according to different payment plans, hospital *charges* are often an inappropriate surrogate for hospital *costs.*[14] Large studies involving patients under a single-payer such as Medicare can adjust charges using a standard cost-to-charge ratio to gain acceptable estimates of costs, but this is less reliable with more heterogeneous groups of patients and payers.

As nursing time, monitoring costs, physician costs and certain laboratory and radiology ordering practices are linked to a patient's presence in an intensive care unit (ICU), ICU length of stay is considered by many to be a reliable and convenient surrogate for ICU costs. In one frequently cited model that is based on the relative costs per day of hospital admission, 4.5 units are assigned to the first day of each ICU stay, 2.5 units for each additional ICU day, and 1 unit for each non-ICU day after the first ICU discharge.[15]

For comparisons between institutions, length of stay can be confounded by differences in ICU admission criteria, nurse-to-patient ratios, presence of intermediate care or "stepdown" units, and transfers to other acute care facilities. To standardize resource use between different ICU settings, instruments such as the Therapeutic Intervention Scoring System (TISS) can be used.[16] The TISS instrument assigns

TABLE 67-1: TYPES OF ECONOMIC ANALYSES

Type	Comparisons	Result	Advantages/Disadvantages
Cost-Minimization	Costs of therapies with similar efficacies	Cost difference	Few therapies have similar efficacies for multiple outcomes
Cost-Benefit	Monetary value of costs and benefits of therapies	Cost/monetary benefit	Therapies for different conditions and outcomes can be compared, but it is difficult to place a monetary value on clinical outcomes such as death or quality of life
Cost-Effectiveness	Therapies with efficacies measured using similar clinical outcomes	Cost/clinical outcome (e.g. life-years saved)	Utilize clinically relevant outcomes. Analyses using different outcomes cannot be compared
Cost-Utility	Therapies for which mortality and quality of life are important outcomes	Cost/QALY	Different therapies with different efficacies can be compared; includes patient-centered outcomes; difficult to comprehend

Abbreviation: QALY, quality-adjusted life-years.

weights to seventy-six ICU interventions based upon the severity of illness associated with the need for each intervention. Intensity of ICU care can then be assessed by comparing the added weights or TISS scores between intervention groups, and costs can be standardized by applying a specific cost to each service.

Cost data for economic evaluations can come from multiple sources, but the most common approach is to collect cost data prospectively during clinical trials.[17,18] Utilizing cost data from a single, large clinical trial has the advantage of uniform methodology, but it may not be generalizable if the trial involved highly selected patients managed in ways that are not standard to the typical clinical setting. When clinical trial data are not available, cost and outcome data can be derived from cohort studies. With this approach, sensitivity analyses to account for clinical variability and potential biases in the cohort studies are particularly important. A combined approach that begins with data from a large clinical trial and adds multiple scenarios that account for clinical variability is useful.

Types of Economic Analyses

Economic analyses function to provide more than just a description of the costs of a therapy. Their role is to compare costs between therapies relative to the benefits or efficacies of those therapies. Table 67-1 describes the four primary types of economic analyses.[3,4,17] Cost-effectiveness analysis, the most useful approach to economic analysis, is described in more detail below.

COST-EFFECTIVENESS ANALYSES

Cost-effectiveness analyses use standard clinical measures such as life-years gained or quality of life units rather than monetary units to assess benefit. Outcomes are expressed as a ratio of cost to measure of benefit, for example, cost per life-year gained. Cost-effectiveness analyses are easy to understand for clinicians and have the advantage of not having to assign a monetary value to outcomes. Consequently, they are the most common type of economic evaluation performed. They can, however, only compare the costs of therapies that have a common clinical outcome.

COST-UTILITY ANALYSES

An important and common subgroup of cost-effectiveness analysis is cost-utility analysis, which is performed when therapies are likely to have an impact on quality of life as well as mortality. The level of well-being for a given health state (*utility,* rated from 0 for worst health or death to 1 for best health) is multiplied by the amount of time spent in that health state. The resulting index is called a *quality-adjusted life-year* (QALY). For example, a therapy that results in a health state valued at 0.5 for 2 years would yield 1 QALY. Utilities can be measured by interviewing participants of a clinical trial, or predetermined values measured in similar groups of patients can be utilized. Results of a cost-utility analysis are expressed as cost per QALY. Results of selected cost-utility analyses related to mechanical ventilation and ICU care are listed in Table 67-2.

The advantages of cost-effectiveness analyses are that costs and benefits of different therapies involving different types of patients can be compared, and outcomes beyond survival are factored in. The disadvantage is that many clinicians have difficulty understanding the complexity of the studies, and the models can involve numerous assumptions that vary across patient populations. Therefore, strict guidelines[19] must be followed in conducting the studies to ensure transparency in how utilities are assigned, and rigorous testing in the form of sensitivity analyses should be performed to determine how variability in clinical factors could affect results of the models.

Cost-effectiveness analyses can aid decision making by providing data on how much therapies cost relative to the outcomes that are achieved, particularly if one therapy has greater benefits than the alternative, but the costs are greater as well. Cost-effectiveness analysis is not a cost-containment tool. Instead, it should be considered a method to improve

TABLE 67-2: COST-EFFECTIVENESS OF SELECTED MECHANICAL VENTILATION-RELATED INTERVENTIONS

Intervention	Cost/QALY
Mechanical ventilation for respiratory failure related to pneumonia or ARDS[28,86]	$29,000 (estimated 2-month survival > 70%) $44,000 (estimated 2-month survival 51%–70%) $110,000 (estimated 2-month survival ≤ 50%) $32,000 (age < 65 years) $46,000 (age > 75 years)
ICU care for patients with acute respiratory failure *without* chronic lung disease[27]	$11,970[a]
ICU care for patients with acute respiratory failure *with* chronic lung disease[27]	$14,365[a]
Mechanical ventilation to treat acute respiratory failure[87]	€1391[a]
Prolonged mechanical ventilation (>21 days) after acute illness[30]	$82,411 $60,967 (estimated 1-year survival > 50%) $101,787 (estimated 1-year survival ≤ 50%)
Lung-protective ventilation protocol in patients with acute lung injury[52]	$11,690
ICU care for patients with acute renal failure[27]	$30,625[a]
Activated Protein C for severe sepsis[88]	$27,400 (APACHE II ≥ 25) >$100,000 (APACHE < 25)
Ultrasound screening for deep vein thrombosis in ventilated patients with femoral vein catheters[89]	$12,793
Lung transplantation compared to standard care[90]	$44,000 (assuming 10-year survival) $204,000 (assuming 5-year survival)
In-hospital cardiopulmonary resuscitation	$215,000

[a]Analysis did not include costs after hospital discharge.

Abbreviations: ARDS, acute respiratory distress syndrome; *ICU*, intensive care unit; *QALY*, quality-adjusted life-years.

value. The analyses may not always lead to decreased costs for a health care system, especially when underutilized services that increase cost but improve value are identified and encouraged.[20] In most Western health systems, an incremental cost per QALY of less than $20,000 is strong evidence for adoption of a therapy. Incremental costs per QALY of between $50,000 and $100,000 provide moderate evidence for adoption. If the incremental cost per QALY is greater than $100,000, the therapy may not be considered cost-effective, although more recent recommendations raise that boundary to a range of $183,000 to $264,000.[21] These boundaries of cost-effectiveness are somewhat arbitrary however. Ultimate decision making must take into account other factors such as seriousness of the health condition, availability of alternatives, and number of patients who would receive the therapy (total budgetary impact).[3,22]

COSTS OF MECHANICAL VENTILATION IN THE INTENSIVE CARE UNIT

The average total cost of hospitalization for a critically ill patient ranges from $14,135 to $32,253, depending on the study methods and patient population.[23,24] This is nearly three times the cost of a hospitalized patient managed on the medical or surgical floor. Two-thirds of the costs associated with critically ill patients are accrued during their stay in the ICU. For those whose length of stay in the ICU is more than 5 days, as much as 80% of their hospital costs are accrued in the ICU. Hospital costs for ICU patients who require mechanical ventilation is significantly higher than for nonventilated patients in the ICU (e.g., $47,158 vs. $23,707 in one study).[23] It is important, however, to understand that the difference in cost between ventilated and nonventilated patients is a factor of higher illness severity rather than the cost of providing mechanical ventilation.[25]

Maintaining a mechanical ventilator accounts for less than 5% of direct ICU costs for a ventilated patient.[9] A ventilator includes a one-time cost of $20,000 to $45,000 for the hospital plus nominal maintenance charges, and it is used for a number of years. A respiratory therapists' time ranges from $70 to $130 per day depending on local salary and staffing levels, and administrative costs are a smaller factor. Rather than the mechanical ventilator itself, the major contributor to variable costs for a ventilated patient is the nursing effort assigned to the patient (Table 67-3).[26,27] The nurse-to-patient ratio for acutely ill, mechanically ventilated patients is usually 1:1 or 1:2.

One study assessed the fraction of total costs attributable to variable and direct-variable costs for mechanically ventilated patients at an urban teaching center.[9] The average total cost for each patient was $69,472. Costs were highest during the first 2 days of intensive care and decreased significantly

TABLE 67-3: COSTS OF MANAGING INTENSIVE CARE UNIT PATIENTS BY HUMAN AND CAPITAL COMPONENTS

Component	% Component Cost	% Total Cost
Human	–	63.8
Nursing	64.6	41.2
Medical	15.1	9.6
Professional	14.3	9.1
Support	6.1	3.9
Supplies	–	11.7
Laboratory	–	11.4
Chemistry	62.0	7.1
Hematology	23.5	3.3
Microbiology	9.9	1.1
Other	4.6	0.5
Medication	–	7.4
Diagnostic imaging	–	4.5
Capital equipment	–	1.2

Source: Used, with permission, from Noseworthy et al.[26]

thereafter (Fig. 67-1). Only 18.4% were direct-variable costs (costs not attributable to overhead, staff, or equipment). Direct-variable costs were highest for the blood bank (44%) and pharmacy (48%), and lower for radiology (8%) and respiratory care (3%).

Is Mechanical Ventilation Cost-effective?

Thorough economic analyses of mechanical ventilation have been limited because of difficulties in applying adequate study methods in this complex patient population. One high-quality study, however, addressed the question of cost-effectiveness of mechanical ventilation in severely ill patients who required mechanical ventilation for pneumonia or acute respiratory distress syndrome (ARDS).[28] In the analysis, patients were stratified based upon likelihood of 2-month survival (Table 67-4). The incremental cost per QALY of providing mechanical ventilation to these patients was $29,000 for low-risk patients (>70% estimated survival), $44,000 for medium-risk patients (51% to 70% estimated survival), and $110,000 for high-risk patients (≤50% estimated survival). Sensitivity analyses that increased mortality and costs to twice the baseline estimates resulted in incremental costs per QALY that were still less than $80,000 for low-risk and medium-risk patients. In another cost-utility analysis from France,[27] cost-utility ratios for ICU care of patients with acute respiratory failure were estimated to be $11,970 for patients without chronic lung disease and $14,365 for patients with chronic lung disease (see Table 67-2). This analysis did not include costs of care following discharge, so it is relevant only from the hospital's perspective.

These data suggest that mechanical ventilation for patients with acute respiratory failure as a consequence of pneumonia or ARDS meets standard criteria for cost-effectiveness

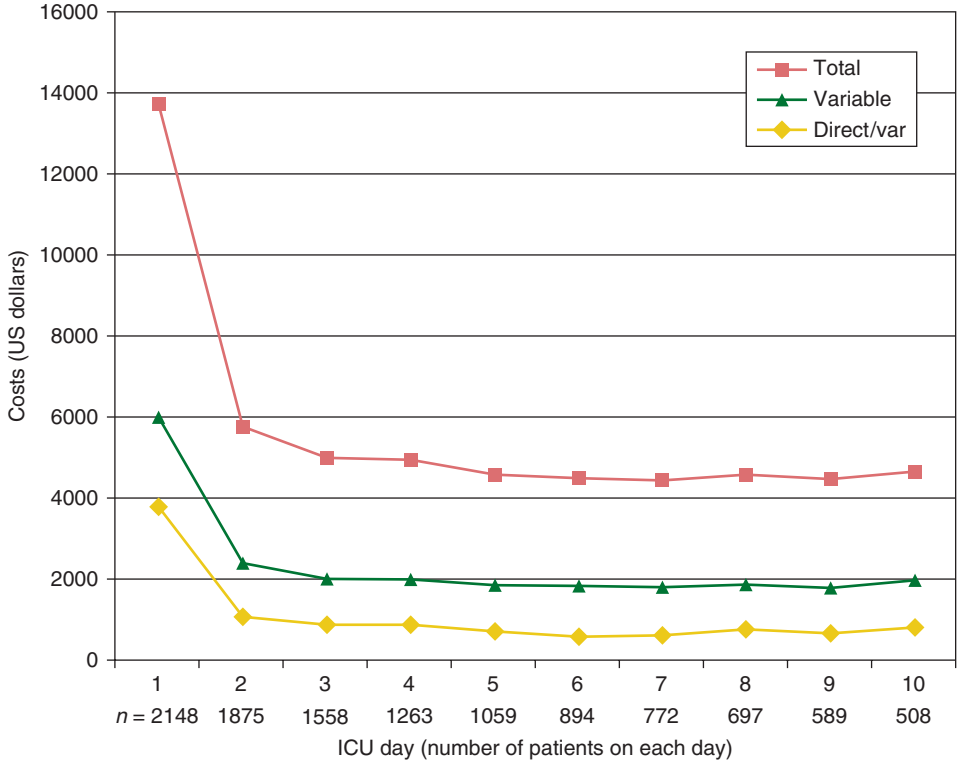

FIGURE 67-1 Mean costs by ICU day for patients receiving mechanical ventilation. Mean total (*Total*), variable (*Variable*), and direct-variable (*Direct/var*) costs by day for each ICU admission. (Used, with permission, from Kahn et al.[9])

TABLE 67-4: COSTS OF MECHANICAL VENTILATION FOR PATIENTS WITH ACUTE RESPIRATORY FAILURE SECONDARY TO PNEUMONIA OR ACUTE RESPIRATORY DISTRESS SYNDROME

	>70% Estimated 2-Month Survival	51% to 70% Estimated 2-Month Survival	≤50% Estimated 2-Month Survival
Hospital costs	$59,096 ± $64,336	$70,130 ± $85,300	$59,310 ± $54,590
Physician costs	$5,034 ± $6,705	$6,162 ± $5,264	$6,474 ± $7,426
Costs through the year after discharge	$22,037 ± $44,847	$18,772 ± $42,253	$11,994 ± $34,475
Annual costs after first year	$18,265 ± $48,078	$13,053 ± $26,519	$28,102 ± $86,998
One-year survival	0.62	0.39	0.21
Cost per QALY	$29,000	$44,000	$110,000

Patients were enrolled in the SUPPORT (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments) trial. Index hospital costs were derived from hospital charges using Medicare cost-to-charge ratios. Physician costs and costs of hospitalization after the index hospital discharge were estimated from Medicare financial data. Two-month survival estimates were determined at the time of diagnosis of acute respiratory failure.

Abbreviation: QALY, quality-adjusted life-year.

Source: Used, with permission, from Hamel et al.[28]

for all but the highest-risk patients. It may be reasonable to assume that mechanical ventilation for patients with conditions that afford better prognoses, such as asthma, chronic obstructive pulmonary disease (COPD), or routine postoperative patients, will be similarly cost-effective, and mechanical ventilation for patients with worse prognoses, such as pulmonary malignancies or hematologic malignancies, may be less cost-effective. Of course, it is rather difficult to apply these principles in bedside practice. When resources are available, mechanical ventilation should be utilized according to how the expected benefit matches the patient's wishes for invasive care.

Costs of Prolonged Mechanical Ventilation

Patients who require more than 7 days of mechanical ventilation represent only 10% of ICU patients, but they consume up to 40% of ICU resources.[29] More than 20% of those resources are consumed after the seventh day of ventilation. In 2005, patients requiring prolonged mechanical ventilation ranked third in summative inpatient charges by diagnostic group and first in diagnostic charges per patient.[30] The number of patients in the United States requiring at least 7 days of mechanical ventilation has been increasing steadily since 2000, and by 2020, the number is projected to double.[31] This is projected to require an absolute increase of over 2.1 million mechanical ventilator days, 3.2 million ICU days, and 6.5 million hospital days over year 2000, at a total inflation-adjusted cost over $64 billion.[32]

Health care costs associated with prolonged ventilation remain high even after patients are liberated from mechanical ventilation and discharged from the hospital. Readmissions occur in up to 40% of patients within a year, and total health care costs that accrue for patients during the year after discharge are almost as high as their index hospital costs because much of their time is spent in institutional care such as nursing homes or rehabilitation facilities.[33] In one single-center cohort study, prolonged ventilation patients who survived their acute hospitalization experienced a median of four transfers between different care centers, and 74% of days alive were spent in institutional care (Fig. 67-2).[34]

One-year survival of patients requiring prolonged ventilation ranges from 23% to 50%.[35,36] Considering their poor long-term outcomes and very high costs, the question inevitably arises as to whether or not prolonged care for these patients is cost-effective. In one economic analysis, investigators measured the cost-effectiveness of mechanical ventilation beyond 21 days compared to withdrawal of life-sustaining therapies as a hypothetical comparison.[30] They determined that providing prolonged mechanical ventilation cost $82,411 per QALY. Cost-effectiveness ratios were most sensitive to variation in age, hospital costs, and probability of readmission (Fig. 67-3).

CONTROLLING COSTS OF MECHANICAL VENTILATION

From the perspective of patients and society, mechanical ventilation results in significant and sometimes catastrophic charges, especially when provided in the ICU of an acute hospital. From the hospital perspective, more than half of the patients managed in the ICU generate costs that are greater than the average payment in the Medicare Diagnostic Related Group (DRG) system, leading to financial losses for the hospital.[24]

To control costs associated with mechanical ventilation, a patient's time on the ventilator and in the ICU should be limited as much as safely possible. Strategies to reduce duration of mechanical ventilation include prevention of intubation, efficient management of the ventilated patient, and withholding or withdrawal of mechanical ventilation in terminally ill patients (Table 67-5).[25] For the hospital, savings can be achieved by transfer of the ventilated patient to lower-intensity sites of care. It should be noted that none of these strategies will significantly reduce overall costs if they merely shift costs from one cost center to another (e.g., from an ICU

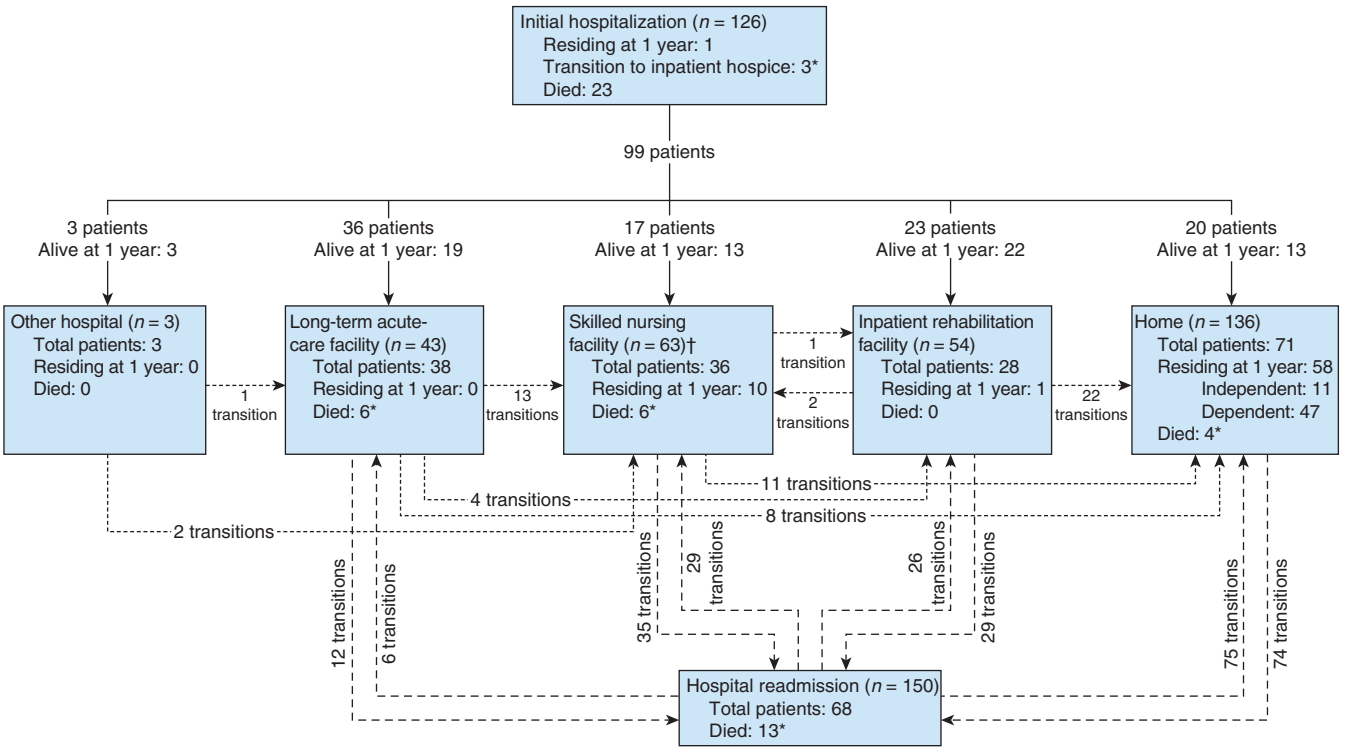

FIGURE 67-2 Trajectories of care over the first year after discharge for a cohort of patients requiring prolonged mechanical ventilation in a U.S. tertiary care hospital. *Arrows* between locations indicate both the direction of patient transitions and the total number of patients transferred between locations over 1 year. *Solid lines* represent initial transitions between the hospital and other locations. *Dashed lines* represent subsequent hospital readmissions and discharges involving postdischarge care locations. *Dotted lines* represent transitions among postdischarge care locations, including home. Each box summarizes the total numbers of both readmissions and patients admitted, as well as how many patients remained or died in each location of care at 1 year. *, Seven transitions to inpatient hospice and death not shown (three from the acute hospitalization and one each from home, long-term acute care facility, skilled nursing facility, and hospital readmission); †, one transition from skilled nursing facility to skilled nursing facility not shown. (Used, with permission, from Unroe et al.[34])

to a weaning facility).[8] Furthermore, one less day of mechanical ventilation and ICU care does not amount to savings relative to the average daily cost of ICU care, but rather to the last day of ICU care, which is much lower than the average daily cost.[9] And, finally, most of the costs associated with a day of mechanical ventilation are fixed costs rather than variable costs or direct-variable costs (see Fig. 67-1). Therefore, reducing time on a ventilator only lowers costs significantly if it leads to fewer days in the hospital and reductions can be sustained across enough patients over enough time to allow for closure of ICU beds and hospital beds.[8,37] With these caveats in mind, some strategies to reduce costs of care for the ventilated patient are discussed below.

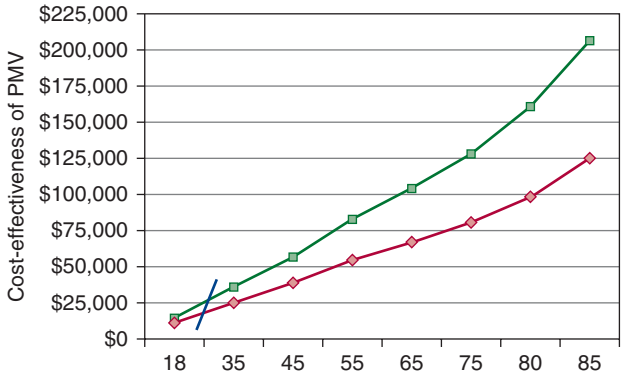

FIGURE 67-3 Incremental costs per life-year (*red line*) and incremental costs per quality-adjusted life-year (*green line*) of prolonged mechanical ventilation (*PMV*). (Used, with permission, from Cox et al.[30])

Prevention of Intubation

One effective means of preventing mechanical ventilation in the ICU is to intervene with appropriate resuscitative efforts before respiratory failure occurs. Early recognition and intervention for conditions that will predispose patients to respiratory failure such as sepsis, cardiogenic pulmonary edema, or acute bronchospasm may reverse processes enough to avoid intubation. Rapid response teams can facilitate early interventions, but some models require significant additional staff and may not improve hospital survival.[38–40] Protocols for early goal directed therapy in septic shock may reduce ICU resource requirements,[41] but confirmation of early findings await results of ongoing clinical trials. Perioperative clinical

TABLE 67-5: COST-CONTAINMENT STRATEGIES FOR MECHANICAL VENTILATION

Accepted strategies
Prevention of intubation
Rapid response teams
Noninvasive mechanical ventilation
Efficient management practices
Daily screening and performance of spontaneous breathing trials
Daily interruption of sedative infusions
Use of short-acting sedatives
Early mobilization
Prevention of ventilator-associated pneumonia
Prevention of intravenous catheter-related infections
Intensive care unit (ICU) organization
Critical care trained medical director
Closed ICU format with full-time intensivist coverage
Nurse-driven sedation protocols
Nurse-driven or therapist-driven weaning protocols
Flexible nurse staffing
Continuous medical education
Continuous quality improvement
Telemedicine
Transfer to lower-intensity sites of care
In-house respiratory care units
Long-term acute care hospitals or regional weaning centers
Acute rehabilitation hospitals with mechanical ventilation capabilities
Skilled nursing facilities with mechanical ventilation capabilities
Home mechanical ventilation
Unproven strategies
Withholding or withdrawing mechanical ventilation from terminally ill patients
Advanced directives are uncommon and do not influence practice
Very poor prognoses are often not evident until well into the ICU course
Cost savings are reduced if the patients require continued hospitalization for palliative care

management pathways have benefitted from fast-track anesthesia, and enhanced care in postanesthesia care units have greatly reduced the need for ICU care in cardiac, thoracic, and head-and-neck surgical patients.[42–45]

NONINVASIVE MECHANICAL VENTILATION

Noninvasive ventilation for acute respiratory failure secondary to severe COPD exacerbations decreases the likelihood that a patient will need intubation.[46,47] This is associated with significantly lower hospital mortality and decreased ICU and hospital length of stay. Noninvasive ventilation has also been shown to decrease likelihood of intubation in patients with congestive heart failure without shock or ischemia, patients with community acquired pneumonia if they have underlying COPD, patients with acute-on-chronic respiratory failure associated with obstructive sleep apnea, and in immunocompromised patients who have early ARDS.[48]

Avoiding intubation does not eliminate all of the costs associated with mechanical ventilation. Noninvasive ventilation in the setting of acute respiratory failure still requires a significant investment in respiratory therapist time in addition to equipment and administrative costs. More importantly, if the patient requires monitoring in an ICU, the actual cost savings will be reduced.[49] Many hospitals manage patients with acute respiratory failure requiring noninvasive ventilation on a stepdown unit or hospital floor that has lower nurse-to-patient ratios than in an ICU. Although achieving some cost savings, this approach should be implemented only if well-trained staff and sufficient monitoring are available to be able to respond to patients who fail noninvasive ventilation. Utilization of noninvasive ventilation in patients with less-severe COPD exacerbations would result in financial losses because it requires a higher level of monitoring than standard therapy and does not improve outcomes.[50]

Efficient Management Practices

Because decreasing time on the ventilator and time in the ICU is the mainstay of cost reduction for mechanical ventilation, recent clinical trials have focused on these issues as important outcomes. Use of normal tidal volumes (6 mL/kg predicted body weight) in patients with acute lung injury or ARDS rather than tidal volumes of 12 mL/kg of predicted body weight results in fewer ventilator days in addition to lower mortality.[51] As a result, it is a proven cost-effective therapy.[52] Daily screening for readiness to wean and initiation of spontaneous breathing trials does reduce ventilator days by 1.5 days compared to usual care.[53] Similarly, daily awakening of patients receiving continuous infusions of sedatives can decrease ventilator days by 2.4 days compared to usual care.[54] Use of a short-acting sedative rather than long-acting sedatives can reduce ventilator days as well, in part by reducing delirium.[55,56] These practices by themselves have a negligible impact on mortality, and total hospital costs are not dramatically impacted by a few less days of ICU care. But when these practices are applied in combination, long-term survival of patients can be significantly improved, indicating clear benefit.[57] Early mobility protocols are an extension of this concept of animating the ventilated patient to enhance cognitive and physical function.[54,58,59] Because some of these practices have not been standard care at many medical centers, clinicians have been slow to adopt them for their daily routine. Practice guidelines and nurse-driven or therapist-driven protocols have been very useful in these settings to change practice.[60–63] A meta-analysis evaluating the benefit of instituting formal weaning protocols indicated that they can result in decreased duration of mechanical ventilation and ICU stay, especially in surgical units, but mortality and hospital length of stay are not greatly affected.[64]

Individual practices that decrease time on the ventilator may decrease the risk of ventilator-associated pneumonia.

Ventilator-associated pneumonia can occur in up to 30% of ventilated patients, depending on the type of ICU. It is associated with longer time on the ventilator and longer ICU stays.[65] Ventilator-associated pneumonia may also result in higher patient mortality, although the attributable mortality of ventilator-associated pneumonia remains uncertain.[66] Therefore, prevention of ventilator-associated pneumonia is likely to be important for minimizing costs.[67] Early tracheostomy is another practice that is associated with fewer ventilator days and fewer days in the ICU. Most studies, however, do not demonstrate a mortality benefit, and not all studies result in fewer hospital days.[68–70] None of the clinical trials assess the additional costs associated with tracheostomy placement and care, or how discharge disposition is affected (e.g., discharge to a nursing home rather than home because of tracheostomy care needs). Early tracheostomy remains an ongoing area of clinical research, with the largest challenge being accurate identification of patients who are likely to proceed to prolonged ventilation so that unnecessary tracheostomy can be avoided.

Intensive Care Unit Organization and Staffing

A dedicated critical care-trained medical director is essential to maintaining an efficient ICU, and a closed ICU organization with intensivists managing all aspects of patient care is the ideal. The rationale for maintaining high-intensity ICU staffing (mandatory intensivist consultation or a closed ICU setting) is supported by multiple studies in the literature, although none of them are randomized trials. A systematic review of studies comparing high-intensity staffing to settings with no intensivists or only elective intensivist consultation revealed a pooled estimate of relative risk for hospital mortality of 0.71 (95% confidence interval, 0.62 to 0.82).[71] Although some studies noted greater use of ICU interventions, such as mechanical ventilation or pulmonary artery catheters, in the closed ICUs, high-intensity staffing reduced ICU length of stay in fourteen of eighteen studies, including the two studies using case-mix adjustment. Importantly, the degree of illness severity increased for many of the ICUs when they adopted high-intensity staffing, suggesting that dedicated intensivists achieve more appropriate use of ICU resources. Although the closed ICU model is the norm in Europe and Australia, only 30% of ICUs in the United States have adopted such forms of organization.[72] This proportion may increase as quality initiatives by various health consortiums and industry groups have identified 24-hour intensivist coverage for ICU patients as an important priority.

Although a closed ICU model is advocated for better outcomes, there are limited data to clarify the best ratio of intensivists to patients. Furthermore, there will be an insufficient number of available intensivists in the United States to staff all ICUs in a closed model for the foreseeable future.[72] Therefore, another relevant question is what type of clinicians, besides intensivists, provide the most efficient care. As a result of decreased availability of resident trainees, a number of models involving hospitalists, nurse practitioners, and physician assistants are being evaluated.[73,74] Another approach is to utilize evolving technologies in telemedicine. This expensive technology can be associated with improved hospital mortality and decreased ICU stay if there is broad physician acceptance, and if the intervention is focused on adherence to evidence-based practices and enforcement of daily patient goals.[75,76]

Withholding or Withdrawing Mechanical Ventilation in Terminally Ill Patients

Up to 12% of health care expenditures and 27% of Medicare expenditures are spent on patients during the last year of their lives.[77,78] For Medicare patients who die, 40% of their Medicare expenses are generated during the last month of their life. Seventy percent of their total expenses are spent on inpatient care. Dying patients often endure a period of critical illness before their death. Limiting ICU care for patients at the end of their life might seem like an obvious target for reducing ICU resource consumption and limiting health care costs, but realizing true cost savings in practice has been very difficult to accomplish for a number of reasons.[37,79]

Advance directives are relatively uncommon and often countermanded in the setting of acute respiratory failure if palliative measures are not already in place. The SUPPORT (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments) trial[80] and other studies have demonstrated that interventions to make physicians more aware of patient prognoses and preferences for end-of-life care do not alter outcomes or result in reductions in resource use. Once patients have been intubated, early withdrawal of support for those with the worst prognoses could potentially result in cost savings, but only if it resulted in death in a much shorter period of time than would have occurred with continued care. Prolonged palliative care in an inpatient setting would significantly reduce any incremental cost savings.

One study of an intervention to improve communication of prognosis and goals of care highlights the difficulties of achieving true cost savings from interventions that reduce ICU length of stay. In a before-and-after study design,[81,82] investigators found that implementation of regular, structured family meetings emphasizing clinical milestones by the ICU team reduced median ICU length of stay from 4 to 3 days. ICU mortality rates also decreased, which the authors attributed to earlier triage of severely ill patients who were likely to die, with subsequent admission of less severely ill patients. So in effect, more efficient use of ICU beds in the care of severely ill patients did not result in any change in fixed ICU costs, because less-severely ill patients who were previously managed on the general wards were admitted to the ICU as more resources became available.

Transfer to Lower-Intensity Sites of Care

For critically ill patients, the highest intensity of care usually occurs within the first few days of ventilation. As gas exchange and hemodynamics improve, the level of nursing required to manage them decreases. As long as they remain in an ICU, however, the associated nursing commitment and costs remain substantial. When the lengths of stay extend beyond approximately 14 to 21 days, hospitals begin to assume considerable financial losses. Therefore, hospitals are quite motivated to find less-intensive sites of care for these patients.

Options for lower-intensity sites of care for patients requiring prolonged ventilation include (a) stepdown units or dedicated respiratory care units within the acute hospital, (b) transfer to separate acute care hospitals dedicated to weaning patients from mechanical ventilation such as regional weaning centers, long-term acute care hospitals (LTACs) or specialized rehabilitation hospitals, (c) transfer to skilled nursing facilities that offer ventilator care, or (d) discharge to home with home ventilation.[83] When ventilated patients are transferred from the acute ICU to stepdown units, some variable cost-savings are achieved primarily because of lower nurse to patient ratios. Prolonged weaning of weak patients demands a high degree of therapist monitoring, and aggressive physical rehabilitation during weaning is felt to be important for good outcomes. Therefore, in well-managed weaning units, savings in nursing costs are balanced by additional expenses for respiratory therapists and physical and occupational therapists. Custodial care of ventilated patients in skilled nursing facilities that does not include active weaning or rehabilitation is less expensive on a daily basis, but complete failure to wean patients results in higher long-term costs.

Hospitals realize the largest cost savings and open the most ICU beds by transferring ventilated patients to freestanding weaning hospitals, such as LTACs. These financial and resource incentives have driven considerable growth in the largely for-profit LTAC industry in the United States, resulting in an 8.8% increase in the number of LTAC hospitals per year between 1997 and 2006.[84] The number of patients transferred to LTACs for prolonged ventilation increased from 10,389 in the period between 1997 and 2000 to 30,877 between 2004 and 2006. It should be emphasized that transferring a ventilated patient to a freestanding weaning facility will result in cost savings for the hospital, but not necessarily for the health care system. Recent analyses sponsored by the Center for Medicare and Medicaid services have indicated that for patients transferred to LTACs, costs for the total episode of care (hospital and LTAC) were significantly higher than for similar patients whose total episode of care was managed completely at the acute care hospital. Whether this is secondary to additional costs and complications of transfer, less efficient management at the LTACs, or selection bias in the analysis, it certainly suggests that transferring patients to LTACs may ultimately result in cost shifting rather than overall cost savings.

THE FUTURE

Continued advances in technology will increase the gap between what critical care medicine can do and what is economically feasible to do. The formal application of health economics to guide decision making in the delivery or organization of critical care is in its early stages. Economic analysis will become more influential as providers become more familiar with its benefits and its limitations. Investigators can improve upon limitations by applying better methodology, especially relating to measurement of costs across various levels of care. Increasing sophistication of clinical information systems and inclusion of economic components in the design of clinical trials will provide higher quality data.[17,18] Investigators are continuing to refine quality-of-life assessments, and better understanding of long-term outcomes of critically ill patients is an area of growing research interest. More research into the behavioral aspects of medicine including social and professional expectations for distribution of resources will provide guidance to societies and health plans on how to utilize the data from economic analyses.[85]

Economic pressures and financial constraints will continue to have a beneficial effect on efficiency of care in the ICU by reducing waste and redundant services. ICU directors, however, need to exercise caution in the persistent drive for efficiency. Overly aggressive measures to discharge patients from the ICU and maintain high occupancy of only severely ill patients can worsen outcomes. For example, discharges from the ICU at night and ICU admissions during periods of peak occupancy and high nursing workload are associated with higher hospital mortality. From the perspective of society and health care systems, savings generated from reductions or restrictions in critical care services are justified only if those savings are invested in more effective services elsewhere in the system.

SUMMARY AND CONCLUSIONS

The high costs of critical care services will always make this area of medicine a target for cost containment. Patients requiring mechanical ventilation consume a disproportionate share of hospital resources, especially those requiring prolonged ventilation. Despite the costs, mechanical ventilation for patients with acute respiratory failure meets current standards for cost-effectiveness except for patients with the highest likelihood of short-term mortality. Strategies to reduce hospital costs are directed toward decreasing the duration of mechanical ventilation. These strategies include prevention of intubation by rapid response to illness and noninvasive ventilation when indicated, efficient evidence-based management practices, and optimal ICU organization including continuous quality improvement. Economic analyses will assume a greater role in decision making related to mechanical ventilation as investigators include cost and quality-of-life components in the design of clinical trials and as providers gain a better understanding of how to utilize the data.

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LONG-TERM OUTCOMES AFTER MECHANICAL VENTILATION

Margaret Sutherland Herridge

When the first edition of this book was published in 1994, the standard metric of outcome after critical illness was 28-day all-cause mortality. Since that time, there has been a revolution in the way we view critical illness, its treatment, and its lasting effects both for the patient and the family caregiver. The dramatic rise in the number of longer-term outcomes reports published over the past 5 to 10 years clearly reflects this point. It is now apparent that most patients who have survived an episode of severe critical illness requiring mechanical ventilation will sustain some compromise in physical function related to intensive care unit (ICU) acquired weakness and a myriad of other physical disabilities.[1–5] This acquired disability may be permanent.[5] Patients may also sustain an important new or incremental decline in neuropsychological function, including neurocognitive impairments, and neuropsychiatric or mood disorders.[6–8] The constellation of muscle, nerve, and brain dysfunction[3,9–13] may permanently alter disposition for those who were previously independent and who, post-ICU, now require assisted living or comprehensive care.[1] ICU-acquired morbidity may result in an additional cost burden in health care utilization that is similar to patients with chronic disease,[1,5,13–14] and this traumatic life event may completely erode the reserve of family members and they may also acquire new mood disorders.[15–18]

This chapter reviews the literature on physical and neuropsychological outcomes after critical illness and highlights important emerging data that link patient characteristics, burden of comorbid disease, and ICU practice patterns to acquisition of new morbidity. In addition, newer data on psychological disability in family caregivers and models of rehabilitation and intervention after critical illness are discussed. To date, the outcomes literature has been dominated by reports on survivors of acute respiratory distress syndrome (ARDS), but there are emerging data on other vulnerable patient subgroups, such as the frail elderly and the chronically critically ill. Outcomes in these populations add insight to the current understanding of the diversity in post-ICU disability and also are discussed. The chapter concludes with a commentary on a proposed framework for a continuum of rehabilitation for patients and families after critical illness.

PHYSICAL MORBIDITY AFTER CRITICAL ILLNESS

The current state of the outcomes literature suggests that the greatest short-term morbidity after critical illness is diminished physical health-related quality of life as a consequence of ICU-acquired weakness.[3,5,9,10,13,19–22] Reports from long-term follow-up studies suggest that by 5 years, patients complain less of physical disability and more of a decline in general health, diminished vitality, and mood disorders.[5] The finding of compromised physical quality of life has been robust across many studies since the early 1990s, as discussed in detail below. An understanding, however, of the specific determinants of this reported decrease in physical function was not well known until more than a decade later.

Patients with acute lung injury and ARDS represent some of the most complex critically ill and long-stay ICU patients and have been the most rigorously studied group of ICU survivors to date. More than 100,000 patients survive acute lung injury and ARDS every year[24] and their outcomes dominate the review that follows. The emerging outcomes literature on the chronically critically ill, elderly, and sepsis patient populations adds nuance and depth to our understanding of the spectrum of disability and is also included.

Physical Function and Health-Related Quality of Life

Health-related quality of life is a set of causally linked dimensions of health, including biologic/physiologic, mental, physical, social function, neurocognitive, and health perception.[21] Measures of health-related quality of life have emerged as important patient-centered metrics of recovery from critical illness. These questionnaires provide ease of administration and ready interpretability with published normative data for comparison, although fail to yield crucial details about the exact nature of any reported disability. Without this insight or more detailed understanding, the investigator is left to blindly hypothesize about the etiology of the reported disability and limits her or his ability to construct appropriate interventional or rehabilitation programs.

There is emerging evidence that the degree of disability acquired after critical illness and resultant health-related quality of life is variable and relates to differences in premorbid functional status, burden of comorbid illness, and nature and duration of critical illness.[1,3,4] Although there is some heterogeneity across different study samples of patients with ARDS, there is less variability in reported health-related quality of life among this group than in general populations of critically ill patients.[24] The following is an overview of the literature on ARDS health-related quality of life and these data highlight the consistent signal of diminished physical function reported up to 1 year after severe lung injury, and also the controversy that still continues about the relative contribution of pulmonary disability to functional decline after ARDS and severe critical illness. In 1994, McHugh et al were the first group to prospectively evaluate the relationship between pulmonary dysfunction and functional disability in patients with ARDS.[19] They noted that scores for the Sickness Impact Profile (a generic quality-of-life measure of the subject's self-perceived physical and psychological condition) rose substantially to 3 months postextubation with only minimal further improvement to 1 year. Using a lung-related Sickness Impact Profile score, only a modest proportion of the patients' overall physical dysfunction was attributed to pulmonary difficulties. Weinert et al[20] documented functional impairment in a cohort of lung injury survivors using the Medical Outcomes Study 36-item short-form health survey (SF-36) and reported the largest decrements in role-physical and physical-functioning domains, which patients attributed to global disability.[25] Similar observations were made by other groups who inferred that disability in their patients with ARDS was secondary to pulmonary dysfunction in the absence of any direct pulmonary measurement[26] or through administration of pulmonary disease-specific measures and this failed to differentiate between pulmonary and extrapulmonary disability.[22] Others have made comparisons to control populations of patients with known pulmonary disease (e.g., cystic fibrosis), but after health-related quality-of-life measures had been disaggregated, symptom burden was seen to be related to musculoskeletal or constitutional issues.[10] In the context of outcome evaluation after a trial comparing higher versus lower tidal volumes during mechanical ventilation, some have demonstrated very modest abnormalities of pulmonary function, which correlate with reduced function on health-related quality-of-life metrics, and maintain that there is an important relationship between pulmonary and functional outcomes in ARDS survivors.[28]

In 2003, Herridge et al reported on 109 ARDS survivors at 3, 6, and 12 months after ICU discharge and captured function as distance walked in 6 minutes, pulmonary function, and health-related quality of life using the SF-36. The investigators also did a detailed in-person interview and physical assessment as part of each follow-up visit. In their relatively young patient sample (median age: 45 years), with few comorbidities and who had been working full time before their critical illness, 6-minute walking distance was 66% at 1 year and pulmonary function was normal or near normal. They noted that the major morbidity after ARDS and sepsis was muscle wasting and weakness.[3] In-person evaluation of patients and the collection of multiple outcome measures led the investigators to different conclusions about the major contributors to morbidity after severe lung injury and also facilitated the generation of a catalogue of physical disabilities that contribute to poor health-related quality of life (Fig. 68-1).

Impaired physical function is a robust observation across different studies, countries, and investigators, and may persist for years after ICU or hospital discharge and be irreversible (Fig. 68-2).[4,5] Health care costs generated by relatively young, previously working patients in an ARDS cohort followed to 5 years were higher than predicted for this age group and comparable to patients with chronic disease (Fig. 68-3). It was not expected that this patient group would not fully recover from their critical illness in terms of physical functioning, emotional outcomes, or quality of life, and this finding has significant public health ramifications.

RISK FACTORS FOR POOR FUNCTIONAL OUTCOME AFTER CRITICAL ILLNESS

The ARDS outcomes data are instructive because most of these study samples involved younger patient groups with few or no premorbid conditions. It was a surprising and striking observation that these patients did not fully recover

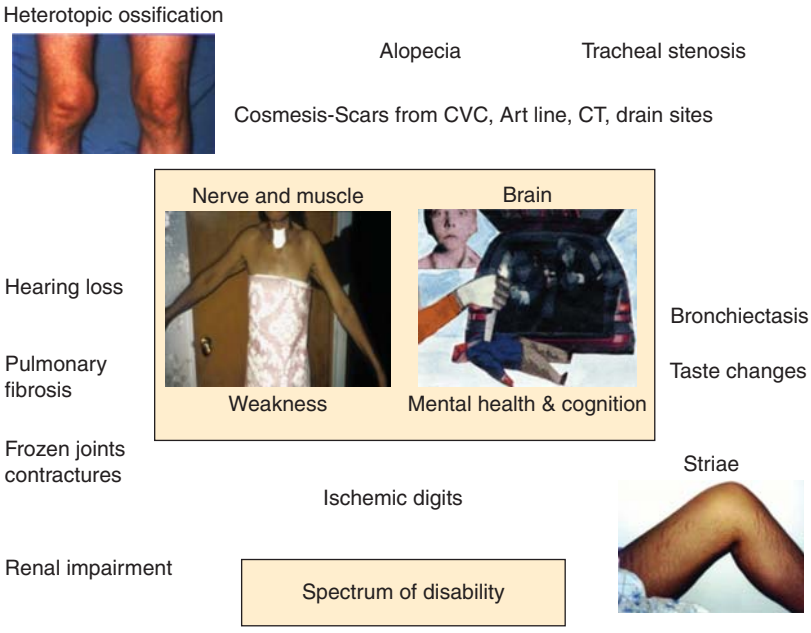


FIGURE 68-1 The spectrum of disability in survivors of critical illness. Brain, muscle, and nerve are the major morbidities; others are less common.

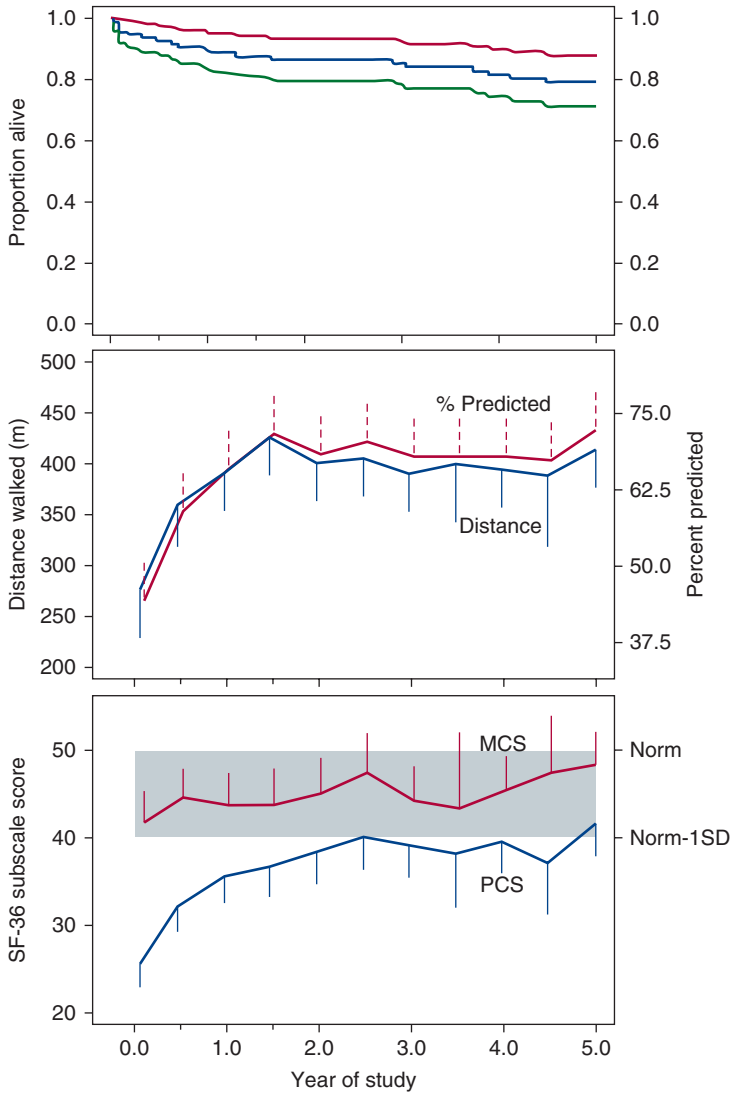
and had important and persistent morbidity for years after their critical illness. These data establish that there is a physical and neuropsychological "cost" to a severe episode of critical illness, and that most patients, particularly those in more vulnerable groups, such as patients requiring prolonged mechanical ventilation, patients with a significant burden of comorbid illness, and the elderly, may suffer even greater functional decline and require dependent care as a result of their critical illness.

Studies on survivors of prolonged mechanical ventilation have helped in elucidating important risk factors for outcome and change in disposition. Chelluri et al evaluated factors associated with mortality and quality of life in 817 patients 1 year after prolonged mechanical ventilation.[28] The median age of their patients was 65 and 1-year survival was 44%. Those patients surviving their ICU stay had fewer comorbidities, lower severity of illness scores, and less premorbid dependence in activities of daily living. Fifty-seven percent of surviving patients needed caregiver assistance at 1 year of follow-up. A French study by Combes et al evaluated 347 patients receiving mechanical ventilation for equal to or greater than 14 days.[29] Factors associated with death in the ICU included age greater than 65 years, preadmission New York Heart Association functional class of equal to or greater than 3, preadmission immunocompromised status, septic shock at ICU admission, need for renal replacement therapy in the ICU, and nosocomial septicemia.

Unroe et al evaluated the trajectories of care and resource utilization for 126 patients with a median age of 55 years who also required prolonged mechanical ventilation. These patients had, on average, two comorbid conditions, and most were not working, retired, or disabled at the time of ICU admission. At 1 year, only eleven patients (9% of the cohort) were alive and without functional dependency. Patients with poor outcomes were older, had more comorbid conditions, and were more frequently discharged to a post–acute care facility. The mean cost per patient was $306,135 (standard deviation [SD]: $285,467) and total cohort cost was $38.1 million, for an estimated $3.5 million per independently functioning survivor at 1 year.[1]

Iwashyna et al noted persistent reduction in functional status after sepsis and critical illness, again echoing the theme of acquired disability after critical illness. Among older patients (median age: 77 years), they observed a high rate of new functional limitations in those who had no limits before their episode of sepsis (mean: 1.57; 95% confidence interval [CI]: 0.99 to 2.15). In patients with reductions in activities of daily living before sepsis, they noted an important further decrement in function. Neurocognitive and physical decline persisted for at least 8 years after the episode of sepsis and altered patients' ability to live independently.[4]

The impact of increased age, however, on outcomes after critical illness remains somewhat controversial. Some studies report higher mortality with advanced age[30] and others do not.[31,32] Khouli et al[33] recently evaluated 484 patients, who were age 65 years and older, and administered an health-related quality-of-life instrument to the patient or proxy at ICU admission and 6 months after hospital discharge. One-third of these patients died within 6 months of hospital discharge. Independent predictors of death at 6 months were: number of days during the 30 days before hospitalization that the patient felt their "physical health was not good," a higher Acute Physiology and Chronic



N at risk	109	92	86	79	77	74	69	64
N for 6 min walk	80	78	81	60	64	64	57	54
N for SF-36	67	74	74	56	57	57	49	50

- Exact survival times were used for these analyses whereas deaths indicated in the consort diagram were included between scheduled follow-up visits.

Top Panel - Kaplan-Meier curve to 5 years. Dashed lines represent the 95% confidence interval
Middle Panel - Distance walked in 6 minutes (meters and % predicted); Distance in meters is a solid line; and % predicted is a dashed line.
Bottom Panel - SF-36 Subscale scores for Physical Component Score (PCS) and Mental Component Score (MCS)

FIGURE 68-2 *Top Panel:* Survival—Kaplan-Meier curve to 5 years. *Dashed lines* represent the 95% confidence interval. Exact survival times were used for these analyses. *Middle Panel:* Six-minute walk distance—Distance walked in 6 minutes (meters and % predicted); distance in meters is a *solid line* and % predicted is a *dashed line*. *Bottom Panel:* Quality of life to 5 years after ICU discharge—SF-36 Subscale scores for Physical Component Score (PCS) and Mental Component Score (MCS). (Used, with permission, from Herridge et al.[5])

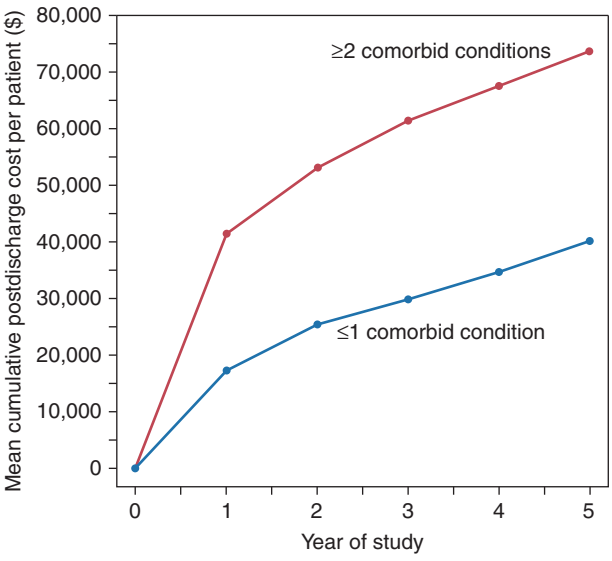


FIGURE 68-3 Cumulative costs to 5 years after ICU discharge stratified by number of comorbid conditions at ICU admission. *Lower line* is less than or equal to one comorbid condition and *upper line* is greater than or equal to two comorbid conditions. (Used, with permission, from Herridge et al. *N Engl J Med*. 2011.[5])

Health Evaluation (APACHE) II score, and chronic pulmonary disease. This same group also found that the oldest survivors (age 86 years) had worse health-related quality of life over time, including more days spent with poor physical and mental health, compared to baseline. There appears to be a clear prognostic signal in the elderly in terms of physiologic reserve, burden of chronic organ dysfunction, and nature of the health trajectory before the critical illness with regards to prognostication for survival, function, and health-related quality of life; emphasis on physiologic rather than chronologic age may provide valuable insight into projected outcome.

Neuromuscular Dysfunction

Muscle weakness and impaired function constitute an important morbidity of severe critical illness. A continuum of weakness begins within hours of mechanical ventilation,[34] is demonstrable by bedside evaluation within 1 week of ICU admission using the Medical Research Council scoring system,[35] and may persist with incomplete recovery for years after ICU discharge[5,36–41] (see Fig. 68-2). In the ICU context, muscle weakness has been linked to prolonged mechanical ventilation,[42,43] delay in ICU and hospital discharge, increase in associated costs,[44,45] and increased likelihood of death.[46]

Many challenges confound the ability to characterize and intervene in neuromuscular disability after critical illness. Important heterogeneity exists in susceptibility and risk factors across different critically ill patient populations. There are no validated measures to reliably risk stratify patients according to physical disability and no consistent nomenclature for the spectrum of lesions that constitute muscle weakness and wasting. Currently, different terminologies coexist in the literature and include critical illness polyneuropathy, critical illness polyneuropathy and myopathy, critical illness neuromyopathy, ICU-acquired paresis, critical illness myopathy and/or neuropathy. This complexity is compounded by the observation that nerve and muscle injury may coexist, and it is difficult to delineate discrete risk factors and natural history. There are obstacles in terms of the variety and sensitivity of testing methods, criteria for diagnosis, surveillance and selection bias in evaluation and reporting. Sensory and motor evaluations are limited in heavily sedated patients, and, therefore, clinical bedside testing and determination of the prevalence of these lesions may be unreliable.

Despite these limitations, a recent classification system was proposed by Stevens et al (Table 68-1).[47] This system is simple, accessible, and clinically relevant, and emphasizes clinical assessment and bedside testing. It proposes a broad classification for ICU-acquired weakness and highlights it as a diagnosis of exclusion, onset during the critical illness, ventilator dependence, and weakness demonstrable by use of bedside hands-on muscle testing (Medical Research Council score). A diagnosis of critical illness polyneuropathy is made in those who meet criteria for ICU-acquired weakness and have electrophysiologic evidence of a sensorimotor axonal polyneuropathy. A diagnosis of pure critical illness myopathy is made in patients who meet criteria for ICU-acquired weakness and who have myopathic features on electromyelography during muscle contraction and/or myopathic biopsy.

This section discusses the pathophysiologic mechanisms for muscle and nerve injuries (Fig. 68-4). Given the limitations in this distinction, as outlined above, the mechanisms are broadly grouped as critical illness polyneuropathy and critical illness myopathy.

CRITICAL ILLNESS POLYNEUROPATHY

Background and Incidence. Bolton et al published a landmark study on critical illness polyneuropathy in 1984.[48] They described a primary axonopathy that presented as a mixed sensorimotor neuropathy in five critically ill patients who were ventilator dependent. Detection of the true incidence of critical illness myopathy is complicated by poor consensus on surveillance, timing, and nature of testing, and formal definition and diagnostic criteria (as outlined above). When patients are evaluated solely on the presence of clinical weakness, studies demonstrate an incidence of 25% to 36%.[35,49] A review of 1421 critically ill patients, evaluated using diagnostic tests (nerve conduction velocities, needle electromyography, direct muscle stimulation, histopathology of muscle or nerve tissue) or a combination of test findings and clinical findings, reported an incidence of critical illness neuromyopathy of 46% (95% CI: 43% to 49%).[50]

TABLE 68-1: SUMMARY OF DIAGNOSTIC CRITERIA FOR INTENSIVE CARE UNIT-ACQUIRED WEAKNESS, CRITICAL ILLNESS POLYNEUROPATHY, AND CRITICAL ILLNESS MYOPATHY

Diagnostic criteria for ICU-acquired weakness (ICUAW) 1, 2, 3 or 4, 5 below
1. Generalized weakness developing after the onset of critical illness
2. Weakness is diffuse (involving both proximal and distal muscles), symmetric, flaccid, and generally spares cranial nerves
3. MRC (Medical Research Council) sum score[a] <48, or mean MRC score <4 in all testable muscle groups noted on two or more occasions separated by >24 hours
4. Patient dependent on mechanical ventilation
5. Other causes of weakness not related to underlying critical illness have been excluded

Diagnostic criteria for critical illness polyneuropathy (CIP)
1. Patient meets criteria for ICUAW
2. Compound muscle action potential amplitudes are decreased to <80% of lower limit of normal in two or more nerves
3. Sensory nerve action potential amplitudes are decreased to <80% of lower limit of normal in 2 or more nerves
4. Normal or near-normal nerve conduction velocities without conduction block
5. Absence of a decremental response on repetitive nerve stimulation

Diagnostic criteria for critical illness myopathy (CIM)
1. Patient meet criteria for ICUAW
2. Sensory nerve action potential amplitudes are >80% of the lower limit of normal in two or more nerves
3. Needle electromyogram in two or more muscle groups demonstrates short-duration, low-amplitude motor unit potentials with early or normal full recruitment with or without fibrillation potentials
4. Direct muscle stimulation demonstrates reduced excitability (muscle-to-nerve ratio >0.5 in two or more muscle groups)
5. Muscle histology is consistent with a myopathy

Probable CIM: criteria 1, 2, 3, or 4; or 1 and 5 (listed above)
Definite CIM: criteria 1, 2, 3 or 4, 5 (listed above)

[a]MRC Sum score assesses three muscle groups in each of the upper and lower limbs. Each muscle group score ranges from 0 (paralysis) to 5 (normal muscle strength), and the overall score ranges from 0 to 60.

Source: Adapted, with permission, from Stevens RD, Marshall SA, Cornblath DR, et al. A framework for diagnosing and classifying intensive care unit-acquired weakness. *Crit Care Med.* 2009;37(10 Suppl):S299–S308.

Etiology and Pathophysiology

Systemic Inflammatory Response Syndrome and Sepsis

Critical illness polyneuropathy has been associated with sepsis and systemic inflammatory response syndrome in multiple cohort studies.[50] In sepsis, critical illness polyneuropathy is linked to microcirculatory perturbations with resultant axonal injury and degeneration. A recent report describes proinflammatory cytokine (tumor necrosis factor-(and interleukin-1)-mediated increased expression of E-selectin on the endoneurial and epineurial vessels

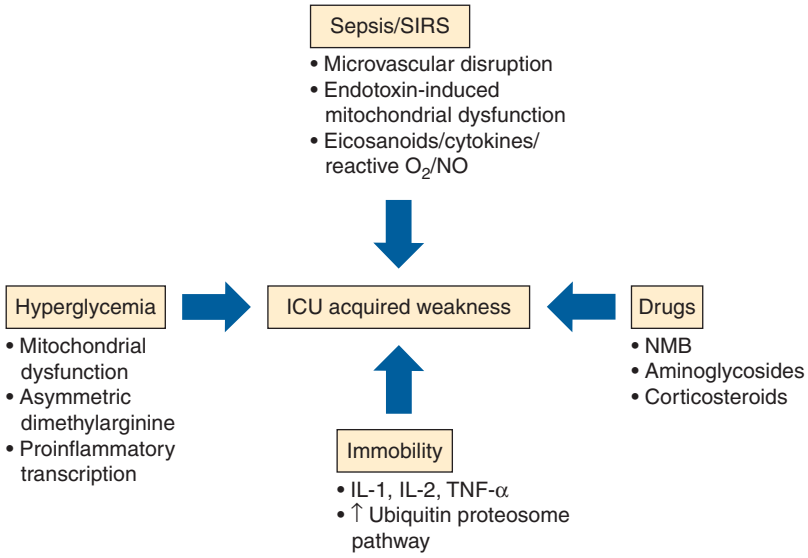


FIGURE 68-4 Risk factors for ICU acquired weakness. *IL-1*, interleukin-1; *IL-2*, interleukin-2; *NMB*, neuromuscular blockers; *NO*, nitric oxide; *TNF-α*, tumor necrosis factor alpha. (Adapted, with permission, from Stevens RD. *Crit Care Clin.* 2008;24:1–24.)

of peripheral nerves.[51] There may be functional disruption of nerve action potential early in the course of disease, which may be a harbinger of later structural derangement of the nerve.[52]

Hyperglycemia Hyperglycemia in critically ill surgical and medical populations is consistently associated with ICU-acquired weakness.[53,54] Van den Berghe et al demonstrated that tight glycemic control reduced critical illness polyneuropathy in defined by neurophysiologic testing, from 51.9% in control subjects to 28.7% among insulin-treated patients.[53,54] Hyperglycemia may be harmful based on mitochondrial dysfunction and the deleterious effects of oxidant injury and apoptosis.[55,56] Derangement of nitric oxide production is also a postulated mechanism,[57] as is the role of insulin in inhibiting proinflammatory transcription factors and promotion of neuroregeneration during critical illness.[58,59]

Pharmacologic Agents Early reports suggested an association between neuromuscular dysfunction and exposure to neuromuscular blockers and systemic corticosteroids.[60–62] This risk was profiled in patients with status asthmaticus who developed ICU-acquired weakness and received treatment with both agents.[63] These risks have not been borne out in systematic review because of confounding by exposure to aminoglycosides, vasopressors, and renal replacement therapy in sepsis and systemic inflammatory response syndrome patients.[50,64–65] In a 1-year outcomes study in patients with ARDS, exposure to any systemic corticosteroid was significantly associated with a decrease in 6-minute walking distance at 3 months in a multivariable model, and patients demonstrated important proximal weakness in the shoulder and hip girdle at that time point.[3] A recent trial using 48 hours of continuous paralytic in patients with severe lung injury saw significant organ function improvement, and the continuous paralytic was not associated with an increased risk of ICU-acquired weakness assessed by manual muscle testing at ICU discharge.[66] No long-term follow-up, however, was done, and there is concern that manual muscle testing may not have adequate sensitivity to detect ICU-acquired weakness.[66] Early corticosteroid use appears to be strongly associated with ICU-acquired weakness, although the risk associated with paralytic use remains somewhat uncertain.

CRITICAL ILLNESS MYOPATHY

Background and Incidence. Critical illness myopathy currently encompasses critical illness myopathy, acute quadriplegic myopathy, thick filament myopathy, and necrotizing myopathy, and the incidence varies between 48% and 96% in studies that included muscle biopsy.[65] Critical illness myopathy is a nonnecrotizing diffuse myopathy associated with fatty degeneration of muscle fibers, fiber atrophy, and fibrosis.[67] This lesion has also been linked to corticosteroid and paralytic exposure and may be clinically indistinguishable from critical illness polyneuropathy because patients are also weak, paretic, and difficult to wean.

Thick-filament myopathy shows a selective loss of myosin filaments in the context of significant corticosteroid or neuromuscular blocker exposure and immobility.[68] Acute necrotizing myopathy is distinguished by extensive myonecrosis with vacuolization and phagocytosis of muscle fibers, and is linked to corticosteroid and neuromuscular blocker exposure and multisystem organ dysfunction.[69]

Etiology and Pathophysiology. The pathophysiology of critical illness myopathy involves catabolism, inflammation, and derangement of membrane excitability. An increase in urinary nitrogen loss, low glutamine, protein, and DNA levels in muscle biopsies, and upregulation of the calpain and ubiquitin proteolytic pathways and apoptosis have all been documented.[70]

Inactivity in critically ill patients propagates inflammatory mediators, which stimulate protein loss in differentiated muscle cells, activate signaling events that promote oxidative injury and disruption of insulin receptor signaling with resultant substrate reduction and impairment of myofibril growth and repair.[71] Interleukin-1, interleukin-6, and tumor necrosis factor-α have proinflammatory properties and have all been implicated in muscle degradation in critical illness and augmentation of proteolysis and muscle loss. Muscle membrane inexcitability may also contribute to weakness and is related to inactivation of sodium channels. Allen et al recently reported altered muscle-fiber excitability and evidence for muscle membrane dysfunction as the principal underlying abnormality in critical illness myopathy.[72]

Pulmonary Function

Pulmonary function outcomes may be heterogeneous after an episode of ARDS. Many ARDS survivors have persistent pulmonary function impairments: typically, mild restrictive changes with an associated reduction in diffusion capacity.[3,19] Others have documented more diversity in outcome, with significant variability in the proportion of patients with obstructive (0% to 33%) and restrictive (0% to 50%) defects, as well as compromised diffusion capacity (33% to 82%).[73] There are reports of mild pulmonary function abnormalities associated with decreased health-related quality of life 1 year following hospital discharge[27] and no improvement in pulmonary function after the first year.[74] Most recent data from a 5-year outcomes cohort study in patients with severe ARDS shows normal to near normal pulmonary function achieved by 6 months to 1 year after ICU discharge and continued stability over the 5-year study period.[5]

There are imaging studies of ARDS survivors at 6 to 10 months,[75] 3 years,[76] and 5 years.[5,77] Investigators have noted that most patients with ARDS had minor localized changes in the nondependent lung zones (Fig. 68-5), and were able to document some association with severity of lung injury

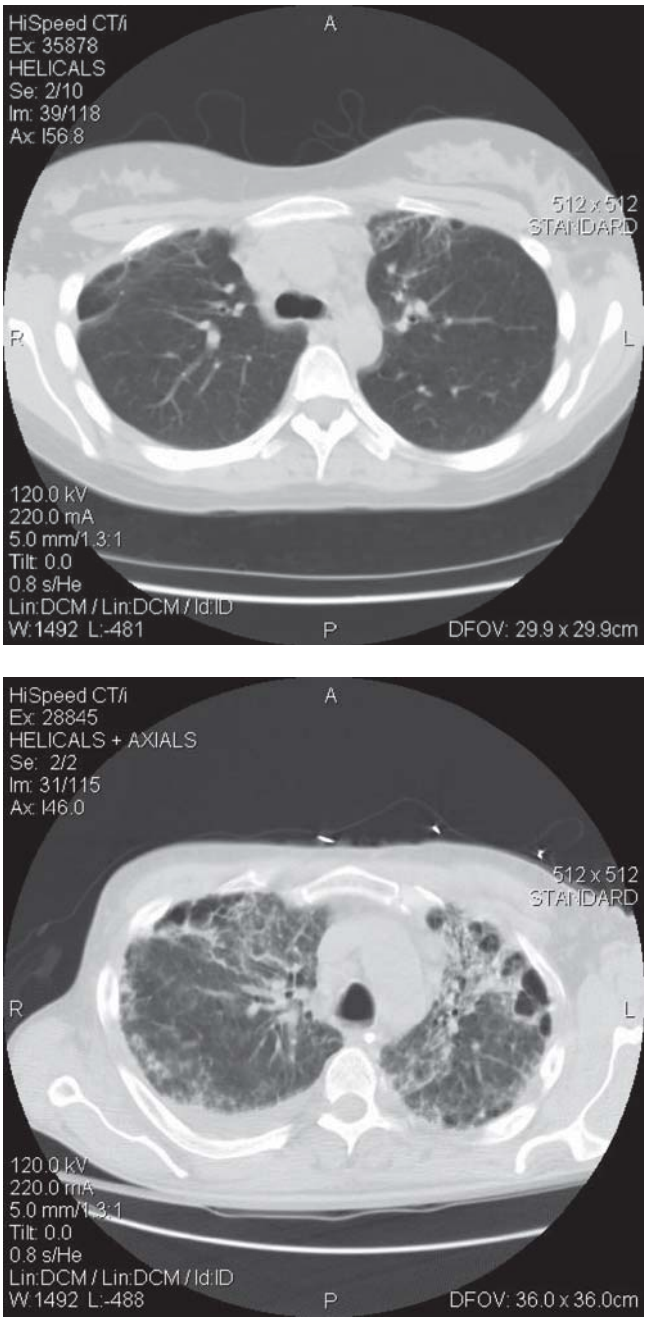


FIGURE 68-5 *Top Panel:* Computed tomography (CT) findings at 1 year after acute respiratory distress syndrome (ARDS) in a young, previously healthy person without preexisting lung disease. Finding of minor nondependent fibrosis and minor cystic changes were most common in this group. *Bottom panel:* CT findings at 1 year after ARDS in same group of ARDS survivors with an example of a rare finding of more marked nondependent fibrosis, bronchiectasis, and cystic changes.

and duration of mechanical ventilation.[75,76] There were also findings of bronchiectasis or new pulmonary fibrosis in one-third of patients in one study[5] (Fig. 68-5) and loss of ventral distribution in reticular pattern in patients treated with extracorporeal membrane oxygenation.[77]

The variability in reported pulmonary outcomes to date suggests possible confounding by smoking history, preexisting obstructive or restrictive pulmonary disease, physiologic restriction related to ICU-acquired weakness affecting respiratory muscles, presence of other pulmonary processes that fulfill the ARDS definition but that have a very different natural history (e.g., cryptogenic organizing pneumonia), and loss to follow-up that continues to challenge validity and interpretation of follow-up data. Most outcome studies found ARDS survivors are often unable to resume their prior physical function, and the degree of pulmonary dysfunction documented across studies does not solely explain their degree of functional limitation.

Additional Physical Morbidities

The spectrum of physical morbidities after critical illness is shown in Figure 68-1.

ENTRAPMENT NEUROPATHY

The Toronto ARDS Outcomes study observed a 6% prevalence of peroneal and ulnar nerve palsies.[3] Although this represents only a small proportion of patients, these nerve palsies complicated rehabilitation therapy and precluded return to original work in some cases. Recovery was protracted, although by 5 years all had resolved.

HETEROTOPIC OSSIFICATION

Heterotopic ossification is the deposition of paraarticular ectopic bone and has been previously associated with polytrauma, burns, pancreatitis, and ARDS.[78] Heterotopic ossification is linked with paralysis and prolonged immobilization. There was a 5% prevalence of heterotopic ossification in the Toronto ARDS cohort study with all patients having large joint immobilization, leading to important functional limitation.[3] Heterotopic ossification is remediable with appropriate surgical intervention, and screening for it may help to improve long-term functional outcomes (see Fig. 68-1).

COSMESIS

After a life-threatening event, concerns about cosmesis might be considered trivial. The physically transformative nature of critical illness, however, cannot be overstated. Many patients suffer from the often devastating emotional effects related to their altered appearance. From the 5-year ARDS outcomes study by Herridge et al,[5] patients had ongoing concerns about cosmesis, including scars from laparotomy; chest tube; central line, arterial line, and tracheostomy insertion; burns; striae from volume overload (see Fig. 68-1); and facial scars from prolonged noninvasive mask ventilation. Many patients underwent tracheostomy revision. Patients reported that cosmetic concerns contributed to social isolation and sexual dysfunction.

CRITICAL ILLNESS AND BRAIN INJURY

Psychiatric Morbidity

Psychiatric disorders are common among survivors of critical illness. The prevalence of depression and anxiety in different samples of ICU survivors ranges from 10% to 58%.[12,79–82] In a recent systematic summary, Davydow et al reported that 28% of post-ICU patients had clinically significant depression.[81] Neither sex, age, nor severity of illness at ICU admission were consistent risk factors for this, but early post-ICU depressive symptoms were a strong risk factor for subsequent depressive symptoms and associated with a reduction in quality of life.[82]

Depression in ARDS survivors ranges from 17% to 58%, with some suggestion that patients with ARDS have a greater degree of depression compared to populations of general critically ill patients.[8,20,79,81,82] Risk factors associated with depression in patients with ARDS have included duration of mechanical ventilation, ICU length of stay and sedation, alcohol dependence, female gender, and younger age.[8,82] Predictors of anxiety at 1 year included ratio of arterial oxygen tension to inspired oxygen fraction and duration of mechanical ventilation; prediction of anxiety at 2 years was anxiety at 1 year.[82] A recent study found that hypoglycemia may be an important risk factor for depression in ARDS survivors and this warrants further investigation.[83] Post-ICU affective disorders are likely multifactorial and further study will be needed to better understand patient predisposition, illness, and treatment-specific determinants of affective morbidity, and appropriate tools for diagnosis and monitoring.

Posttraumatic stress disorder (PTSD) is the development of characteristic symptoms that occur following a traumatic event(s) where triggers include a serious personal threat experienced with helplessness and intense fear.[84] The diagnostic criteria include a history of traumatic event(s) accompanied by symptoms from each of three symptom clusters: hyperarousal symptoms, intrusive recollections, and avoidance or numbing symptoms. A number of studies have examined relationships between life-threatening critical illnesses and its treatment and the development of PTSD. Schelling et al published a landmark paper on PTSD after critical illness.[26] These authors evaluated health-related quality of life and PTSD in a cohort of eighty ARDS survivors 4 years after ICU discharge. Almost one-third of the ARDS survivors reported impaired memory, bad dreams, anxiety, and sleeping difficulties after ICU discharge. The prevalence of PTSD was 28% and the number of adverse ICU-related memories recalled by patients was the major risk factor for PTSD. Kapfhammer et al found that 44% of critically ill patients developed PTSD at hospital discharge and 24% had PTSD symptoms 8 or more years later.[85] Davydow et al reported the median point prevalence of questionnaire-ascertained "clinically significant" PTSD symptoms was 22%, and the median point prevalence of clinician-diagnosed PTSD was 19% in populations of general critically ill patients.[86] Prior psychopathology, greater ICU benzodiazepine administration, post-ICU memories of frightening and/or psychotic experiences in the ICU, and absence of any ICU memory were consistent risk factors for post-ICU PTSD.[87]

Patients with ARDS may be more susceptible to PTSD than are critically ill patients in general, and these symptoms may persist for years. The prevalence of PTSD, as diagnosed by a psychiatrist, has been reported to be 44%, 25%, and 24% at hospital discharge, 5 years and then 8 years later, respectively.[8]

The etiology of psychiatric disorders following critical illness may be secondary to sequelae of brain injury sustained from critical illness and/or its treatments, a psychological reaction to the emotional and physiologic stress of critical illness, or both. Factors such as medications, physiologic changes, pain, altered sensory inputs, and an unfamiliar environment are all potential contributors to the development of psychiatric sequelae.[88–90] A recent review article found an association between recall of delusional memories after ICU discharge and PTSD-related symptoms, depression, and anxiety.[91] Factual memories do not seem to protect survivors from experiencing symptoms of PTSD. A study by Myhren et al, which evaluated 194 patients, found that 27% had symptoms of posttraumatic stress and predictors of PTSD were higher education level, optimism, factual recall, and memory of pain.[92]

Although we are just beginning to appreciate how long-standing and debilitating psychiatric disorders are following critical illness and the important contribution they make to decreased health-related quality-of-life and functional outcomes, recent studies are beginning to investigate potential interventions to prevent or reduce psychiatric sequelae. A recent review paper suggests that corticosteroid administration may be protective for post-ICU PTSD.[93] A novel study suggests that use of ICU diaries in critically ill patients may reduce the incidence of PTSD. Jones et al conducted a randomized, controlled trial, in which patients were provided with an ICU diary that contained information and photographs from their ICU stays.[94] Of the patients who received the diary, only 5% had clinically significant PTSD symptoms as compared to 13% of controls. Furthermore, the patients who experienced the greatest benefit from the ICU diary intervention were those who had substantial early PTSD symptoms.[94]

Neurocognitive Impairments

Critical illness is associated with new neurocognitive impairments[7,11,12] that may be permanent. In their landmark paper in 1999, Hopkins et al were the first to demonstrate that all survivors in their ARDS cohort had cognitive impairment, including deficits in memory, attention, or concentration, and a global loss of cognitive function at hospital discharge and continued dysfunction in 30% of patients at 1-year follow-up.[11] These findings persisted at 2-year

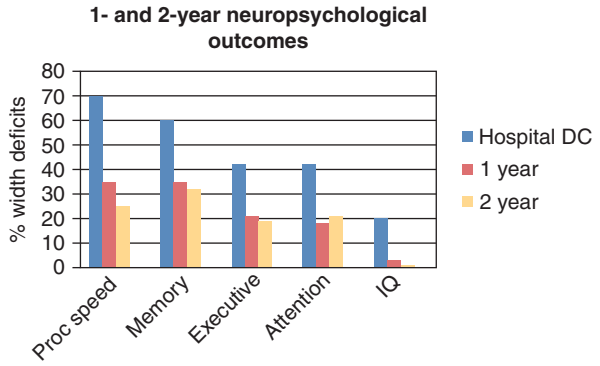


FIGURE 68-6 Domains of persistent neurocognitive dysfunction 1 to 2 years after an episode of acute respiratory distress syndrome. These include reductions in processing speed, memory, executive function, attention and concentration, and IQ. (Adapted, with permission, from Hopkins et al.[11] *J Int Neuropsych Assoc*. 2003;9:584.)

follow-up (Fig. 68-6).[12] These observations are robust and other investigators have documented the persistence of neurocognitive impairments in large numbers of patients at 2 months,[9] 9 months,[95] 1 year,[11] 2 years,[12] and 6 years.[96] Neurocognitive dysfunction appears to improve during the first 6 to 12 months after hospital discharge. The neurocognitive impairments are often long lasting and quite severe, and many patients continue to experience significant chronic neurocognitive impairments years after ICU discharge.[96] To date, almost 1000 patients in fifteen cohorts[79,96–100] have had some form of neurocognitive assessment after critical illness. Risk factors have included the nature of the insults experienced during critical illness and its treatment, presence of preexisting neurologic abnormalities, older age, and comorbid disorders that might render specific domains more vulnerable to critical illness-induced brain injury. For example, patients with ARDS with neurocognitive sequelae all fell below the sixth percentile of the normal distribution of neurocognitive functioning, and had significant deficits in wide-ranging cognitive domains, including memory, executive functioning, and mental-processing abilities.[2]

The question remains whether critical illness and/or its treatment is the cause of observed neurocognitive impairments or if the impairments disclose preexisting subclinical brain dysfunction. A recent longitudinal cohort study in older adults without premorbid neurocognitive impairments or dementia assessed neurocognitive function before and after an acute care or ICU hospitalization.[101] Those who underwent acute care or critical illness hospitalization had a greater decline in neurocognitive function and new incident dementia compared to individuals who were not hospitalized. The Health and Retirement Study findings were consistent with this observation. That study followed more than 27,000 older Americans who had neurocognitive assessment both before and after sepsis.[4] Patients with severe sepsis developed new, important, and persistent neurocognitive impairment. Thus, factors associated with acute or critical illness may be causally related to neurocognitive decline in older critically ill patients.[4,101]

PATHOPHYSIOLOGIC MECHANISMS OF NEUROCOGNITIVE IMPAIRMENTS

The etiology of neurocognitive dysfunction is complex, multifactorial, and interacts with concurrent comorbidities and individual susceptibility. It cannot be explained by severity of illness and, specifically, is not related to severity of illness scores, medical data, age, smoking, alcohol abuse, ICU length of stay, duration of mechanical ventilation, tidal volume, or days receiving sedative, narcotic, or paralytic medications.[12] Candidate pathophysiologic mechanisms may include hypoxemia,[11] sedatives or analgesics,[102] hypotension,[99] delirium,[103] hyperglycemia,[83] and sepsis and inflammation.[104]

Hypoxemia. Hopkins et al evaluated pulse oximetry in a prospective cohort of mechanically ventilated ARDS survivors and studied the relationship between the duration and severity of a mean oxygen saturation below 90 and neurocognitive outcome.[11] Mean saturations were below 90% for 122 ± 144 hours per patient, and the extent of hypoxemia correlated significantly with neurocognitive dysfunction (r^2 0.25 to 0.45; all $p < 0.01$).[11] Hypoxia may be associated with cortical atrophy[103–107] and ventricular enlargement consistent with neuronal cell loss, as well as an increase in ventricular volume.[106–108]

Hypotension. The relative contribution of hypotension to poor neurocognitive outcomes may be more equivocal. Previous studies have demonstrated a correlation between mean blood pressure less than 50 mm Hg and memory scores at hospital discharge.[109] Others have reported that the duration of hypotension only modestly correlated with impaired memory at hospital discharge and 1 year, but not at 2 years.[12]

Delirium. Delirium affects 60% to 80% of mechanically ventilated patients and often goes undiagnosed in the absence of systematic screening.[110–113] It is an independent risk factor for ICU and hospital length of stay,[113–115] increased cost,[116] long-term neurocognitive impairment,[117–118] and death.[119–121] In addition, there are studies that link the disturbing dreams or persecutory delusions experienced as part of delirium as important risk factors for the long-term development of PTSD (Fig. 68-7).[122]

There are emerging data highlighting the importance of delirium either as a marker for or part of the causal pathway for long-term neurocognitive dysfunction. A review of the association between delirium and long-term cognitive dysfunction[103] reported four studies with greater decline on neurocognitive measures at follow-up among patients experiencing delirium during hospitalization and four studies that found a higher incidence of dementia at long-term follow-up in elderly patients.[103] More recent studies in patients who had documented delirium have revealed long-term neurocognitive impairment in one-third of patients at 6-month follow-up.[7] This relationship has also been observed at 3 and 12 months in a different patient sample, and neuropsychological impairment was also significantly linked to days of delirium.[123]

FIGURE 68-7 Picture drawn by a critically ill patient illustrating the violent and persecutory delusions experienced during active delirium while in the ICU. This picture illustrates how patients perceive threats to their safety and violent acts being perpetrated upon them during their stay in the ICU. (Used, with permission, from Griffiths and Jones.[9])

Glucose Dysregulation. The relationship between blood glucose dysregulation and neurocognitive function has been evaluated at 1-year posthospital discharge,[124] and demonstrated an important relationship between moderate hyperglycemia during ICU and compromised neurocognitive outcomes in ARDS survivors. Recent data from surgical critically ill patients showed that hypoglycemia, hyperglycemia, and important fluctuations in blood glucose were also associated with compromise in cognitive outcome.[125] Hypoglycemia has been associated with a 3.6-fold increased risk of depression in patients with ARDS, further underscoring the relationship between glucose levels and neurological sequelae.[126]

Sedatives or Analgesics. The impact of sedatives, narcotics, and anesthetics on long-term neurocognitive function is conflicting, although there may be an important early signal in reports suggesting that neurotoxic effects are more pronounced in high-risk groups, such as the elderly (>75 years) or those who have sustained recent brain injury or neurocognitive impairment.[127,128] A recent substudy of the Awakening and Breathing Trial, however, showed that composite cognitive scores at 3-month and 12-month follow-up were similar between the intervention arm (spontaneous daily awakening and spontaneous breathing trials, with consequent less sedation exposure) compared to usual practice with spontaneous breathing trials.[129]

Inflammation, Systemic Inflammatory Response Syndrome, and Sepsis. Neurocognitive morbidity may also be generated by inflammatory mediators and cytokines propagated by sepsis and the systemic inflammatory response syndrome. The brain is vulnerable to systemic inflammatory reactions in sepsis[104] that penetrate the blood–brain barrier and may modulate brain activity. Endotoxin-induced inflammation and cytokine activation are associated with impaired learning and memory,[130] and neurocognitive dysfunction.[131] Animal models of sepsis demonstrate increased levels of interleukins 1 and 6 in the prefrontal cortex and hippocampus that are associated with learning and memory tasks.[132–133] Congruent with this finding, a recent long-term outcome study showed that sepsis survivors had neurocognitive impairments several years after hospital discharge.[134]

CAREGIVER AND FAMILY BURDEN IN CRITICAL ILLNESS

The impact of a severe episode of critical illness on the caregiver and family has only recently gained momentum as an important issue in critical care medicine. There is no question that the caregiver suffers enormously during and after the illness. Caregivers conduct bedside vigils for their loved ones during the ICU stay, and then are saddled with virtually complete responsibility for the medical and psychological care of their family member who often has new complex medical needs, perhaps unresolved delirium, and new functional dependence. In some ways, it is surprising that it has taken so long for the caregiver issues to have been prioritized and acknowledged as a key component in the patient's rehabilitation program and ultimate outcome.

Recent work indicates that close to 60% of ICU survivors who received long-term mechanical ventilation still required the assistance of a family caregiver 1 year after their critical illness.[28] Existing evidence suggests that providing such care may have a deleterious impact on caregivers, and may compromise health-related quality of life compared with age-matched and sex-matched persons.[18] There are also reports of important mental health issues in caregivers, including PTSD,[135] emotional distress,[18,136–138] caregiver burden,[139] depression,[140] and anxiety.[141]

In a recent review, Johnson[144] concluded that caregivers experience burden because of the patient's physical and psychological dysfunction and the challenges of managing complex care in the home. Lifestyle disruption and provision of high levels of care[19] also contribute to poor caregiver outcome.[19,145] Much of the current research work has been limited by the cross-sectional design and follow-up to 1 year after hospital discharge. It is likely that caregiver needs will change over time as patients move through different transitions in their recovery[146] and attempt to return to work and resume their prior lifestyle.[147]

CONTINUUM OF CARE DURING AND AFTER CRITICAL ILLNESS: INTENSIVE CARE UNIT AND POST-INTENSIVE CARE UNIT REHABILITATION

There are many barriers to improving outcome after critical illness in patients and family caregivers. First, we need to embrace the concept of a family-centered longitudinal

model of care and recovery where we acknowledge that both patients and family caregivers have important needs during and after the ICU stay and that these needs will evolve and change at different transition points during recovery.[146] Second, we need to be honest and acknowledge that current ICU practice patterns may result in additional injury to vulnerable end organs, and that muscle, nerve, and brain need to be prioritized as key organ systems that largely determine functional, neurocognitive, and health-related quality-of-life outcomes in our patients. Third, we need to design studies that help elucidate the relationships between practice and long-term outcome so we can better determine which morbidities are potentially modifiable. Fourth, we need to understand how to risk stratify and optimize subsequent acute and chronic rehabilitative needs, functional independence, and return to work and/or previous lifestyle. Fifth, we have minimal understanding of the basic science of ICU-acquired morbidity, and this needs urgent attention. Finally, we need to embrace, empower, and educate each member of our interprofessional teams to help them understand that what we practice every day may change the long-term outcome for our patients and their families.

Figure 68-8 outlines the concept that rehabilitation begins the moment the patient is admitted to the ICU and that the way in which we conduct our treatment may have important downstream ramifications. The effectiveness of resuscitation affects mortality and propagation of organ dysfunction and perhaps this also has implications for muscle, nerve, and brain injury.[147] The diaphragm is very vulnerable to rest and undergoes rapid proteolysis within hours of controlled mechanical ventilation.[34] Attempting to prioritize spontaneous ventilation modes to preserve the diaphragm makes sense but there are no studies that link spontaneous ventilation to improved longer-term outcome. The indication for and use of neuromuscular blockers and steroids remains controversial.

Perhaps one of the most fundamental limitations in constructing appropriate rehabilitation programs after critical illness is our current inability to risk stratify our patients. Risk stratification is a fundamental tenet upon which many other disciplines devise robust algorithmic treatment approaches to clinical problems. The heterogeneity of critically ill populations is an important barrier that needs to be addressed to be able to understand differences in functional outcome across different patient groups and the various factors that appear to drive a broad spectrum of outcome. For the sake of discussion and contrast, there is an enormous difference in functional outcome between relatively young survivors of ARDS[3,24] compared with older chronically critically ill patients,[1] despite the apparent similarities of severity of illness and a protracted ICU length of stay. The young, previously working, lung-injured group had few comorbid disorders, very low mortality after ICU discharge, and a significant, albeit less than predicted, improvement in

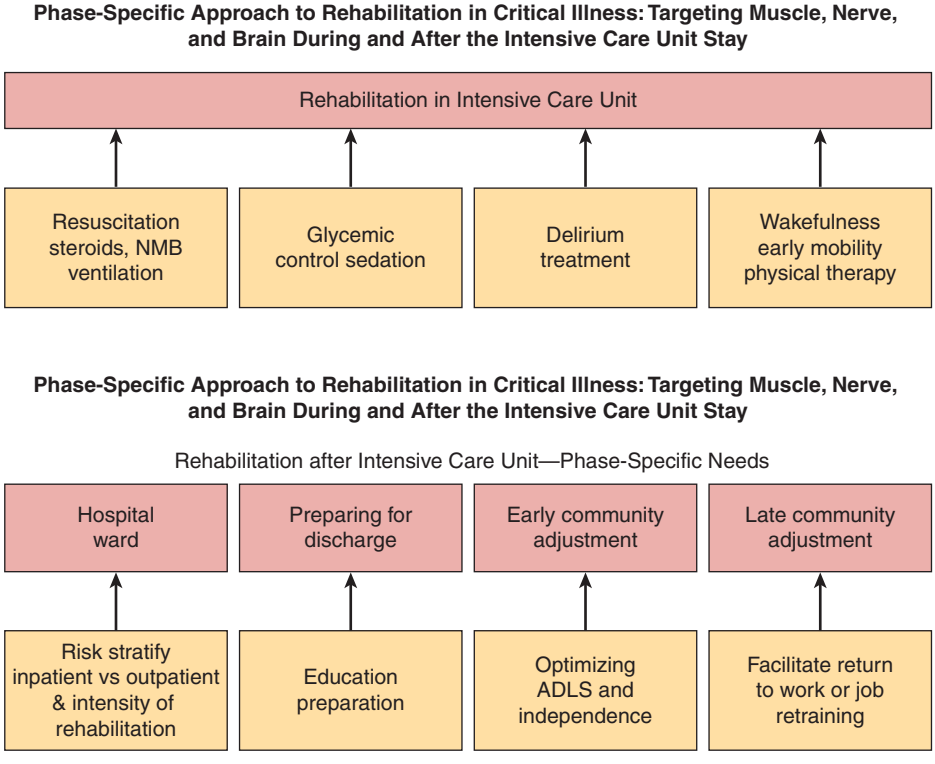


FIGURE 68-8 Rehabilitation continuum during and after the ICU stay. This highlights the concept that rehabilitation begins the moment the patient is admitted to the ICU and that our daily management may have an important impact on long-term outcome. It also highlights the various patient needs after they leave hospital and attempt reintegration into their prior lifestyle. (Adapted, with permission, from Herridge MS. Legacy of intensive care unit-acquired weakness. *Crit Care Med.* 2009;37[10 Suppl]:S457–S461.)

functional status at 1 year, and virtually all returned to independent living. This is in stark contrast to an older group of chronically critically ill patients with a significant burden of comorbid disease, with a 44% mortality at 1-year after ICU discharge and only 11% achieving a good (alive with no functional dependency) outcome.

Current interventional work has focused on early mobility, which a number of studies has shown to be safe and feasible and alters short-term outcome in those patients who were previously functional.[148–153] It is practical and logical to trial physiotherapy and occupational therapy interventions in those for whom there is a high likelihood for benefit.[152] This approach, however, although important and laudable, will not determine how interventions should be tailored to meet individual needs nor differentially applied because there are almost no guidelines on specific patient subgroups. For example, offering such interventions to subpopulations of patients whose muscles and nerves have sustained such profound injury that they have lost any potential for rehabilitation raises inappropriate expectation. There are currently many proposed models for complex rehabilitation after critical illness, but none has focused on how to tailor the program to individual need nor shown long-term efficacy.[154–157] A recent multicenter randomized trial of 286 critically ill patients assessed health-related quality of life and compared outcomes from a nurse-led intensive follow-up versus usual care at 12 months. There was no difference in health-related quality of life on the physical or mental health component scores, and the nurse-led follow-up program cost significantly more than usual care.[158] A self-help manual with instructions for physical therapy, however, improved 6-month outcomes in physical function assessed using the SF-36 health-related quality-of-life instrument; perhaps, patients and families could tailor this guide to individual need, although this consideration was not studied explicitly in this trial.[159]

I have outlined important neuropsychological disabilities in this chapter, and there has been some early work evaluating potential interventions to improve these outcomes. Jones et al evaluated whether a prospectively collected diary of a patient's ICU stay could reduce the development of new onset PTSD during convalescence after critical illness.[94] Patients with an ICU stay of more than 72 hours were recruited to the study and intervention patients received their ICU diary at 1 month after ICU discharge, and assessment for the development of PTSD was made at 3 months. They found that use of the diary was associated with a decrease in new-onset PTSD. These early data are very promising but further understanding of the longer-term effect of the diary intervention is warranted.

SUMMARY AND CONCLUSION

The current state of the art in the outcomes literature suggests that patients will sustain some degree of neuromuscular, functional, and neuropsychological morbidity as a result of their critical illness, and this does not appear to be wholly reversible over time, even in younger patients who were previously working and highly functional. Pulmonary outcomes will likely be very good in those who are younger and have no premorbid pulmonary disease. Health care costs after critical illness mirror those of chronic disease, but younger patients who receive support in transitioning back to work will overwhelmingly return to work. Patients with more comorbid illness and premorbid functional disability will have poor longer-term outcomes. Family caregivers may acquire new mood disorders that impair their health-related quality of life and may modify outcomes in patients. ICU-acquired weakness and brain injury represent major morbidities. Further basic science studies to elucidate the pathophysiology of brain, nerve, and muscle injury are urgently needed, as is work on risk stratification so that rehabilitation programs can be tailored to individual and family needs.

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